129th COSMETIC INGREDIENT REVIEW EXPERT PANEL

MEETING

BREAKOUT SESSION

Washington, D.C.

Monday, December 9, 2013

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Voting Members:

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P R O C E E D I N G S

(8:55 a.m.)

DR. MARKS: Let's do that. And again for the record, I have Ron Shank's input on these ingredients, which I'll refer to intermittently as we go along if Ron Shank doesn't conference call in with us. He's supposed to, but we'll see.

So the first ingredient is the amino acid alkyl amides.

DR. BERGFELD: Can I just ask you a question? How will you know he's called in?

DR. MARKS: I think very once in a while we'll take it off of hold. Hey, Tom, are you there?

(No response.)

DR. MARKS: So in September, the expert panel concluded these ingredients were safe in the present practices of use and concentration cosmetics when formulated to be non-irritating. We have the draft final report in front of us, and I think we can move forward and issue a final report. I had no comments. I thought it was well

written, Christina. Ron Shank didn't have any comments in terms of editorial. We can certainly get Tom Slaga's and Ron Hill's afterward.

So let me see. If we have the meeting tomorrow morning, we also talked about potentially moving this up. But when we have the expert panel meeting to go over each one of these ingredients, I'll move that we issue a final report with that conclusion, safe when formulated to be non-irritating. Christina, any comments or Wilma?

MS. BURNETT: Did you want to include the fact that the discussion was expanded to include the impurity information on the amines?

DR. MARKS: Yes.

DR. BERGFELD: And the sensation of the triethyl amine?

DR. MARKS: Can you hear that? Did you hear Dr. Bergfeld once she said that? Good.

DR. BERGFELD: And we had made a point to clarify that this was a pH adjuster. Is that correct? No?

DR. MARKS: Let me look at the minutes.

MS. BURNETT: I don't recall.

DR. BERGFELD: You don't recall that? You would know better. Then I must've misheard that. Okay.

MS. BURNETT: I don't have --

DR. BERGFELD: You don't have that.

MS. BURNETT: I don't have that listed as --

DR. BERGFELD: Okay, that's fine. That's fine. There was another one that I must've just written down.

DR. MARKS: Okay. Any other comments?

(No response.)

DR. MARKS: If not, then we'll go ahead and move onto the next ingredient. So again, for these amides, final report with "safe when formulated to be non-irritating" And, Christina, I think for our team, as the whole day moves forward, I think if there's any editorial comments, I'll depend on my team members to get them to you.

MS. BURNETT: Okay.

DR. MARKS: Again, for the record, Ron Shank, he will not be making the meeting. He will be sending his flash drive with comments.

Okay. The next ingredient or ingredients are the alkyl betaines. At the September 2013 meeting, the expert panel issued an insufficient data announcement where method of manufacturing and impurities. And I thought that was met, and so did Ron Shank. So I think we've met the insufficient data, and that we could move forward issuing a tentative report on the alkyl betaines with a "safe when formulated to be non-irritating." And I will be presenting that at the combined meeting.

Comments, Christina or Wilma? And then let me go back and let me -- Tom. Tom, can you hear me? Apparently not. He's not speaking to American Airlines anymore. And you had mentioned to Carla that -- Tom is up, so if we could get Tom on the phone, that would be good.

DR. BERGFELD: This is one that I had made a note to myself that the references for the

studies were in the table. But I wanted to go back and re-check whether I had seen them in the text, because I think I did not. That's why I was --

MS. BURNETT: No. I had summarized --

DR. BERGFELD: Yeah, you summarized -- no, it doesn't matter to me, but not all the documents do it that way.

MS. BURNETT: Right. Right. Well, we'll work together to make sure that we're consistent.

DR. BERGFELD: Whatever you do, yeah. Okay. No. No, I just wondered, I was going back. Do you say see table or anything?

MS. BURNETT: Yes.

DR. BERGFELD: Okay. That's fine. That would be fine with me. But then when I went to other documents, they're in both places, and then --

MS. BURNETT: The Council made some comments.

DR. BERGFELD: Okay.

MS. BURNETT: And I think when we just briefly discussed some of them, I think it depends on how much data we were summarizing. If it was a lengthy thing, people kind of put the references in. If it's a short thing, then we tend to just let the table speak for itself. But we'll make sure that we're all doing it consistently so that it's --

DR. BERGFELD: Yeah, that would be nice.

MS. BURNETT: It's really easy just to insert --

DR. BERGFELD: All right.

DR. ANSELL: We also have a comment concerning the referencing of the REACH. We think it's great that the ECHA date is being included, but we should be clear that ECHA itself is not an author. These are being authored by consortia.

MS. BURNETT: Right. We're at odds with the Legal Department then because the Legal Department told us that it was perfectly appropriate to reference ECHA because Joe Q. Public --

DR. ANSELL: No, no, no. We agreed to the referencing. We don't think we should call them the author of the reports.

MS. BURNETT: Oh, I see that.

DR. ANSELL: ECHA is the source of the reports. They don't actually author anything.

MS. BURNETT: Is it in the text or in the reference section?

DR. ANSELL: They should not be listed as the author in the references section.

DR. BERGFELD: How would you list them?

DR. ANSELL: Source.

DR. BERGFELD: Source?

MS. BURNETT: We're going to have to manually put in "source" because how the reference program puts it you have to put in author, whether it's an actual entity or not. So we'll figure out how to do that. It's just for public. You know, when we're referencing website, they're going to see that they're going to be ECHA --

DR. ANSELL: Right. No, we think that all that's fine.

MS. BURNETT: Okay.

DR. ANSELL: You will note that Carol (inaudible) every single time.

MS. BURNETT: Yes.

DR. BERGFELD: Could I also make a comment? This is one that some of the documentation was scanned sideways.

DR. MARKS: Thanks, Wilma.

DR. ANSELL: Which is terrible on the iPad because when you turn the iPad sideways --

DR. MARKS: It turns, too.

DR. BERGFELD: Can you turn this on the computer?

MS. BURNETT: Which PDF page, please?

DR. BERGFELD: Well, it's right above the comments.

DR. ANSELL: Somewhere in view it should say.

DR. BERGFELD: View?

DR. ANSELL: Yes, ma'am.

DR. BERGFELD: Rotate view?

DR. ANSELL: Right, rotate --

MS. BURNETT: Everything is showing up --

DR. MARKS: You can see at what level of sophistication we are in using this.

DR. BERGFELD: Oh, my god. Yeah.

DR. MARKS: Yeah.

DR. BERGFELD: Thank you.

DR. MARKS: Okay.

DR. BERGFELD: Not all of them are that way, so --

DR. MARKS: So to save us from having to manually go in and rotate, let's see if we can't --

Any other comments? If not, then I will move tomorrow we move forward with a tentative report on the alkyl betaines with the conclusion of "safe when formulated to be non-irritating."

Okay. Any other comments?

(No response.)

DR. MARKS: Next ingredient is the polyvinyl alcohol. And this is a re-review. In '98, the CIR Final Report came to the conclusion

"safe as used in cosmetics." The uses have increased significantly as has the concentration gone up to 15 percent. The original report had an HRIPT of okay at 13 percent, so I thought that was not that much different from the present use concentration. It's medically used in transdermal patches and rapid drying jelly, so if there's a situation where there should be case reports of allergic to these, you would've thought those would've appeared since patients are getting essentially HRIPT within a patch or the jelly.

So I felt the new use concentration at 15 percent was fine, and felt that we did not need to reopen. Ron Shank also felt there needed to be no reopening.

DR. BERGFELD: No reopening.

DR. MARKS: Okay. Tom Slaga, Ron Hill, any comments?

(No response.)

(Laughter.)

DR. MARKS: Next alumina, yes, and we've discussed about these ingredients are different

from aluminum. And in September the Panel reviewed the draft final report of alumina and aluminum hydroxide. It was tabled at the request of PCPC to incorporate some edits. We now have those edits, particularly with the discussion not connecting the toxicity of aluminum with these ingredients. So we're at the point now where we can issue a final safety assessment for alumina and alumina hydroxide with a conclusion of "safe."

DR. BERGFELD: Agreed.

DR. MARKS: Okay. And Ron Shank agreed that it could move forward with "safe." Jay, from the PC's point of view, is the wording now in dealing with aluminum and the edits that were made, has Lillian captured those well?

DR. ANSELL: Yeah. We thank the author for making the corrections. There are still a few technical errors, which we provided directly, but with those corrections we have a --

DR. BERGFELD: Did that happen? Did it happen? The corrections occurred already?

DR. ANSELL: Well, there are a few more

corrections that --

DR. BERGFELD: A few more?

DR. ANSELL: -- we've provided, but they're C.F.R. References, correcting the numbers. But we've sent those along, and with those comments included, we think it's ready to go final.

DR. MARKS: And none of those edits from your point of view, Jay or Lillian, substantially change the document.

DR. GILL: No. No.

DR. MARKS: They're more corrective sort of --

DR. GILL: Yes.

DR. MARKS: Nothing that changes the intent of the document.

DR. GILL: Nothing that's going to change anything in the outcome.

DR. MARKS: All right, good. Okay. So presumably I will be seconding a final report tomorrow with a conclusion of "safe." Thank you, Jay. And thanks to the PCPC and Lillian for --

DR. GILL: And Ivan.

DR. MARKS: And Ivan. Thank you, Ivan. We don't want to leave you out, Ivan. You've been silent so far. Feel free to jump in anytime.

The next is yarrow, achillea millefolium derived ingredients. So I assume if Tom were here, he would let us know. Do you want to press anymore buttons here, Bob?

DR. HELDRETH: Carla said she was going to email him.

DR. MARKS: Oh, okay. So in September, the panel changed the conclusion for these ingredients from "safe as used" to "safe as used when formulated to be non-sensitizing." And that referenced what you commented on this morning, Wilma. We don't have -- let's see what -- Ron Shank had some comments about this, and maybe I should bring them up. I briefly wrote them down here. So final amended safety assessment, we have the draft in front of us. The question is do we move onto a final.

DR. BERGFELD: I think we have to be

careful with what we're doing with this non-sensitizing, that we clearly understand it's because there's increased sensitivity of these botanicals, and that they're frequently mixtures with some what I would consider contaminants.

DR. MARKS: Yeah.

DR. BERGFELD: And that may increase the sensitivity.

DR. MARKS: That's, of course, covered in our boilerplate, the final formulation. Let me mention what Ron Shank and then we'll go back because I didn't have this in mine, and it wasn't left over from our September meeting. And let me make sure I read it correctly. He has "Manufacturing and impurities for cosmetic grade." I had that question on another botanical. Can we say that the same as GRAS, I guess is what Ron was asking. So let me just take a look and see. Excuse me.

I should ask Carla to probably print out Ron's. I didn't print it out last night. I think she was copied. No, maybe this is not the one.

This is the second one. There's alumina. Okay, he has some edits. Conclusion, okay. I had it in the wrong ingredient. I did that this morning. So he was also fine as I was.

I thought "formulated to be non-sensitizing," the precedent has been set with "non-irritating." I think it's a good way to handle this when we have the potential of multiple botanicals we know occur. Any other comments? Otherwise we'll move the final amended safety assessment. Yeah, Jay?

DR. ANSELL: We have an editorial comment as it relates to Table 3. For some reason in the NTP conclusion for male rats, the NTP conclusion, the results for male rats are italicized, while the results for the female rats and male and female mice are not. And it suggests somehow you're pulling this out for specific reference.

DR. BERGFELD: Page 23?

DR. ANSELL: Yes, PDF page 23.

DR. GILL: No, it was probably just left

over from a --

DR. BERGFELD: No problem. Thank you.

DR. MARKS: Anything else, Jay?

DR. ANSELL: No. I mean, we sent a lot of --

DR. MARKS: Yeah, but editorial comments.

DR. ANSELL: -- detailed comments along to staff, but that was the one we wanted to mention here in the meeting.

DR. MARKS: Okay. Anything else?

(No response.)

DR. MARKS: If not, then, let me see. Who's going to be presenting this tomorrow? Dr. Belsito presumably. I will be seconding a non-sensitizing conclusion, "safe." Okay.

Tom, you're still not on. And Ron Shank -- she emailed him.

DR. GILL: She's emailing them. They need to call back in.

DR. MARKS: Yeah, okay. Probably trying --

DR. ANSELL: You'll hear a "ding."

DR. MARKS: Yeah, exactly. I guess the other could be -- does she have their phone number rather than email?

DR. HELDRETH: I'll have her check.

DR. MARKS: Okay, next. Of course, if we keep at this pace.

DR. BERGFELD: We'll be done before you know it.

DR. MARKS: Next is the phytosterols. And let's see here. We have before us the draft final report on the safety assessment of the phytosterols. The conclusion is "safe," and we can issue a final report with that conclusion.

DR. BERGFELD: May I ask Lillian a question?

DR. GILL: Sure.

DR. BERGFELD: It has not particularly to do with this. But when you're writing the abstract, do you have a format for the abstracts?

DR. GILL: Yes. You guys have set up one.

DR. BERGFELD: We have one?

DR. GILL: We have the first sentence to last sentence. The instruction sentence where we're reviewing and what their functions are. The conclusion is last. The boilerplate sentence, "The Panel reviewed relevant animal and human data."

DR. BERGFELD: Okay.

DR. GILL: And then anything else is something that is important that we need to mention. And we're still at a 150-word limit.

DR. BERGFELD: Okay. Now, the reference to "including results test for estrogenic effects," all right, I assume that because the next sentence says it's safe, basically that's negative statement there, "there are no estrogenic effects."

DR. GILL: Would you like that --

DR. BERGFELD: Yeah.

DR. GILL: -- finessed a little?

DR. BERGFELD: Yeah. I'd like that sentence a little bit different.

DR. GILL: Sure.

DR. BERGFELD: Just if that is the truth of the sentence.

DR. ANSELL: Well, and we were suggesting that, yeah, that it be estrogenic activity.

DR. BERGFELD: Yeah. Okay. Thank you. Have no estrogen. They did have something in one of the tests, but it wasn't anything significant. No significant estrogen.

DR. GILL: Relevant?

DR. BERGFELD: Relevant, that's good.

DR. MARKS: Okay. I don't actually have Ron's input on this. I can't imagine there's anything significant from what we already have. So phytosterols, tomorrow I'll move that we issue a final report "safe." Any other comments, Lillian, Jay?

DR. HELDRETH: There's a correction with the CR references.

DR. MARKS: Okay. But nothing that alters the conclusion.

Next is the camellia.

DR. BERGFELD: Wait. Before you go --

DR. MARKS: Oh.

DR. BERGFELD: I'm sorry.

DR. MARKS: No, that's okay.

DR. BERGFELD: It's hard for me. My fingers are getting numb. Going to your, I believe it's the summary, and the last two paragraphs, "There is little or no estrogenic activity detected in the phytosterols using in vitro." Little or no, what does that mean, "little or no?" Relevant? How about using the word "relevant" there again?

DR. GILL: "No relevant," sure.

DR. BERGFELD: Estrogenic activity is so important.

DR. MARKS: Yeah, thank you. And I don't think we have a boilerplate, but I remember when we had the presentation on the testing for estrogenic effects where it's really still, I would say, in the development stage, as I recollect, the presentation. Okay. It sounded

like somebody was --

DR. SLAGA: I'm on. Tom is here. I just took the American Airlines to Cuba.

(Laughter.)

DR. MARKS: Hey, Tom, before we get into -- we're already halfway through. And I can review those for you quickly just so you know what we did.

DR. SLAGA: Okay.

DR. MARKS: But the prediction tomorrow is as bad as it was yesterday, two to four inches of snow, maybe some ice mixed in. So you might reconsider. What we heard was that you're going to try and get in tomorrow morning. You may --

DR. SLAGA: Well, the flight gets in at midnight, but I told them to put it on hold until I talk to you.

DR. MARKS: Yeah. I would --

DR. BERGFELD: Cancel.

DR. MARKS: Yeah. I'll use Lillian's -- when I talked to her, I was in the middle of a snowstorm yesterday in Frederick, Maryland. And

she said, Jim, do you what you think is best. And I would tell you the same. Wilma suggests cancelling. I agree with that. I would second that. I would just stay home, Tom.

DR. SLAGA: Well, we'll do conference calls.

DR. MARKS: We'll do conference call, yes. Okay. So let me go over, Tom, and actually I got Ron's. Ron sent a memo, and you may want -- you can do the same if you want, it's up to you. It was very brief. So for the amino acid alkyl amides, issue a final report "safe when formulated to be non-sensitizing." Does that sound good?

DR. SLAGA: Yes, Bob. As stated, it was a good abstract (inaudible) conclusions.

DR. MARKS: Great. And then if you have editorial comments, what Ron is going to do is send his flash drive to Carla, so you could always send your flash drive.

So the next one -- let me kind of go down these. The next one, just so you're caught up. I probably won't do it depending on how far

we're along. The alkyl betaines, "safe, formulated to be non-sensitizing." Ron Shank felt that was fine.

DR. SLAGA: And I totally agree with that. I have the same thing. The beta group was fine, okay?

DR. MARKS: Polyvinyl alcohols. This was that review from 1998, and both Ron Shank and I felt due not reopen.

DR. SLAGA: Yeah.

DR. MARKS: Okay. Super. And then the next one is the alumina and aluminum hydroxide. And if you'll remember, that was tabled to get the PCPCs, significant edits. That's been done, and we felt that we could move forward to a final conclusion as "safe." And Ron Shank was good with that also.

DR. SLAGA: I am, too. That's exactly what I have.

DR. MARKS: Super. Now, the next is achillea millefolium, and again, issuing a final amended safety assessment with a conclusion "safe

when formulated to be non-sensitizing." Ron Shank was good with that. Wilma is here with us in the room.

DR. BERGFELD: Hi, Tom.

DR. SLAGA: Yeah. Hi, Wilma.

DR. BERGFELD: Hi.

DR. MARKS: And Wilma and along with the support staff here, and Wilma brought it up at our combined session before we broke out into teams just to alert to the non- sensitizing. And Wilma was fine with that also, as is Jay is here also.

DR. SLAGA: There was a comment about to be "formulated to be non-sensitizing." Is that correct?

DR. MARKS: Correct. Yeah, that's correct. That's, of course, in my mind to cover when you mix a number of botanicals together that you end up with a final product which is non-sensitizing.

DR. SLAGA: I totally agree.

DR. MARKS: Okay. Super. You're now caught up, Tom.

DR. SLAGA: Oh, great.

DR. MARKS: We heard you earlier. Somehow we got on the conference call that you had with American Airlines, so we could hear some of the difficulty you were having.

DR. SLAGA: Right.

DR. MARKS: Okay. So let me see. I have on the screen phytosterols, but I thought we did that.

DR. BERGFELD: We did that.

DR. MARKS: Yeah. Final as "safe" with the phytosterols.

DR. ANSELL: Yeah, and I think we were talking about the sentence "Reviewed relevant to animal and human data related to these ingredients, including the results of tests for estrogenic activity."

DR. MARKS: Yeah. Yeah.

DR. SLAGA: And I have "safe," too, and I thought it was a very good report.

DR. MARKS: Great.

DR. GILL: Thank you.

DR. MARKS: So next we're into, I think, tea leaves, is that right?

DR. GILL: Yes.

DR. BERGFELD: Now, here I think we ought to discuss the use of the GRAS data and just make a decision to use or not.

DR. MARKS: And so, this is camellia sinensis, is that right? I said sinensis. Who's the botanist in here?

DR. ANSELL: Sinensis. Sinensis.

DR. MARKS: Sinensis.

DR. BERGFELD: Sinensis.

DR. MARKS: And then how about is the first correct, the camellia? Okay. Tea is easy. These are ingredients derived from green, black, and oolong tea. And so this is the first time we've seen this report. You know that, Tom. I'll bring up Ron's in a second. I think he had a lot of the same ideas that I did when I looked at this.

So, yeah, the first thing was I had, Tom, what about the oral tox? There was some

question whether we could deal with that.

DR. SLAGA: Well, to me, the oral tox, it's already a GRAS substance, and there's been a tremendous amount of study saying it's safe, you know, in drinking. So I thought that the oral tox, that there was no data needs, and it's "safe as used."

DR. MARKS: Okay. Okay. I'll read what -- thanks. One of the questions was did we remove the seed oil. That was in a previous report. That's a judgment call. It was "safe." And then the other, of course, do we include the leaf water. There is a question whether that's a -- I don't have to bring out my cell phone.

DR. SLAGA: I had that down, too, but until we really know for sure, I'd leave it in.

DR. MARKS: Lillian, do you know? Did we get any clarification whether the leaf water was a fragrance?

DR. GILL: No, we did not.

DR. MARKS: So I guess we'll leave it in at this point, particularly if we're going to come

to a "safe" conclusion. If we're going to have otherwise, then maybe we would defer.

How about the seed oil since that was in a previous report? Would you leave it in or take it out?

DR. SLAGA: Well, it would be nice having it all combined in one, wouldn't it?

DR. BERGFELD: That's what I thought.

DR. MARKS: Yeah, I agree. We have boilerplates on page 13. Here we go. And I think this is the same that Ron had. I had do we need the manufacs for cosmetics. That's on page 12 of their report. We have manufacturing for GRAS, so let me see. Ron Shank says, "Discussion. Need method manufacturing of purity data to be certain that cosmetic grade ingredients are chemically the same as food grade ingredients." Okay.

DR. SLAGA: I agree with that. That's important. There was no information on that.

DR. MARKS: So, Jay, can you comment on that at all?

DR. ANSELL: This would be the

relationship between the cosmetic grade and tea grade.

DR. MARKS: Yes, exactly.

DR. ANSELL: I have no information on that.

DR. MARKS: Okay. So I guess Ron Shank has it in a discussion. If we don't have any data, can we in the discussion handle this? We'll change the conclusion. And I have some insufficient data anyway, so we'll get to that in a minute. So I would put that in one of the potential needs or at least address. And, Jay, maybe the PCPC can alleviate that.

Lillian, I have in here -- so I'll go back to Ron Shank says. "It seems that the leaf and leaf extract would be substantially different from the extracts of the flower, root, and seed. This prevents read-across from the compounds and the toxicity database, the leaf, leaf extract." So just deleting the following materials: Flower, root, seed powder, seed extract, seed oils. Of course we can't remove seed oil if we have a

previous report which is safe.

What do you think, Tom, about the read-across?

DR. SLAGA: I have no problem with the read- across.

DR. MARKS: Yeah, neither did I. I didn't put that as an issue also. So what we can do is when we have the discussion, we'll see what the Belsito team does. I feel a little lonely, Tom. I'm the only team member here of our team. The Belsito team, the only one missing is Dan.

DR. SLAGA: But you have lovely Wilma with you.

DR. MARKS: I know, exactly. Wilma was kind enough to join me so I wouldn't feel all alone here. So at any rate, we'll bring that up as a discussion. I have it here in my notes, and I'll mention that tomorrow. Do we need the manufacturer for cosmetics.

Lillian, on page 12, I have linalool concentration, 198,000 parts per million. Is that right? And if it is, that means it's like 19

percent of the tea is linalool?

DR. GILL: Page 12 of the PDF.

DR. SLAGA: Well, the (inaudible) 20 to 30 percent, but I didn't think there was anything else that high.

DR. MARKS: Well, let me see what I have highlighted. I'll go to that page. Maybe I read it incorrectly, Lillian. Oh, yeah, there it is. If you see under constituents of concern.

DR. GILL: Yes.

DR. MARKS: And if you look under leaf essential oil, it has 198,400 parts per million of linalool. So that seems mighty high.

DR. ANSELL: Well, we do suggest that the seed oil be removed from the report for a couple of reasons, including that it's already been reviewed, but also that it's --

DR. GILL: It's different.

DR. ANSELL: It's different, yeah.

DR. MARKS: Okay. So that's easy since it's already been removed. It's interesting. Since it's different, how do you mean, Jay?

DR. ANSELL: Different composition, triglycerides, than the rest of the ingredients in the report.

DR. MARKS: Okay. Tom, what do you think about that? It's already been --

DR. SLAGA: Yeah.

DR. MARKS: Let me see if Ron Shank has removed them or anything. Yeah, Ron mentions again page 13, impurities. So let me go back, Lillian. Do you think it's that high for linalool? Do you see what I'm looking at, Jay? Page 12 of the PDF, and it's under "constituents of concern." It's the first sentence where it has linalool, and you see under leaf essential oil, it ranges up to 198,400 parts per million, so potentially close to 20 percent of the constituent could be linalool. And I didn't look up under the fragrance, but, boy, that's very high I would think. And this is a fragrance sensitizer. Although when I go back, I'll give you my needs in a second.

So, Lillian, I might ask you to just

check that.

DR. GILL: I'm doing it now.

DR. MARKS: Yes.

DR. HELDRETH: I understand the Council's contention that the seed oil would be primarily triglycerides, but that doesn't make it different from all the ingredients in this report. We also have a leaf oil, and that would be triglycerides as well.

DR. GILL: And this is also the correct according to the statement.

DR. BERGFELD: Which is correct?

DR. GILL: The high amounts in the essential oil.

DR. BERGFELD: So you're saying it's the same.

DR. GILL: Right, but this is the plant, essential oil --

DR. BERGFELD: Right.

DR. GILL: -- that might be very different for what they actually use in cosmetics after processing.

DR. BERGFELD: Right.

DR. MARKS: Well, we'll be reassured when we have the sensitization study, so I just want to be sure that even -- let me see if this thing will respond here. Oh, good.

So let's go back up to the seed oil. So I have, Tom, you are fine with not having it included. Ron Shank didn't mention anything. Jay, you would like it removed because of the triglycerides, but, Bart, you say the other ingredients have triglycerides.

DR. HELDRETH: At least one.

DR. MARKS: Yeah. Would you remove it just because it's already in another report, Tom?

DR. SLAGA: Yeah, I'd remove it.

DR. MARKS: Okay. So let me see what else. Impurities, ocular. So I'll let you, Lillian, Ron Shank had a question on page 19, third paragraph under ocular. Which is it, 0.093 or 0.1? But again, that can be -- those are editorial comments. My concern was the leaf extract has 1,700 uses, so it's got a lot of uses.

The leaf itself is applied to eyelids at 97 percent. So it sounds like what they do is put the whole leaf there. They probably have little else.

So I felt we needed an HRIPT on both of these at use concentration. So the extract has used up to three percent, and then I wanted to see leaf meet HRIPT. And what we have now is we don't have HRIPT at those concentrations. So I would put it as an insufficient data announcement with the needs of the HRIPT on the leaf extract and the leaf --

Ron Shank didn't mention that, Tom.

DR. SLAGA: I didn't have any -- I would go with the -- it's the first time.

DR. MARKS: Yeah, exactly, and this is just an announcement. This is not an insufficient data.

DR. SLAGA: Right. I would go with that.

DR. MARKS: Okay. Wilma, do you have any comments? I don't know whether you noticed

that when you reviewed it.

DR. BERGFELD: I wrote and said it needs irritation and sensitization.

DR. MARKS: Yeah, which would be gotten with the HRIPT.

DR. BERGFELD: Yeah, right.

DR. MARKS: Okay. So let me see. Who does this tomorrow? It'll Don, and we'll see how that works out. But right now, we'll remove the seed oil. We'll leave the water in for the time being. I'm going to call it now the botanicals boilerplate because that includes pesticides, metals, and aflatoxin. We need the method of manufacture, or we need the method of manufactures for cosmetics addressed.

And then it looks like the linalool concentration actually is 19 percent based on that.

DR. GILL: So maybe needs method of extracting that.

DR. MARKS: Yeah. Yeah, exactly. And then the HRIPTs. Okay.

DR. BERGFELD: What are you going to do about the use of the GRAS food data? Are you going to from this team say you accept it?

DR. MARKS: Yes.

DR. BERGFELD: Okay.

DR. MARKS: I go with Tom. Tom said --

DR. BERGFELD: You have to say that, I think.

DR. MARKS: Okay. Let me put that up here.

DR. BERGFELD: The aflatoxins that are described in the impurity data, you're just going to put the boilerplate in to cover that.

DR. MARKS: Yes. Yeah.

DR. BERGFELD: Okay.

DR. MARKS: Oil tox, okay. Where am I? Thank you, Wilma.

DR. BERGFELD: Now, I was quite taken with the fact that if you drink too much of this tea, you can have liver damage.

DR. GILL: Yeah.

DR. MARKS: Okay. So I guess the moral

to that story is don't drink it or put it on your skin, or don't drink too much. Like everything else it's in moderation.

DR. BERGFELD: Well, people drink a lot of black tea.

DR. MARKS: Yeah, exactly. It's in moderation. Okay, Tom, does that sound good to you?

DR. SLAGA: Yeah. When I'm drinking tea and it drips on my skin, it kind of hurts.

(Laughter.)

DR. MARKS: So I'm going to put here oral tox, using that is okay. Remove the seed oil. We still don't know about the leaf water, the boilerplate, the manufacture of cosmetics. It looks like there's a high linalool concentration, and I'll see what Don's team says. And then the irritation sensitization and HRIPT on the leaf extract, the highest use, three percent, and on the leaf.

Okay. Any other comments?

DR. SLAGA: No.

DR. MARKS: Good. Thanks, Tom. Thanks, Lillian.

DR. GILL: You're welcome.

DR. MARKS: Okay, let's see. They make quite a few comments, so I'm going to give you this. This is Ron Shank's. Oh, good. You have it.

DR. GILL: He made copies.

DR. MARKS: So next is hydroquinone and para-hydroxyanisole. Is David here? Good, because this is interesting, hydroquinone. Let me bring that up.

So this is a draft report that Lillian put together as used in nail products. It's interesting. So let me go back here. In March there was a request to amend the 2010 conclusion to include the use of nail polishes that require UV curing with these ingredients. As you remember we reopened it to evaluate the safety of these ingredients in UV nail adhesives.

Hydroquinone was found to be safe in 2010 was the most recent report.

Para-hydroxyanisole was found to be unsafe in 1985 because of its de-pigmenting toxicity of the skin. Interestingly, the most recent wave, Wave 2, there are no reported uses for these ingredients, so the question is do we reopen it.

I actually had reviewed it and had the irritation sensitization UV ultraviolet light was okay was nail use. That was on page 22, 25. I felt we could amend it with a "safe." The hydroquinone conclusion would be the same, but the para-hydroxyanisole in the conclusion would be "safe only in nail products." And then I had some questions a little bit, Lillian, about the format.

But at any rate, if it's being used, then do we need to reopen? And Ron Shank felt that Wave 2 states no uses, so don't reopen. So, David, do you have data that the PCPC doesn't have --

DR. ANSELL: It's being used extensively --

SPEAKER: Didn't we agree to reopen it at the last meeting?

DR. BERGFELD: Yeah, I think so.

DR. MARKS: Well, we agreed to reopen it, but if you remember, the reopening is, and we can always shut it again so we don't have to reopen it if we find as we go through the reopening and analyzing, we could go back and say, and remember it should be a non-brainer if we reopen on.

DR. ANSELL: Well, I think the question on the table then would be do we close it since we have reopened it.

DR. MARKS: Yes, okay. Okay, thank you, Jay. You're being very, how do I want to say, precise in the terminology. So thank you.

So the question is do we close it. So, Lillian, you were going to say something.

DR. GILL: I will point out that are uses in the BCRP.

DR. MARKS: Pardon?

DR. GILL: There are uses in the BCRP, involuntary reporting to the FDA.

DR. MARKS: Oh, there are uses?

DR. GILL: Yes. And on page 19 -- nobody reported any to the Council, but they did report to the FDA that there are uses.

DR. MARKS: Okay, so there are uses.

DR. GILL: Seven nail extenders and 11 skin preparations. No uses were reported for the hydroxyanisole.

DR. MARKS: None for the para-hydroxyanisole.

DR. GILL: Right.

DR. MARKS: So I'm glad I read the report before I saw Wave 2 because I would've said why are we spending more time.

So with that in mind that there are uses, so there are uses for the hydroquinone, the para-hydroxyanisole. At least in the database we don't have uses, but, David, you feel they are being used in nail adhesives?

SPEAKER: Not nail adhesives. Well, they could be used in nail adhesives. The main thing is the nail polish.

DR. MARKS: Okay.

SPEAKER: MEHQ, which is how (inaudible) is the preferred polymer inhibitor industrially, and you could go back to your 85 conclusions. It's cited that its big use in industry where they're taking acrylic acid or anything thereof, and inhibiting polymerization until you get polymerization.

We have in, with maybe the only exception being the adhesive use, up until a few years ago, we never sold monomers to consumers. So it was never considered an ingredient, and what's happened is technology has changed, and the most important thing that has happened is the use of the gel nail polishes which are cured by light. And these are safe and are being used by consumers. So the issue is now we have an inhibitor that's in the raw material. We do not put it in. This how the raw material is purchased from your large chemical companies, and it has to be there.

And the polymerization process destroyed the inhibitor. That's how polymerization takes

place. And so the question came back that we had an unsafe report from 1985 and then now we're using it safely in nail polishes right now, the gel nail polishes.

DR. MARKS: Right. Okay.

SPEAKER: So that's why we requested it to be reopened for that specific use.

DR. MARKS: Tom, did you hear all that?

DR. SLAGA: Yeah, and I agree with David. This is completely different, and I'd just leave it in as "safe as used."

DR. MARKS: So the way I had it we would issue -- it open, as Jay pointed out. Now hearing this, I have a feeling Ron Shank wouldn't say do not reopen, or he would say do not close. And I would propose -- let's see, who's presenting tomorrow? Oh, I am. That we issue an amended report, so this would be what, Lillian, a tentative amended report with hydroquinone, the same conclusion because that was found to be safe. And the amended would be para- hydroxyanisole as "safe only in nail products," as used.

Tom, do you have any problems with that?

DR. SLAGA: I do not.

DR. MARKS: Okay.

DR. BERGFELD: I don't either. That's what I put.

DR. MARKS: Good. Thanks, Wilma. And we'll get Ron Hill and Ron Shank's input, but I have a feeling. Now, and I think one of the things that's reassuring to me, David, is, as you said, these gels. I have not seen any case reports, and you didn't find any, Lillian, in the literature of periungual de-pigmentation of using this in these gels. So that's reassuring, plus I suspect it is all used up very quickly once the polymerization begins.

SPEAKER: Right. And the other thing is the instructions, and these are the critical safety issues as far as I was concerned was what happens if the woman accidentally puts the gel on her skin. Well, the gels are very (inaudible). It falls off. It's removed. And you don't want to have nail polish on your skin. So it's quickly

removed.

The other thing is what happens is it gets on the cuticle, and the instructions are very clear that you can't have it on your cuticle because when it cures, what will happen is the cuticle will cause the gel to (inaudible) like this instead of like this, which is not very satisfactory with nail polish. It'll just come off. So there are common sense reasons why it's just avoid skin contact. And one of the reports says is what happened with the cuticle and the nail --

DR. BERGFELD: I think that should be included in the discussion.

DR. MARKS: Exactly, Wilma. So could you summarize that in a couple of sentences, David, and give it to Lillian so it can appear in the discussion? I think that's --

SPEAKER: Sure. Yeah, I believe that we have in my report, but I'll be glad to --

DR. MARKS: And then, Doug, are you from the --

SPEAKER: I'd like to introduce some people who -- and Doug is with the (inaudible). Sunil is with OPI, one of the largest producers. Larry, who just came in, is with Keystone Laboratories. They are one of the largest manufacturers of these gels for the industry. And Kevin works for Larry. So there are all experts in the world in this type of technology here to answer any of your questions.

DR. MARKS: Yeah, I recognize Doug from the phthalate discussions in the past.

DR. BERGFELD: And before.

DR. MARKS: So any comments that you have? I want to be sure that we capture this, David. It sounds like you've summarized it very well. You've been quiet, Doug, or your colleagues there.

DOUG: I think the only thing I would add is these products are educated for use by professionals, and they're educated to avoid skin contact. So they understand it's important to avoid skin contact for one reason -- for the

reasons Dave has pointed out. But the product will lift and come up if they do touch the skin. It'll separate from the nail because oils can go underneath the coating. So the skin contact is avoided.

DR. MARKS: Good. Tom and Wilma?

DR. SLAGA: Yes?

DR. MARKS: How did you like the format of this? If we're going to send an amended report, Lillian did a lot of, I guess, summary sections. Wilma, how do you -- I mean, Lillian, how do you want to -- let me see. I'll go on page 15, and it says "summaries of the hydroquinone safety assessments." Do you like the -- first, there's '86, then '94, and then 2010. And it's kind of interesting, you know, when you normally think of a final report it has section and not a whole bunch of summaries in there. So I just wanted to bring that up and make sure that was fine for an amended report.

DR. BERGFELD: Well, as long as you refer back to the references, and I just went back

to look at them, and it's under reference two, three, and four, and actually five, and six. So you do have those references. But why do references two and three have no authors?

DR. GILL: Because that's the way they originally published them, Allen as the editor.

DR. BERGFELD: That wasn't the original. That was the second wave of change.

DR. GILL: Yeah.

DR. BERGFELD: Is there a reason? I mean, that looks sort of funny --

DR. GILL: He's technically the editor. We have put him as the author. We can go either way.

DR. BERGFELD: Yeah, I think you ought to have somebody there. You've got Anderson (inaudible) if that was the case.

DR. MARKS: Yeah. Anything else, Wilma, that you --

DR. BERGFELD: I thought the summaries were fine. As long as these references were there, that's why I went back to check them, and

we asked that question.

DR. MARKS: Tom, were you fine with them?

DR. SLAGA: I thought the summaries were good. It really brought me up to speed.

DR. MARKS: And then if an individual wants to go back to the original report, they can.

DR. GILL: Correct.

DR. MARKS: And what you added, Lillian, was just essentially updates when you went in the irritation sensitization and such that weren't in the originals.

DR. GILL: Correct.

DR. MARKS: So, good. I just wanted to be sure that we were okay with the formatting.

DR. BERGFELD: I think when you present it, you should that, too, because that may be (inaudible) of the group. I mean, when we're introducing it, somewhere you just say something about the format being --

DR. MARKS: Okay.

DR. BERGFELD: That would be good.

DR. GILL: When I originally put them in, it was mostly for your context.

DR. BERGFELD: But everybody else is, too, that reads it. But the references are key to match up with it.

DR. MARKS: Okay.

DR. ANSELL: We do have a comment that within the discussion of dermal penetration, dibutyl phthalate is selected as a surrogate. It's not exactly clear why. And we'd like to see at least some discussion as to why we think that's an appropriate surrogate for dermal penetration.

DR. SLAGA: Yeah, I had the question. I couldn't come up with why it should be a surrogate. Hello?

DR. MARKS: Oh, we hear you. I was waiting for David or Doug to comment or his other two colleagues about that.

DR. SLAGA: Okay.

SPEAKER: It's very difficult to get anything to penetrate the nail. If we could get things to penetrate the nail, there are a lot of

diseases or nail conditions that we could treat, which we just do by oral ingestion that (inaudible) satisfactory. And one of the studies that was done, which was in terms of looking at the safety of dibutyl phthalate, which was a plasticizer for normal nail polishes, showed how difficult it was to even get something like dibutyl phthalate to penetrate the nail. So that was published in a paper and just shows, you know, we just can't get things through the nail.

DOUG: Even when penetration answers (phonetic) are mixed in with the ingredients it's difficult to get penetration. So without them, it's insignificant.

DR. BERGFELD: Is that documented somewhere?

DOUG: I'm sorry?

DR. BERGFELD: Documented somewhere? Is there a reference we could have for that?

DOUG: The paper?

DR. BERGFELD: Yeah, or the absorption which you just said. I mean, it's an

understanding that you have because you've tried, but has anyone written --

SPEAKER: The penetration paper is published.

DOUG: Well, and there are also published reports from dermatologists who have developed antifungal compounds for the nail plate to get these antifungal ingredients into the nail plate to use penetration enhancers. And even when they do that, there's like an eight percent efficacy rate. It's so low. And they cite the lack of penetration of the nail plate as the reason.

DR. BERGFELD: But no one officially has done it. I mean, these are clinical studies? Do they not have any basic science about their absorption through the nail plate like they do with skin?

DOUG: Yes, there are. There are studies. I can't cite them right now, but they do exist.

DR. GILL: If you can send me one, I'd

be glad to stick it in.

DR. BERGFELD: That would be -- we think it's good to have a document and source.

DR. MARKS: Lillian, where exactly in this document does it have the previous conclusion for hydroquinone as "safe?" Can you find that for me? I was looking for it because tomorrow if I say, hey, our conclusion is "safe." Were there any caveats to that safety with hydroquinone or was it just "safe as used?" Oh, hydroquinone was safe at a concentration of less than one percent for cosmetic formulations, designed for discontinuous brief use followed by rinsing from the skin and hair. Hydroquinone is safe for use in nail adhesives in the private practice. Hydroquinone should not be used in other leave-on cosmetic products. So that was the conclusion in 2010. That's page 15, so I'll reference that. It's page 15 right above the summaries of the hydroquinone safety assessments. Do you see that, Wilma and Jay?

DR. BERGFELD: I picked it up out of the

article.

DR. MARKS: Yeah.

DOUG: The other thing to consider, if I might add, is that once these materials polymerize on the nail plate and solidify, now you're looking at just the fusion from a solid coating into the nail plate, which even further slows the penetration.

DR. MARKS: Okay. Page 18, okay. Tom, any other --

DR. BERGFELD: Do you have any data on the UV damage to the nail bed after this polymerization?

DOUG: You're talking about the safety of the UV nail lamps. Yeah, there's actually three studies that have been performed on the safety of these (inaudible). But I can send you that information.

SPEAKER: There's one in here --

DOUG: There's a Brown University study. And there was also a study by Dr. Robert Sayer studying these lamps through using RP-27 ANSI

Standard, and all the conclusions that they're safe, that there's very little risk. And David is going to get you that information.

DR. BERGFELD: Okay.

DOUG: So we think there's pretty strong evidence that these lamps are safe.

DR. MARKS: Yeah. That was documented in there. Okay. Tom, any other comments?

DR. SLAGA: That's all I have.

DR. MARKS: So tomorrow I'll recommend or I will move that a tentative amended report with the 2010 conclusion of hydroquinone be reaffirmed, and that we change para-hydroxyanisole from unsafe to safe in nail use only. Does that sound good?

DR. SLAGA: Sounds good.

DR. MARKS: Okay.

DR. GILL: Question. In the discussion, you won't mention the nail lamps at all.

DR. BERGFELD: I think so. What do you think? I think just to clarify that because every dermatologist or someone in clinical medicine will

ask that.

DR. MARKS: Okay. Any other comments?

(No response.)

DR. MARKS: Next is the sulfonates. Huh?

DR. BERGFELD: Sulfonates.

DR. MARKS: So this is a re-review. In '98, the Panel found that sodium alpha-olefin sulfonate was safe as used in rinse-off products and safe up to two percent in leave-on products. The concentration at gamma sultone impurities of any formulation be leave-ons or rinse-off is limited. The alkane sultones limited, and the chloro sultone is limited. That's in the first paragraph there.

So it's a pretty lengthy conclusion. The impurities, the limitation was because they were sensitizer. So the question is, let's see what --

DR. ANSELL: Do we reopen?

DR. MARKS: Yeah, do we reopen?

DR. BERGFELD: I said yes.

DR. MARKS: I have reopen safe and formulated to be non-irritating, and continue those limits on impurities.

DR. BERGFELD: We had increased concentrations, increased use, and a request to add some salts.

DR. MARKS: Yes.

DR. BERGFELD: I thought we added, we reopen.

DR. MARKS: Oh, yeah, have to. So let me see. Tom, what did you feel?

DR. SLAGA: I felt that we didn't need to reopen them.

DR. MARKS: You did not feel to reopen. Okay. Let me see. I was with Wilma feeling that we could reopen to go to a non-irritating conclusion, but --

DR. SLAGA: Even for the leave-on?

DR. MARKS: Yeah. Let me take a look here. No additional ingredients were identified that might be added. So, see, no --

DR. BERGFELD: I thought it said salt.

DR. MARKS: No additional.

DR. ANSELL: Yeah. It's our recommendation that this not be reopened.

DR. MARKS: Let me take a look here. I had a question mark -- reopen. Let me see what -- "New data don't present any new information. Use in leave-ons as now. In order of magnitude, greater the limits set by CIR." This is Ron Shank. "If report is reopened, then the conclusion should be changed to 'formulated to be non-irritating.' Remove the two percent leave-ons, Table 2." So I could go --

DR. BERGFELD: Either way.

DR. MARKS: -- either way. No reopen. Ron says if reopened, then formulate to be non-irritating, that's right. The previous conclusion, leave-on safe to two percent, there's new use for the C-14, 16. Leave-ons is 13 percent now, but the new ECHA guinea pig max is okay up to 25 percent. So irritation or sensitization wasn't an issue with me.

DR. ANSELL: Well, you know, we think

the current conclusion continues to be appropriate. There's really no data. If someone is using it significantly outside that, that that's not justification to reopen. That's a justification for them having data substantiating the safety outside of the CIR conclusions. So it's our suggestion that this not be reopened.

DR. MARKS: Interesting.

DR. SLAGA: I don't see any reason to reopen it just to add "non-irritating."

DR. BERGFELD: I would not either, only if the salts were involved, and I thought they were --

DR. MARKS: No, they are not. Okay. So not reopen. Lillian, this is an editorial. In Table 8, if you're going to include that in the re-review summary, I'd have it that's it from ECHA, and it's referring to C-14 and 16, I think if I read that correctly.

DR. GILL: Okay.

DR. ANSELL: And we have the same comment about citing ECHA as an author.

DR. MARKS: Yeah.

DR. BERGFELD: Your comment is to cite them as an author or --

DR. ANSELL: No, no, that it's inappropriate to cite them as an author. Yeah.

DR. BERGFELD: Okay.

DR. MARKS: Okay.

(XXXTRACK 2XXX)

DR. MARKS: For some reason my computer is actually pretty well today. So interesting, Jay. Even though there's data in the ECHA guinea max that it's okay up to 25 percent, we would expect what the manufacturer is using at greater than two percent to come forward and say we want it reopened, and this is the data, the reason why.

DR. ANSELL: Yeah.

DR. MARKS: Yeah. Okay. So let's see. Who presents that tomorrow? It will be me, and I will move not to reopen this re-review. Any other comments, Tom, Wilma?

DR. SLAGA: No.

DR. MARKS: Good. Okay.

DR. SLAGA: A minor editorial, but --

DR. MARKS: Okay. Great. Next is the re-review summary of iodopropynyl butylcarbonate. And Lillian is going to -- I assume this is Lillian Gill, not Lillian -- and Ron Shank felt the report was okay, no changes. He thought it was fine. Tom, did you have any comments?

DR. SLAGA: I'd say no changes.

DR. MARKS: Okay. And that was in the administrative portion of the report we have. Okay.

DR. ANSELL: We had a comment concerning the reference for the.01 percent.

DR. MARKS: Okay. You'll take care of that one.

DR. ANSELL: Yeah.

DR. MARKS: Okay. Next I have on my agenda, infant skin, but we will defer that until after we have the presentation right after lunch by Elias and Williams. Let's see --

DR. SLAGA: Where is Elias and Williams?

DR. BERGFELD: They're in San Francisco,

I believe, and they're married.

DR. MARKS: That's correct. Yeah, they're in San Francisco.

DR. BERGFELD: And they're at the University of California.

DR. MARKS: And they're going to be commenting from afar actually. They're going to be telephoning in, so this is going to be interesting. I don't know how. Tom, you'll be able to hear them when they call in, too. So that'll be good.

There were a number of comments. Again, we'll go back to that. There were a number of comments that the Council had, which I thought were good. So, Ivan, I know in the next edition of this document, you'll be taking those in consideration. We'll have Elias and Williams' input. And the one input -- here, I'll give you this -- that Ron Shank had one or two.

DR. BOYER: And we have confirmation that Peter, Dr. Elias is going to talk with us.

DR. MARKS: Oh, okay.

DR. BOYER: We don't know yet whether Mary is going to be joining him.

DR. MARKS: And my understanding, and, Wilma, you can correct me. Mary was Peter's student.

DR. BERGFELD: I think so, yes. Long-time marriage, though.

DR. MARKS: Oh, yes.

DR. BERGFELD: Thirty-five years.

DR. MARKS: Okay. That's just for informational purposes. So next I have was rosmarinus officianalis, rosemary.

DR. BERGFELD: Insufficient.

DR. MARKS: So, you're already -- did you hear Wilma, Tom? She's already taken the thunder out of this. Wilma said "insufficient" over there. We saw the first report of this in September. We gave an insufficient data announcement, and the memo from Monice -- is Monice here?

DR. HELDRETH: She's not.

DR. MARKS: So, Bart, are you going to

go ahead and take care of this?

DR. HELDRETH: Yes.

DR. MARKS: At any rate, there were four needs requesting to follow the dermal sensitization. We did not get that, so we're going to have to move forward obviously with an insufficient conclusion. The chemical characterization of the flower, the deodorizing process, and the issue of pregnancy, which was in the PDR. Ron Shank also felt insufficient, "Need to have human skin sensitization for the leaf extracted, 10 percent." And the other three items, apparently he was not concerned about.

DR. BERGFELD: I think we got the fourth.

DR. MARKS: Did we get the fourth?

DR. BERGFELD: There was some mention of it in the text.

DR. ANSELL: Yeah.

DR. SLAGA: Yeah.

DR. BERGFELD: So we didn't get one through three.

DR. SLAGA: -- the first one (inaudible) that I have a concern. The rest of it can be done.

DR. MARKS: Okay. Good, Tom. And I think we're all on the same page then is that we need 10 percent thermal sensitization for leaf extract. And the reasoning is that is that undiluted leaf extract is a sensitizer. So at what level is this a non-sensitizer?

DR. BERGFELD: What is the threshold?

DR. MARKS: Yeah, what's the threshold? Yeah?

DR. ANSELL: We can have sensitization data at lower concentrations.

DR. MARKS: Right, but not even close, 0.2 percent. This is being used up to 10 percent.

DR. ANSELL: So we would find it appropriate to set up a limit to exclude the 10 percent, "safe as used."

DR. SLAGA: I mean, we could set it at two percent.

DR. MARKS: Yeah, we've done that

before.

DR. ANSELL: Yeah.

DR. MARKS: Yeah, okay. Interesting. So we could move --

DR. BERGFELD: We have two options.

DR. MARKS: Yes. And for some reason I didn't think of that second option.

DR. ANSELL: Well, we have reached out to the company, and they are not going to do live data.

DR. BERGFELD: Okay, so that's good.

DR. ANSELL: So we would just as soon proceed.

DR. BERGFELD: Proceed. That we should include in the comments that the company has not responded. Not only not responded, but they haven't --

DR. ANSELL: The data is not available.

DR. BERGFELD: The data is not available. Requested, but not available.

DR. ANSELL: The request and their response really doesn't go to the question of

whether it's safe or not.

DR. BERGFELD: That has nothing to do with that. It has to do with the data lacking. We've made a request. There's been no response, and we're proceeding with what we have. That's what I'm trying to say. But I think you have to present it that way because otherwise you'll hang out for that 10 percent.

DR. MARKS: Well, that'll be in the discussion. Well, you know, it's interesting because we haven't done it before. We just say this is the limit.

DR. BERGFELD: This is all the data we have.

DR. MARKS: And this is the data we have. And then if anybody wants to come forward with the 10 percent, they can.

DR. BERGFELD: At this point, it went out as an insufficient data announcement, did it not?

DR. MARKS: It went out as an insufficient data announcement. We can now issue

it as a tentative report with "safe," with concentration of 0.2 percent. There we go. Thank you, Jay. Tom, does that seem reasonable to you? Am I correct? That's what I have highlighted, the 0.2 percent of the leaf extract.

DR. SLAGA: I have down insufficient at 10 percent, but could be safe at 50.

DR. BERGFELD: Right.

DR. MARKS: Okay.

DR. HELDRETH: So safe as used except for the leaf extract, 0.2.

DR. MARKS: Yeah. Let me see who it is tomorrow. Belsito will be the one, I believe, who's presenting it, but I will either second or propose a counter motion that we issue a tentative, so it would be a tentative report with a conclusion "safe with a concentration of 0.2 percent" for the leaf extract.

DR. BERGFELD: And that was 0.2 or --

DR. MARKS: 0.2. Yeah, it's in the -- let me see. It's in the last paragraph of the memo from --

DR. BERGFELD: Yeah.

DR. MARKS: I'm making some notes on my computer. Tom, I'm making a couple of changes to my notes in the computer, and this is not as -- how do I want to say -- not as easy as just using a pen or pencil and paper. Bart?

DR. BERGFELD: My finger is sore, Tom. Could we look at the abstract when you're done then?

DR. MARKS: Sure. Abstract, that's what page?

DR. BERGFELD: That is, it looks like it's 24.

DR. MARKS: Twenty-four.

DR. BERGFELD: Uh-huh.

DR. MARKS: Okay, abstract.

DR. BERGFELD: It appears to me it's (inaudible). There are just a bunch of phrases in here.

DR. MARKS: I just want to go --

DR. BERGFELD: So you'll have to put in the limitations that you're adding.

DR. MARKS: Yes. Yeah, that last sentence in the abstract is -- Tom, we're looking at the abstract. Wilma made the comment that it looks like it's a little maybe skimpy. I'll use that word.

DR. BERGFELD: Well, they have a word restriction. I guess that could be with the correction of what you just did with the restricted concentration.

DR. MARKS: Yeah, you can see.

DR. BERGFELD: "Drug formulations may contain more than one botanical. The caution is there to avoid reaching levels of toxicity for constituents. So you should good (inaudible) to limit impurities." Why would that last sentence be there?

DR. MARKS: That's from the botanical boilerplate.

DR. BERGFELD: Yeah, but why would that be in the abstract?

DR. MARKS: That's because we have that. There's a portion that goes on the abstract, a

portion that goes in the conclusion.

DR. BERGFELD: We said that in each one?

DR. MARKS: Yes.

DR. BERGFELD: I hadn't seen that.

DR. MARKS: Well, I think it's just we're coming down to perhaps the final edition of the botanical boilerplate. And we'll go over that. It's a little later on in the agenda.

DR. BERGFELD: When you say "toxicity of constituents," what do you incorporate in that terminology?

DR. HELDRETH: (Inaudible) cognitive effect from other botanicals.

DR. BERGFELD: It includes sensitization?

DR. MARKS: Uh-huh.

DR. BERGFELD: I mean, that would be called a toxic effect?

DR. MARKS: Uh-huh. Yeah, that's actually, as I recollect, in the boilerplate, it would be perhaps two or three significant constituents that you're concerned about the

toxicity, and it'll actually name the constituents and the toxicity.

DR. ANSELL: They really are separate statements. The fact that a botanical is a complex mixture is different than the materials when they have an impurity, because they're not impurities. They're constituents.

DR. BERGFELD: Right.

DR. ANSELL: So whether we need to carry it into the abstract or not, I don't know. But it really is a very separate thought. You know, in one case we're talking about impurities. In the other case, we're reminding people that --

DR. BERGFELD: Yeah. I don't think it belongs here.

DR. ANSELL: Yeah.

DR. BERGFELD: I think it belongs in the discussion.

DR. MARKS: Well, let's wait until we get the boilerplate. And this is the specific application, but let's hold that thought for the boilerplate.

DR. BERGFELD: Okay.

DR. MARKS: Because for the boilerplate it's going to be applicable obviously to all the botanicals. That's when we move forward.

DR. BERGFELD: I'm just writing "poor abstract."

DR. MARKS: Good.

DR. BERGFELD: I mean, it doesn't tell me enough. And it tells me --

DR. MARKS: Do you want to talk to Monice so when she reads that she doesn't feel --

DR. ANSELL: Feelings are hurt?

DR. MARKS: Yes, feelings are hurt. At any rate, so we're going to move forward issuing a tentative report "safe with a concentration of 0.2 leaf extract" would be the conclusion.

DR. BERGFELD: How about needs a different abstract?

DR. MARKS: Okay. Thank you, Jay, for providing that clarification and suggestion of moving forward. Rather than "insufficient," we'll put a limit. Okay.

Next, the mono and disaccharides. Let's see here. So this is Monice again. Bart, it looks like you're pinch hitting.

DR. HELDRETH: I think so.

DR. MARKS: This is the first time we've seen these cosmetic ingredients. There are 24 of them that are in this report. They are common dietary sugars, sugar replacements, and they are GRAS. So there are several questions that arise. The first one, of course, are all these ingredients that are included here okay. Is there any one that we want to delete? That's on page 11. Tom, was there any ingredient that stuck out to you that was -- I can tell you, Ron Shank didn't pick out any one that he wanted to delete. And he actually --

DR. SLAGA: Actually, I didn't.

DR. MARKS: He has the --

DR. SLAGA: -- delete, but the other Ron probably will have one or two maybe.

DR. MARKS: Yeah, we'll see what he has to say with that. We'll get that, yeah.

DR. SLAGA: They all look simple enough to me.

DR. MARKS: Okay, good.

DR. BERGFELD: I was amazed at the concentrations in all the products of the sugars. This was amazing.

DR. MARKS: Well, this gets into another -- well, that'll be my issue because Ron Shank said that the conclusion "safe as used, ingredients are GRAS, REACH Article 4 of common food ingredients, non-irritating, non-sensitizing. Wave 2 supports this. Wave 2 support sucrose at a concentration of 14.5 percent in an HRIPT." However, in this report, sucrose is used up to 58 percent. And then Wave 2 data, glucose sensitization was okay up to eight percent, but glucose is used up to 91 percent.

So I had questions. You know, I can't recall, and we didn't see any case of allergy to sucrose or glucose, but there's not data in here to support neither irritation nor sensitization at such high concentration.

DR. BERGFELD: But they eat it.

DR. MARKS: Yeah.

DR. BERGFELD: And that's the point. Here's another GRAS food data piece.

DR. HELDRETH: Right. Those ingredients that are in here that are not GRAS are at various concentrations.

DR. SLAGA: Yeah. The non-GRAS are, what, less than one percent or something?

DR. HELDRETH: Right.

DR. MARKS: Yeah. And then the other question, I think, the Council had was the not identified as common dietary substances, for example, a monosaccharides fructose, et cetera. Can we just use the GRAS and read across? Ron Shank thought it was fine. Tom, do you?

DR. SLAGA: And I do, too.

DR. MARKS: Okay. So I still, you know, I guess I intuitively feel they're safe if such is sugar at this high concentration from the case reports. But I can remember when we had corticosteroids at one time, which is an obviously

natural substance that we secrete ourselves. And if anybody suggests that we were allergic to topically to glucocorticosteroids, you would've said crazy. So I guess I'm fine with --

DR. SLAGA: I think that taking glucose, for example, as you stated, 91 percent in cosmetic comes to 91 percent, 98.

DR. MARKS: Yeah.

DR. SLAGA: Wouldn't there be some reaction to the lips or around the lips if there were something?

DR. MARKS: Oh, absolutely.

DR. BERGFELD: I don't think you test for it. You have no catch test for these saccharides.

DR. MARKS: No, we don't test to it, Tom. And I guess this always gets back to -- I'm surprised Ron Shank didn't mention anything. Having no data is not having data on it. And it's interesting they did HRIPT and say why do you need to do it for sucrose? I think just maybe because that cosmetic product as the total product was

being tested. And it just so happened to have 14.5 percent sucrose in it.

So I agree with you. I would expect we would see a number of case reports of cheilitis if either one of these were a sensitizer. And so I think I've got to go with clinical experience here that this is okay at these high concentrations.

DR. BERGFELD: You'd want to put that in your discussions.

DR. MARKS: Yeah. I would like to put it in the discussion part just to indicate, because if anybody is looking at this and saying, well, what data do you have that's in the report, you really don't. It's the lack of case reports and clinical experience.

DR. SLAGA: Yeah. As long as that's in the discussion, I think we're okay.

DR. MARKS: So I'm going to put in here don't need HRIPT for sucrose because of lack of clinical reports of irritation and sensitization. And then we'll put that in the discussion. Okay.

DR. SLAGA: Great.

DR. MARKS: So it'll be a tentative report with "safe." Good.

DR. ANSELL: We do have an editorial discussion we think is really quite significant. The grouping of all these monodisaccharides when we know that some of them are metabolized, some of them are not metabolized. There should be a much more robust discussion as to why these have all been grouped together. The justification for the family we think would be an important addition to grouping all the monodisaccharides together.

DR. HELDRETH: Yeah, we left out -- for those that are GRAS, we didn't want to go back and reinvent the wheel on those reports. And those that are not GRAS, the only type of absorption and metabolism information is generalized statements out of textbooks. And it's focusing on oral metabolism. And we weren't sure that that really played any role in determining the safety of the cosmetic computation. So that's why we didn't put things like a certain mono-GRAS ingredient might be metabolized and be able to create energy in a

cell. We're not sure that that is particularly relevant to dermal application.

DR. ANSELL: Right. We're not disagreeing with the conclusions. We just think that because of the size of the family and the diversity of these sugars that there should be a much more robust coherent discussion as to essentially just what you're talking about as to why we feel they can all appear in the same report.

DR. HELDRETH: Okay. Is there any specifics? Actually I think delineating between, you know, which ones of these fall under the classical disaccharide definition and those that don't necessarily go through open-closed chain, an isomerization. Is that the kind of things that you're pointing at?

DR. ANSELL: I actually was thinking more what you started with.

DR. HELDRETH: Okay.

DR. ANSELL: Is that, you know, it' recognized that these are metabolized differently,

but that, you know, its relevance to the cosmetic applications. And I think the CSSC might be willing to provide some suggestions in that regard.

DR. HELDRETH: Would that be more of an upfront to the start of the toxicokinetics as opposed to explanation of the chemistry? I just want to give Monice the best direction.

DR. ANSELL: We would have to provide that.

DR. HELDRETH: Okay. We'll be on the look.

DR. ANSELL: These structurally similarities will (inaudible) ingredient into a report. And we think it's more complex than that.

DR. HELDRETH: Okay. We'll be on the lookout.

DR. MARKS: Okay. Any other comments?

DR. SLAGA: No.

DR. MARKS: Okay. Next, the alpha hydroxy acids. Okay. So this is a re-review of the alpha hydroxy acids as used in cosmetics. In

'98, the Panel concluded, and it's a rather lengthy discussion or conclusion, I should say. "Glycolic and lactic acid, they're common salts. They're simple esters. They're safe for use in cosmetic ingredients at concentrations less than or equal to 10 percent, at a final formulation pH of greater than or equal to 3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. These ingredients are safe for use in salon products at concentrations less than or equal to 30 percent, at a final formulation pH of greater than or equal to three percent in products designed for brief discontinuous use followed by thorough rinsing from the skin when applied by trained professionals and when application is accompanied by directions for the daily use of sun protection."

And so, that's a fairly lengthy conclusion that was reached in 1998. The use of the alpha hydroxy acids have increases significantly. Glycolic acid now in 337

formulations, lactic acid in over a thousand formulations. The concentrations of use have also changed. Glycolic acid up to 50 percent ethyl lactate at 95 percent in "other manicuring formulations," 50 percent in nail polish. And myristyl lactate, 13 percent in lipstick formulations.

So the first question, of course, is do we reopen this. Ron Shank's comment was, "All conclusions still valid. Do not reopen this report."

DR. BERGFELD: I felt that way, too.

DR. SLAGA: I had do not reopen. However, there were two carcinogenicity studies that really helped this report out. It doesn't change the conclusion, though, and that's why I think Ron is doing that. But we didn't have any photocarcinogenicity or co-carcinogenicity data in the past one.

DR. BERGFELD: But that could be added in the comment part, the do reopen.

DR. SLAGA: And that's what I finally

thought that that was just good enough in our re-review summary to really emphasize those studies.

DR. BERGFELD: Because we update the references as well in that.

DR. SLAGA: Yeah. Okay. Do not reopen.

DR. MARKS: Okay.

DR. BERGFELD: The only question I have is whether they wanted to add anything to it, but I don't see here that they did. Did I miss that? No.

Another question I had was in formulation of the salts, there are two reasons these are used. They're used as humectants, and they're used as exfoliants basically, okay? I'm not sure I'm clear when I read this that you get the sense that that's how they're being used. We have a sense of concentration restriction, and then you have concentrations and formulations, and in some instance you talk about actual concentrations. In other situations, you just talk about percentages. So I think it's the

actual that you could restrict.

And the actual is that -- let me see -- the three percent. The concentration about 10 percent of final formulation pH of less than 3.5. That's the actual. But through the document, I got a little bit confused if we were talking actual or just what was quoted in the formulation, which does not always translate to actual.

DR. HELDRETH: I see what you're seeing.

DR. BERGFELD: Now is it your opinion in cosmetics that these are used other than humectants and exfoliants? See, the restricted use is for rinse-offs. That's an exfoliant.

DR. ANSELL: I'm not sure I understand that they are used as humectants.

DR. BERGFELD: Oh, yeah, they are. Oh, yeah, they are. Yeah, the old literature really was a great humectant.

DR. MARKS: I don't think that changes the conclusion.

DR. BERGFELD: It doesn't change the conclusion.

DR. HELDRETH: I mean, I think a lot of these can function in multiple ways that maybe we don't necessarily see on the surface.

DR. BERGFELD: Well, I can tell you how it functions. I did the research on it. I can tell you what it does to the dermis.

DR. HELDRETH: But any of these can be like --

DR. BERGFELD: If that's biological activity that you're going to talk about. But a clinical activity is a humectant. I mean, they're (inaudible) dermis.

DR. HELDRETH: But, I mean, any of these could be a pH adjuster as an --

DR. BERGFELD: Yeah, I guess they could.

DR. HELDRETH: And that's not necessarily listed. So, I mean, there are possible functions here, and that's somewhat the problem with relying on cosmetic function is that there's no vetting of that. It's what a submitter that wanted a name for their -- they said it's a pH adjuster. They said it's this particular

function. That doesn't mean it functions like that even in their product or somebody else's product. So they may have multiple cosmetic functions. I think product type and the concentration within that product type is more dependable.

DR. BERGFELD: Am I confusing you with my concept of what I was reading, because what our problem is as dermatologists is that we use it as a therapy. And then we use it as a maintenance therapy for good skin texture, which would be humectant, exfoliant. And that one is restricted here. Physicians' offices are not restricted.

SPEAKER: Yeah. What I think is there are four uses, okay. And they go by actual acid content.

DR. BERGFELD: Right.

SPEAKER: The lowest levels are when you're using it to adjust pH, and you're typically using about a half a percentage, and what happens is you're forming a salt is all you're doing. And you're just using a drop of pH or whatever.

And the second is the consumer use, which is what you describe as the maintenance. Okay. Then there are the two that I put in the categories "professional use." The ones that are used by spas and licensed desmaticians.

DR. BERGFELD: Right.

SPEAKER: And then the last use is the doctor prescribed or given where they're using it at very high concentrations, but that's only under a physician's care.

DR. BERGFELD: Okay.

DR. MARKS: And then, Tom, your comment captured in the discussion again, that was --

DR. SLAGA: Yeah. We should discuss photo carcinogenicity studies which support, you know --

DR. BERGFELD: Safety?

DR. SLAGA: The maximum level was 10 percent.

DR. BERGFELD: Right.

DR. MARKS: Okay. "Discuss photo CA studies," and it was "safe." Okay, good. And

that wasn't in their previous document, so that definitely should capture that. Anything else, Tom?

DR. SLAGA: Not from me.

DR. MARKS: Wilma? Jay?

DR. ANSELL: I'm trying to track this down. Actually, David, the sun safe statement within the report has been updated since the report was published?

SPEAKER: Yes. The FDA issued one, and it's in an FDA guideline.

DR. ANSELL: So if we include the language in here, we might want to tell people to refer to the most recent statement in the case.

DR. MARKS: Great. Thank you. So how should that be? So that would be in the discussion --

DR. ANSELL: Right.

DR. MARKS: -- to latest FDA --

SPEAKER: Guidance document on AHA, the most recent.

DR. MARKS: AHA document.

DR. BERGFELD: Could you remind again on the salon use, is that still considered a cosmetic use? We have the nail salon use.

SPEAKER: Basically you get peels at spas.

DR. BERGFELD: I know, but is that considered under the PCPC umbrella?

SPEAKER: Yes.

DR. MARKS: Yeah.

SPEAKER: But because of the way they are licensed and applied, this is not something that consumers are applying. This is done by professionals or semi- professional --

DR. BERGFELD: Well, I what I'm suggesting, would it be helpful to the reader of this document to define these four parameters in which these products are used in broad categories?

SPEAKER: I think so.

DR. BERGFELD: I think so, too. So I'd like to add to this discussion.

DR. MARKS: Let me see here.

MS. FIUME: I'm sorry, Dr. Bergfeld, I'm

coming in a little late. What did you want defined?

DR. BERGFELD: Well, were discussing the actual use and the restricted concentration these we have currently have. We have restricted -- let me see, I have it underlined here -- concentrations of 10 percent or less and final formulations of pH of less than 2.5. That is the restriction for the cosmetic product, okay?

And we were discussing the actual clinical use of these products for the consumer, the salon, and the physician. For the consumer, it's humectants. For the salon, it's usually an exfoliant/peeler. And it has to do with the concentration. Are they still restricted by this restriction?

DR. MARKS: Yeah, in salon there's different concentrations that they can use and different --

DR. ANSELL: Yeah, that's a very interesting question. I mean, salons fall outside of the scope, but not the scope of the FDA, but

outside the scope of some of the regulatory framework. So I think that's a very good question. I will consult.

DR. BERGFELD: Okay, because it would be nice for the reader to realize that these are used differently by different groups. But what is available for the common consumer is restricted.

DR. MARKS: Actually it says that pretty clearly, I thought, in here. "Safe for use in cosmetic concentration," dah, dah, dah, dah. And then it says in salon -- then it goes into "safe for use in salon products." So they're obviously -- I mean, it' intuitive, and I'm sure it's in the discussion from the original document.

DR. BERGFELD: I'd like to bring that back.

DR. MARKS: Yeah. So, Monice, so far we've come to the conclusion, I don't think that will change. We don't reopen this. We discussed the photocarcinogenic studies that support the safety of these ingredients. We refer to the latest FDA guidance, AHA document. These would be

discussed points.

And then the last point you want to make is about personal and salon use?

DR. BERGFELD: Well, I think if we summarize what we've got here, captured about what happened in '98 and what happened in 2004, I think that probably covers it.

DR. MARKS: Okay. I'll let Monice -- we're going to be --

DR. BERGFELD: Put in the discussion of the non- opened document.

DR. MARKS: Okay. Anything else? Tom?

DR. BERGFELD: And we were going to have them refer to the FDA guideline document, AHA, in the discussion.

DR. MARKS: Yeah. I put that in there. Anything else?

DR. SLAGA: I'm good.

DR. MARKS: Okay, Tom. So don't reopen. Let me go ahead. Any other comments?

(No response.)

DR. MARKS: So, you know, Wilma, I'm not

quite so sure that for personal use these aren't now used as exfoliants also because I think some of the --

DR. BERGFELD: They are.

DR. MARKS: Yeah.

DR. BERGFELD: They are. I said that.

DR. MARKS: Oh, in salons for sure. Personal use, too, yeah.

DR. BERGFELD: Yeah, personal use, humectants and exfoliants.

(Cross talking.)

DR. MARKS: Right.

DR. BERGFELD: Low concentration.

SPEAKER: One application for the consumer use is --

DR. BERGFELD: And it's lower. Somehow the peel is less, so it would be concentration.

DR. MARKS: Okay.

MS. FIUME: Can I --

DR. MARKS: Yes?

MS. FIUME: So you wanted the FDA guidance brought into the discussion?

DR. MARKS: Yeah, in the discussion that there's a new guidance document from the FDA, a more recent one. David, when was that approximately? Yeah, whatever. Since '98.

DR. BERGFELD: I have the 2005 in there.

DR. MARKS: Oh, you have 2005. Do you think that's the one then? It probably is.

SPEAKER: Yeah, I think that's the latest one.

DR. MARKS: Okay.

SPEAKER: We'll check it.

DR. ANSELL: I think the comment was more to rather than relying on this report for the specific labeling language that they reference the most current guidance because we may not get back to this for another 15 years. You actually put the regulatory required text into the report.

MS. FIUME: Okay.

DR. ANSELL: It's our suggestion that we at least point out that they should not rely on this, that they should reference the most current FDA guidance for the exact language.

MS. FIUME: Okay.

DR. MARKS: Sounds good. Any other comments?

(No response.)

DR. MARKS: If not, we move onto the tocopherols. And these ingredients all comprise what is a group known as vitamin E. And so, this is a scheduled re-review of tocopherols. In 2002, the Panel reviewed 10 as listed on a memo, 10 ingredients, finding a safe conclusion. And in this re-review, we want to reconfirm the safety of those ingredients, and then it was suggested to add the tocotrienols to this group. And those four ingredients, again, are listed in the memo from Monice dated November the 15th.

So two questions. Reopen to add on the tocotrienols? If yes, is it a no-brainer? And it appears to be a no-brainer from my point of view.

DR. BERGFELD: I agree.

DR. SLAGA: Yeah.

DR. MARKS: So I would reopen those --

DR. SLAGA: And I agree, too. And it

still would have the same conclusion.

DR. MARKS: So, yeah. And Ron Shank says, "Not much toxicology on the tocotrienols, but ample data on the tocopherols, which can be used as a read-across. Reopen to include the new ingredients, and the conclusion is the same." Let me see. I said in my comments, I didn't say it was necessary. I just said it would be good to have an HRIPT at 5.4 percent. If we reopen it, the use of tocopherol and leave-ons, it's increased by over 100 percent. It's gone from two percent to 5.4 percent.

And we don't have an HRIPT at that concentration, but again, when you look at the clinical data on it, it's got to be safe because we weren't endemics of allergy to tocopherol at that concentration of 5.4. And as far as the add-ons, the tocopherol phosphate, we have good irritation and sensitization data, which is "safe."

DR. BERGFELD: In your patch testing, what is the routine for vitamin E?

DR. MARKS: We used to patch test with it, and the number of individuals with sensitivity was so low, we dropped it. And, Monice, you have that data in here. I forget, it was thousands of individuals, and it was just a couple dozen maybe that were sensitive to tocopherol.

Now, you know, what were we testing with that? We were testing tocopherol. What was in it, which portions of it? I'm not sure we know actually as the North American group. Where is it? I have it highlighted somewhere here. Not a photoallergen. The ECHA, not a sensitizer. That's the tocopherol acetate. Local lymph node, that's with the tocopherol phosphate. Somewhere in here you had the North American group quoted.

DR. BERGFELD: I'm wondering if it's in the original.

DR. MARKS: Maybe it was the original.

DR. BERGFELD: -- don't you think, from the original point, the summary statement?

DR. MARKS: Yeah. Let me see. So I would reopen and "safe." And, Jay, if you had for

the 524, that would be nice. If you don't, unless Don wants it, I think we could move forward.

MS. FIUME: Dr. Bergfeld, it is summarized in the original report. That's where it is. Dr. Marks, under the human dermal irritation and sensitization summary for the original report on tocopherols.

DR. MARKS: What page is that? You can just give me the numbers. It was like 4,000, wasn't it, that was in that review in that article that were tested, and maybe 24 were positive. I forget the exact numbers. It was large.

MS. FIUME: Yeah. I don't have the exact numbers in the original.

DR. MARKS: Okay.

DR. BERGFELD: Did you have the REACH number? I just was looking for it. I didn't see it. Was it under --

MS. FIUME: The summary data was under dermal irritation and sensitization of humans, but I don't have the numbers there. I'm just going to look and see if there were any original reports.

DR. BERGFELD: Here it is, non-human from the original report in rabbits.

MS. FIUME: Are you on page 24?

DR. BERGFELD: I am on 24.

MS. FIUME: Under the human --

DR. BERGFELD: Under human, okay. Human, oh, there it is. It's italicized. Okay.

DR. ANSELL: But it doesn't have --

DR. MARKS: No. Okay. At any rate, we'll move forward. So, Tom, we'll move forward to -- let me see, who presents this? It's me. I'll move to reopen to add the tocotrienols. Am I saying that right, "tocotrienols?" And with the conclusion "safe."

DR. SLAGA: Great.

DR. BERGFELD: Could I go back to this page 23? In the summary it says, "1992 results in a large of number of outbreaks in creams containing tocopherol. Positive patches were seed." I suspect that's leading. That makes you think it's really a sensitizer. You probably need to add that it's rare or whatever term you've used

in the original there.

DR. MARKS: Which page are you --

DR. BERGFELD: That's 23 under "human." It's italicized. It's right on the top.

DR. MARKS: Twenty-three. Was that the one where it was composed of multiple ingredients?

DR. BERGFELD: North American contact -- yeah, that's the one that you suggested that it was probably due to something else. But you also said that there were only 23 out of 45 --

DR. MARKS: Well, I'm not sure. I was doing that out of memory. I wasn't doing that out of --

DR. BERGFELD: But this sounds more, whatever.

DR. MARKS: So 23 --

DR. BERGFELD: It's 23 at the top under "humans."

DR. MARKS: "Human," from the original report. Oh, yeah. To me it was pretty -- they say, however, the outbreaks were thought to be due to a metabolite or contaminant of the product. So

to me, that's directly out. That's why I wasn't concerned about that Swiss outbreak. And in the original report, it was felt to be safe. So I think it's fine.

DR. BERGFELD: You didn't want to put "rare" or something in front of that just to qualify it a little bit more?

DR. MARKS: No. I guess, Monice, what you could do is get the original from the North America. I don't know where I got those numbers. Maybe it was another ingredient.

MS. FIUME: No, that's right. It was between 1985 and 1989, 4,887 patients patches with five percent. Twelve percent were allergic. Twelve patients were thought to have an allergic reaction. Two were irritated, and two were questioned.

DR. MARKS: Yeah, okay. I doubled it. I put it in the 20s. So it's 4,800, and only 12 were felt to be allergic. And these, of course, are highly selected patients because everybody we --

DR. BERGFELD: How did you put the 20 against 4,000?

DR. MARKS: Twelve.

DR. BERGFELD: No, I don't mean that. Incidental, rare?

DR. MARKS: Rare.

DR. BERGFELD: Yeah. I just think that if you add that, it would make more sense.

DR. MARKS: And if we wanted to even be more illustrative, the North America group deleted this as an ingredient to patch test in their screen because it was such a rare reaction.

DR. BERGFELD: That's a discussion.

DR. MARKS: Yeah, that would be discussed. Okay. So we will -- let me see. Let me go back. We will reopen with the adding tocotrienols with the conclusion of "safe as used."

DR. ANSELL: And we had an editorial comment. We've added a section called anticarcinogenicity.

DR. BERGFELD: Oh, that's nice.

DR. ANSELL: Well, it shows reduction in tumor incidence.

DR. BERGFELD: All these medical (inaudible) doesn't do any of that.

SPEAKER: That was our comment that there should be some mention of that rather than just having all the -- leaving it sounding like it's got that anticarcinogenesis activity.

DR. ANSELL: Yeah. First of all, anticarcinogenicity is a claim, not an effect per se.

DR. BERGFELD: Okay. So we'd like to have both elements that these are carcinogenicity studies, which have specific results, and we'd like to mention --

SPEAKER: Epidemiology data that unfortunately doesn't confirm.

DR. MARKS: Did you hear that, Tom? Did you hear these comments?

DR. SLAGA: Yeah, I heard it, but, you know, we have in a number of reports, anticarcinogenicity. And to me, you know, what

that signifies is carcinogenesis study, but the chemical tocopherol, what have you, would have an anti-effect which is in support of the carcinogenicity study, too.

DR. BERGFELD: So where would you put that? Where would you put that anticarcinogenetic activity, in the discussion as a --

DR. SLAGA: Couldn't it be just with the carcinogenesis studies because the controls usually have to have tocopherol or what have you as a control. And if it shows negative, that means it's not carcinogenetic.

DR. ANSELL: Right. I think it is a carcinogenicity result, you know. To put it down as an anti-carcinogen, I just think, as a heading is inappropriate. But we also --

DR. SLAGA: Well, it could be under carcinogenesis, and maybe that's where it should be as a sub under that. Then it doesn't really sound as a separate type of -- we have added that, you know, the writer to put that in a number of extracts from plants. We'd have to go back and

re-amend a lot of reports.

DR. BERGFELD: So are you nixing what Jay suggests, or what are you doing with it? He wants another title, another topic title.

DR. SLAGA: I would put it as a sub-cat under carcinogenesis.

DR. MARKS: Does that sound good to you, Jay?

MS. FIUME: That's actually what it is right now.

DR. MARKS: That's what it is. You just want to get rid of the heading "anti-carcinogenic." Is that it?

DR. ANSELL: Pretty much.

DR. BERGFELD: What do you want to call it?

DR. MARKS: It's just under that called --

DR. ANSELL: Yeah.

DR. MARKS: Either it's pro-carcin or there is anti-carcin. And that would be under the heading, and you'd just read it rather than

highlight it as anti- carcinogenetic. Is that right?

DR. ANSELL: Yeah. It's a result.

DR. MARKS: I think it's just editorial.

DR. SLAGA: Right.

DR. BERGFELD: We don't normally add editorials to studies.

DR. MARKS: No, no, it's the heading. To me it's an editorial change. So, Tom, I'll let you make the final determination. Are you fine with just -- yeah. So, Tom, I think you're fine with that then, just put it under the carcinogenic heading, and that's just another paragraph highlighting as anti-carcinogenetic effect.

DR. ANSELL: Which would be a part of the discussion as to whether we conclude it's carcinogenetic or not.

DR. MARKS: Yeah, I think we're in agreement, Jay, with what you suggest. Is that right, Tom?

DR. SLAGA: Yeah.

DR. MARKS: Yeah, okay. Any other

comments?

DR. ANSELL: Well, the second comment is that there's epi data, which we think is relevant to this whole discussion, too.

DR. MARKS: Epidemiologic data on carcinogenesis or what?

DR. ANSELL: This presumption that it's anti- carcinogenetic.

DR. MARKS: Yeah, okay. Okay, fine.

DR. BERGFELD: Where you put that?

DR. ANSELL: Do we have --

DR. BERGFELD: I didn't see it.

DR. ANSELL: Don't we have epi studies?

DR. BERGFELD: I haven't seen it.

MS. FIUME: No, because they are mostly on pure vitamin E, oral supplementation of pure vitamin E, which I did not think were relevant to the cosmetic safety because the incidental ingestion of tocopherol and tocopherol acetate is no higher than two percent for tocopherol and three percent for tocopherol acetate. And those are generally undiluted vitamin E. If the team

would like, I can find the summery review, but I don't know how much in depth you would like those studies to go.

SPEAKER: I don't think we were thinking in depth at all, just some mention so it's not left -- that the animal data is just kind of left unchallenged.

DR. MARKS: Okay. Have we got that settled?

DR. BERGFELD: With the --

DR. MARKS: Carcinogenesis, good. Tom, that okay with you?

DR. SLAGA: That's okay.

DR. MARKS: Okay. So tomorrow I will move we'll reopen, and we'll add to the tocotrienols with a "safe" conclusion, and note these editorial comments. Tomorrow if you want to make them, Jay, you may or we'll just assume they're going to occur. I mean, it doesn't change the intent of the document.

DR. ANSELL: No.

DR. MARKS: Okay. I'll wait until Ron

comes back.

SPEAKER: Taking a quick break?

DR. MARKS: Yeah. He should've done that first, huh? Let me see here. Next is -- why slow down? Chamomile, chamomilla recutita. And this is German chamomile, I believe, if I've got my German and Romans not mixed up. And, let's see, this is Wilbur.

MS. FIUME: He just started in the other team.

DR. MARKS: Okay. Ron Shank is brief on his next few here. So for the minutes, Ron Hill has appeared.

DR. HILL: I've had my first coffee since --

DR. MARKS: What we're going to do is, as you can tell with morning's discussions, I've taken the comments that Ron Shank has emailed and added those in the discussion of each of ingredient. Tom Slaga has been with us with most of this. Well, actually essentially all of it because I reviewed our initial ingredients with

Tom. And then what I'm going to do with Ron is we're going to finish up the ingredients we have at this point, and then Ron Hill and I will have a side bar this afternoon some time. And I'll just review all the ingredients and what conclusions and discussion we had. And then that way tomorrow Ron Hill -- I think tomorrow. The weather is predicted to be bad tomorrow, so there's --

DR. HILL: It's starting to go in the other direction, too.

DR. MARKS: Exactly. And I'm thinking the same thing. I drove it through it coming down here. I'm not looking forward to that tomorrow. So we may actually have the combined meeting of the teams. How do you refer to that, Wilma, when the whole panel --

DR. BERGFELD: Panel.

DR. MARKS: Yeah, the whole Panel --

DR. BERGFELD: Panel meeting.

DR. MARKS: The Panel meeting, we may move that up from tomorrow or we may have it very early tomorrow, I don't know. We'll see what the

weather forecast is over noon and decide how we want to proceed.

I think the Marks team will be ready to proceed with a Panel meeting by certainly mid-afternoon.

(Laughter.)

DR. MARKS: But at any rate, Tom, there may be an advantage of having these conference calls and emails.

DR. SLAGA: Right.

DR. MARKS: At any rate, so the next is a draft final report on chamomilla recutita. And in September, the Panel concluded that all these components of the flower extract, the powder, et cetera, are safe in the present practices of use and concentration described in this safety report when formulated to be non-sensitizing. It's insufficient for a number of other of these ingredients, which, again, is in the memo from Wilbur, the extract the whole plant, the flower and leaf extract, et cetera. And we'd need an HRIPT at 0.4 percent for the extract to be safe.

And that would be insufficient.

DR. BERGFELD: Do we have that comment in our discussion about why it's insufficient, what was needed?

DR. MARKS: No.

DR. BERGFELD: Because I think you have to put that in the discussion.

DR. MARKS: Yeah, I have that here. We did get some comments from the Council. We had towelettes with 0.01 percent extract, so very low. And then a hair gel with too little to smell here almost,.00006 percent of lower leaf extract was okay for HRIPT. But when I reviewed it, it looked like we would need an HRIPT of 0.4 percent for the extract to be safe.

Now, it's interesting. We could either do the "insufficient" or, as you suggested earlier, Jay, go to a concentration limit of 0.4 percent for the extract, and put the whole thing as "safe when formulated to be non- sensitizing." I think it's interesting because as we go to the Roman chamomile, e say it's non-sensitizing, and

we don't have the data for all the various components of this botanical. So it's non-sensitizing in some ways, in my mind. Why do you have "insufficient" for some of the botanical or plant parts in the other when you just say if it's non-sensitizing. But at any rate, that's sort of my rambling preamble to how I saw it.

So Ron Shank, the conclusion was "safe." Or I should say the conclusion as Wilbur has stated here is fine. Tom, what do you feel?

DR. SLAGA: I think with the new data, I think it could be safe, but we could put the limit on if you want and still be formulated to be non-sensitizing.

DR. MARKS: Yeah. Instead of the insufficient portion of this conclusion, just say that with the limit for everything that we say is insufficient, just put a limit of 0.4 percent. I believe that's the right concentration, is that correct, for the extract. That was the highest concentration for the extract, 0.4 percent?

MS. FIUME: This is Wilbur's, not me.

DR. MARKS: Oh, yeah. And I didn't write a page that I could immediately go to the use table. Usually I do do that. Do you know what page the use table is, concentration on these? Did you find it? It's obviously towards the end.

DR. HELDRETH: PDF page 61.

DR. MARKS: Sixty-one, okay. Let's just confirm where I got that, yeah. I got it from Table 6. If you look at leaf -- I went for the leave-on concentration. If you go under the extract, the highest concentration on a rinse-off is.61, but for a leave-on it was 0.4. So I chose that as my maximum concentration. Do you see where we are, Tom, on page 61?

DR. SLAGA: Yeah.

DR. MARKS: That's how I got, if I we want to set a limit or if we want to know what we need to remove the insufficient, it would've been having an HRIPT of that concentration. What's your sense? Do you want to just leave the conclusion as is, or do you want to put a -- if we

put a limit, I think the limit would have to be, what is it,.0 -- what do we have to test that?

DR. BERGFELD: 0.4.

DR. MARKS: No, it's not 0.4. Where is it in -- it was in the memo what we have there, 0.01. Yeah, I know.

DR. HILL: Well, 0.01 or "when formulated to be non-sensitizing."

DR. MARKS: Yeah, exactly.

DR. HILL: I mean, I guess we've done that approach before.

DR. SLAGA: "Formulated to be non-sensitizing."

DR. HILL: If you say "non-sensitizing," somebody has to prove that, right? But if you say.01, you're good. They can use it. What if you made it either/or? I mean, I don't know how practical.01 is for anybody anyway.

DR. MARKS: Yeah. So Ron Hill, Tom, what's your sense? Ron Shank was the conclusion as it is now. And obviously the manufacturers could come back and give us proof that it's safe

at that concentration of 0.4 in leave- ons,.06 percent for rinse-offs. Leave the conclusion as is?

DR. SLAGA: Yeah.

DR. HILL: Yeah.

DR. MARKS: Okay, good. Let me see who presents that tomorrow. I do. Okay. So we'll do a final report with the conclusion as stated, and then under what's insufficient, we can put in the discussion for an HRIPT for the extract. Okay.

DR. ANSELL: So --

DR. MARKS: Yeah. Actually when I went back and looked at it and re-thought it, Jay, we could only use "safe" up to 0.01 percent. I didn't think that would be very helpful because that's what we have the HRIPT data on. Okay. Why don't we leave it the same? We'll see what the Belsito team thinks tomorrow. We know what the need is, so I would move that we issue a final report. Wilma, any comments?

DR. BERGFELD: No, that was my comment, put it in the discussion.

DR. MARKS: Okay.

DR. ANSELL: I actually think it would be okay, the 0.01 for the plant parts in which it was insufficient.

DR. BERGFELD: So you're requesting it be 0.01 for everything.

DR. ANSELL: That it not be.

DR. BERGFELD: And be non-sensitizing.

DR. MARKS: Yeah, it may be non-sensitizing, and for the ones where it's insufficient, we actually wouldn't put an "insufficient." It would be formulated to be non-sensitizing, and for all those ingredients we have "insufficient," the limit would be 0.01.

MS. FIUME: So were data received on all of those plant particles?

DR. MARKS: No, in my mind, the extract represents all those others, you know, because it's really --

DR. ANSELL: And the 0.01 was on a whole plant.

DR. MARKS: Yeah. Ron, since, Jay, you

feel that would be --

DR. HILL: Yeah. I will reconfirm that.

DR. BERGFELD: Yeah, just like before.

DR. HILL: Well, no. My notes say --

DR. BERGFELD: Okay.

DR. HILL: We put a use limit.

SPEAKER: Yeah, that will protect some uses.

DR. HILL: Yeah.

DR. MARKS: Okay. Trying to do that for you, Jay, here.

DR. ANSELL: Okay.

DR. MARKS: Unfortunately, let's try this one.

MS. FIUME: So, Dr. Marks, I can let Wilbur know 0.01 on the extract.

DR. MARKS: Well, all those. Where it says "available data," are --

MS. FIUME: Because of the data that changed the "insufficient" to 0.01?

DR. MARKS: That towelette down below.

MS. FIUME: On the extract.

DR. MARKS: Yes. I look at the extract to be representative of those three others because it's the whole plant, so it should have all the ingredients within it that you're extracting out.

MS. FIUME: And you've had extract data in the report at a higher concentration, isn't that correct?

DR. MARKS: Yes. Yes. It was up to 0.04 percent in the use table.

MS. FIUME: But under dermal irritation and sensitization, weren't there higher data already in the report last time?

DR. MARKS: For the ones that we say are safe, that was the flower. All of it was relevant to the flower and not the extract. You'll notice we said it's "safe" for the flower. The flower extract, the flower powder, the flower water, and the flower oil are "safe." And then the problem we had was, okay, we had we have that as supporting the flower, but we don't have data for the whole plant. And so now what we're going to do with the rest of it is just have a use limit of

0.1 percent.

DR. HILL: 0.01 percent.

DR. MARKS: I'm sorry, 0.01. Thank you.

DR. HILL: I just wanted to make it's clear.

DR. MARKS: Yes. Thank you. It's important to have the right numbers.

DR. HILL: Those are important.

DR. MARKS: Yeah, instead of "insufficient." Okay. Any other comments? Monice, does that answer your question?

MS. FIUME: I think so (inaudible).

DR. MARKS: Yeah, I hate to surprise Wilbur, that's for sure. Okay. Let me see if I can move this here. Let me put that on here. Okay. Next is the Roman chamomile, anthemis nobilis. And so in September, the Panel came to issue a draft final report with these ingredients, having a conclusion of "safe when formulated to be non- sensitizing." And now we're at the point at issuing a final report.

And it's interesting. This gets into --

this is what I'm going to ask Don tomorrow is are these ingredients okay with no sensitization on the powder and the water. I guess because it's more of the plant, he feels it's okay.

DR. BERGFELD: It's all the flower, isn't it?

DR. MARKS: Yeah. And with a non-sensitizing conclusion. So, Tom, move forward? Let me see what Ron Shank has to say. "Conclusion okay, 'safe, formulated to be non-sensitizing." Ron Hill?

DR. HILL: It's okay.

DR. MARKS: Okay. Tom?

DR. SLAGA: Okay.

DR. MARKS: Okay. Good.

DR. BERGFELD: Okay with me, too.

DR. MARKS: Wilma, Jay, Wilbur's surrogate, all set. Okay. Let's go ahead. Next is formic acid. And this is a draft amended final report on formic acid and sodium formate in September. We reached an amended conclusion "safe in the present practice of use and concentration

when formulated to be non-irritating." Ron Shank said it was fine. Ron Hill?

DR. HILL: I was part of that.

DR. SLAGA: Okay.

DR. MARKS: Okay with you, Tom?

DR. BERGFELD: I would be, too.

DR. MARKS: Okay. Any other comments?

(No response.)

DR. MARKS: If not, Don Belsito will make a motion. Presumably it'll be the same and I'll second it.

And then next, hydroxycinnamate. Yeah, that's a mouthful. So this is the first time we've seen this ingredient. Let's see what Ron Shank -- and he says page 19, "No more data are needed. Large molecule highly lipid soluble and like to penetrate viable epidermis. GRAS compound. No toxicity at a high or chronic use. 'Safe as used.'"

DR. SLAGA: That's what I have, too. There's a lot of data supporting irritation carcinogenicity, genotoxicity, everything. Ron

Hill?

DR. HILL: Yes. The only thing I felt like I was missing was whether there's any capability, particularly in skin, to hydrolyze to the corresponding hydroxycinnamate. I'm not sure we needed to know that, but there is no information as to biological activity of that corresponding hydroxycinnamate, and I didn't go out and do an exhaustive search myself.

And I guess I didn't get any sense that it shows up enough as an impurity in the finished product because it's not made that way to know that we would've captured any toxicology as impurity in testing the substance. Plus we usually don't risk anything on that anyway. So I felt like I would like to have had some information about whether this stuff gets bio converted to the hydroxycinnamate to any appreciable degree. I doubt it because one of those panurethral centers prohibit it, but we don't know that. Otherwise, I didn't have any difficulties with any of them.

DR. MARKS: Interesting. When I looked at this report, my concern was it's being applied on the eyelid and also lips at 0.8 percent, and we didn't have any HRIPT at this use concentration even though it's a large molecule.

DR. HILL: It's not that large.

DR. MARKS: Okay. Well then, for me I would want to see an HRIPT in the eye and lip at the use concentration of 0.1 percent. So I would send it out as just an insufficient data notice and see if we could get that.

DR. BERGFELD: Is that different than an announcement, just out of curiosity. We've been using these terms.

DR. MARKS: Yeah, announcement.

DR. BERGFELD: Announcement?

DR. MARKS: Yeah. This allows industry to respond, and there's not the formal -- it doesn't move onto a tentative. Let's see, who presents that tomorrow? And then the only other thing, Monice and Wilbur, on page 5 where it has the checklist. See under "distributed for comment

only, do not cite or quote." Under irritation sensitization, he doesn't have any animal. That's not checked. There actually is animal data for irritation sensitization. That's a minor point. It's nice when you look back and you see the summary. That's on page 13 where there's animal, so that's a minor point.

So, Tom, what do you think? I was a little uncomfortable just moving forward with "safe" without an HRIPT at use concentration of 0.8 percent, I think particularly for the eye and the lip. You know, the eyelid skin is very thin and easily absorbed into and irritated. That's one of the highest absorption areas of the body. So does that sound reasonable that at least we'll see what --

DR. HILL: Yeah. I think Ron Shank was looking into that, roughly 1,200 molecular weight in the log P of at least greater than eight, and he estimated it to be 20- something.

DR. MARKS: Twenty-three.

DR. HILL: But yet back when Dr.

Branaugh was presenting, there were substances with log P of 35 that were getting far enough into the upper skin to be able to get some access to the bloodstream or at least the estrases in the upper skin.

So my question is really, are we liberating any hydroxycinnamate, or we don't have any data that stuff is innocuous at any appreciable concentrations, and I'm good with that, too.

DR. ANSELL: We have a human at 0.5 percent. I'm not sure --

DR. MARKS: Going from.5 to.8 makes a difference.

DR. ANSELL: Yeah. And we're not going patch people's eyes.

DR. MARKS: Yeah. I'm sorry, which page are you on? Oh, you're on --

DR. ANSELL: Yeah, I actually had a piece of paper --

DR. MARKS: Let me see. Hold on a second. It's somewhere around 13.

MS. FIUME: PDF 14.

DR. MARKS: Yeah. Yes.

DR. ANSELL: It's human?

DR. MARKS: Yeah, it is human, and I have that highlighted, 0.5. Yeah, I think the question there is the difference between 0.5 and -- let me just make sure. Yes, that's true with HRIPT.

DR. ANSELL: And reactions were not observed in any of the substances.

DR. MARKS: Yeah, exactly. I was probably being too conservative, Jay, the first time around.

DR. HILL: Well, let me ask this while you're there. Is that on intact skin with no penetration enhancement at all?

DR. MARKS: Correct. It doesn't look like they did any -- they didn't do any tape stripping.

DR. HILL: I have no reason to believe that the parent molecule would be sensitizing.

DR. MARKS: Yeah, okay.

DR. HILL: My only unknown is given that a membrane like you're talking about where there's a little more penetrability, if we have a hypothetical where that hydroxycinnamate is released, I can at least dream up a mechanism where that would be sensitizing. So, yeah, I don't know. .5 on intact skin is not the same as.8 on dry area. Close enough, do you think?

DR. MARKS: Yeah, I think so. Jay, duly noted, thank you. I had it highlighted and it still --

DR. HILL: It's one of those where if they start seeing a problem clinically, it'll come down anyway.

DR. SLAGA: So we're going back to the original "safe," right?

DR. BERGFELD: Right.

DR. MARKS: Yes.

DR. SLAGA: I agree with that. I think the odds of that being hydrolyzed and penetrating or low would only be a certain percent. So the difference between.5 and.8 are really nothing.

DR. HILL: Could the discussion reflect at least the 1,200 molecular weight and high estimated log P, and then it be juxtapositioned with what was just said there, Tom? I mean, not in the conclusion, just somewhere in the discussion. Because if later people start seeing something going on, they'll have a quick way to figure out what might be -- I'm just saying.

DR. MARKS: Okay. So let me see who has this one tomorrow. Dr. Belsito's team. Don presumably, motion tentative, "safe" conclusion. I will second that.

DR. HILL: And I'll have a question for the toxicology people tomorrow, which was nothing technical about this ingredient, but a generality. On the acute toxicity study on the table, which is not part of the report where he didn't check parenteral, but there was an IP study. So IP is a gray area because it depends on exactly how you do it. It gets a first pass, but not a complete first pass, and beyond that it can be -- so I don't know if we need a separate column there when

those kinds of done. But I certainly interpret IP as different. One should interpret them differently than an oral study because what happens is quite different.

DR. BERGFELD: (Inaudible - 1:24:25).

DR. HILL: Well, I'm just throwing that out there for discussion, which I'll bring up tomorrow because --

DR. SLAGA: So definitely it's a difference, but it's compounded --

DR. HILL: I'm not talking about this compound. I'm talking about generality, but he didn't check the checkbox, and then I saw, whoa, there's an IP, but he didn't mark "parenteral." It's not really parenteral, but it's not oral.

DR. MARKS: I'll let Ron Hill and actually Wilbur have that discussion.

DR. HILL: Okay.

DR. MARKS: Then Wilbur can relay it to --

DR. HILL: I wanted Paul's take on it, but I can get that informally.

DR. MARKS: Yeah. Okay. Any other comments?

DR. ANSELL: Yeah. We are a little concerned that a number of the BASF studies, a number of studies were taken off of the BASF MSDS. And it may appear as separate studies when, in fact, they were part of the ECHA. The BASF MSDS was submitted solely for purposes of correcting a physiochemical property, which was in error. So we just wanted to be clear as we go through that, that the ones taken off the MSDS are already reported through the ECHA data.

DR. MARKS: Okay.

DR. BERGFELD: Editorial.

DR. ANSELL: Yeah.

DR. HILL: Yeah. I had some concerns related to the same body of data in terms of how it's presented.

MS. FIUME: Dr. Marks, for the discussion, other than the molecular weight, the log P, and we have data at 0.5 percent with no results. So we figured the 0.8 percent is okay.

DR. MARKS: Yes.

MS. FIUME: Is there anything else for the discussion?

DR. MARKS: No. Did you have anything else on the discussion, Tom?

DR. SLAGA: No.

DR. HILL: Me neither.

DR. MARKS: Okay. Now we're down to, I believe, the last item, the botanicals boilerplate. That's in the administrative -- did I miss any ingredients?

DR. BERGFELD: We're done.

DR. MARKS: Let me see. Let's go up on the administrative. And then, Wilma, this is page 19 under the administrative.

DR. BERGFELD: We were just going to comment on it. We didn't have to do much with it. We were just --

DR. MARKS: So Lillian is not here, but when you asked about the abstract, see in page 20?

DR. BERGFELD: Yeah, I see it.

DR. MARKS: Tom, how did you like the

revised boilerplate framework for the botanicals?

DR. SLAGA: I thought it was good.

DR. MARKS: I thought it was nice. It was distilled down to something straightforward and very real.

DR. BERGFELD: Right.

DR. MARKS: Okay.

DR. HILL: What I like about it is it particularly captures the idea that it's guidance. It's a starting place, and then it will be tailored for each particular circumstance.

DR. MARKS: Anything else? Tom?

DR. SLAGA: It's lunchtime, isn't it, or almost?

DR. BERGFELD: Yes.

DR. SLAGA: Are you going to fax us lunch?

(Laughter.)

DR. MARKS: It's virtual, Tom.

DR. HILL: Go to the transporter room.

DR. ANSELL: We'll email you a sandwich.

DR. MARKS: Tom, we'll --

DR. SLAGA: What time do you want us back on the phone, at 1:00?

DR. BERGFELD: One, yes.

DR. MARKS: Well, yes.

DR. BERGFELD: Yeah, so that --

DR. MARKS: That's correct because that's 1:00 Eastern Standard Time obviously. It's 11:33 here. We're supposed to do a conference call with Dr. Elias in San Francisco at 1:00 Eastern Standard Time. Does that sound good?

DR. SLAGA: Ten-four.

DR. MARKS: Okay. Thanks, Tom.

DR. SLAGA: Bye.

DR. BERGFELD: Thank you, Tom. Merry Christmas if we don't hear from you again.

(Laughter.)

DR. MARKS: Okay. Shall I put this on hold?

DR. HELDRETH: No, you can just hang up.

DR. MARKS: How do I do that? Hey, Wilbur.

(Whereupon, at 11:34 a.m., the

PROCEEDINGS were adjourned.)

* * * * *

CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

I, Irene Gray, 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

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