128th COSMETIC INGREDIENT REVIEW EXPERT PANEL

MEETING

MAIN SESSION

Washington, D.C.

Monday, September 9, 2013

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P R O C E E D I N G S

(8:30 a.m.)

DR. BERGFELD: We're about to begin, please. This is our 128th meeting of the CIR. This is the day of the team meetings, and we have quite a bit of work to do. But I first want to welcome Lillian Gill, who is our new executive director. (Applause)

And we're looking forward to great things, Lillian -- and new things.

I do want to say that I had an email conversation with Alan, and he's doing well. And we'll share his email with you by email.

We have 18 reports to get through today -- 9 going to final, 5 advancing, 1 re-review, and 3 new. So we have quite a bit of work to do. We also have the botanical boilerplate, and some other issues, including the priority list, to discuss.

So, before I do anything else, I'm going to ask Lillian to address us, and tell us what she needs to tell us about the functions.

DR. GILL: Well, good morning again, and welcome to my inaugural meeting as the director of CIR. As you can imagine, there's been quite a change in the feel of the office, at least, for the past two months. But while it's been a change, and it's very different, I think the staff has worked very hard to make the transition as seamless and as smooth as they can possibly make it.

Wilma just mentioned that we have a lot of work. So, the work doesn't stop even though the change is there.

So, we have a lot to do. I think that you have before us a pretty good set of reports from the staff -- quite a lot of work, Ron. So we're continuing to turn it out.

I also want to make a note and a special welcome to Michael Best, who is also with the Consumer Federation of America. He is here today observing our team meetings. He will be taking Rachel's place tomorrow, as she will be absent. So, welcome.

And Stan has arrived as our FDA liaison, substituting for Linda.

I want to mention that I've given you an article from the New York Times, dated august 16th. Jim ran across the article. I had seen it before. It is on lipstick -- metals in lipstick. You may be interested to take a look at what's said in that article.

The Council has been busy working on this issue. They interviewed Linda, and she's worked -- has quite a lot of quotes in the article from Linda on it. So you may be interested in taking a look at that.

I also want to mention an article that I didn't put in front of you, but I can certainly make sure that you have it by the time the meeting is over today, and it is the public notification from the European Commission on their proposal to restrict the use of methylchloroisothiazolinone and methylisothiazolinone to the use of those as a mixture -- restrict the mixture of those to use to rinse-off products. If you recall, Don raised

that issue with us a couple of meetings ago, suggesting that we take another look at it. We do have that on the agenda for the March meeting.

We're beginning to collect information on it. So we will be addressing that next year.

I also want to mention that the Council has made us aware that as of July 2013, the EU Cosmetic Directive has been replaced with Cosmetic Regulation EC No. 1223/2009. We had a number of comments to our reports from the Council to make that change, and we have noted that, and will make the change.

I don't know if there is anything additional that Halyna or Jay may way want to say about that.

DR. BRESLAWEC: Yes, this is, to some effect, at this point, a major administrative change, but only administrative change in the EU. The regulation was actually passed in 2009, and this had a rolling series of deadlines that have been implemented between 2009 and now.

The important thing, I guess, from the

CIR perspective is that we can't use the term "directive" anymore. It's a regulation.

The annexes -- the numbering of the annexes has changed, so that is going to be, you know, something that needs to be addressed and corrected.

But, by and large, the regulation is the same as the directives over the years, which had been amended several times.

DR. GILL: Don, did you want to make any additional comment on that?

DR. BELSITO: No. My understanding, it's just more of a sort of a name-change, and slightly different approach, in terms of trying to strengthen what their decisions mean, in terms of changing it to "regulation" from "directive." But I don't think it's substantive in any way.

DR. GILL: I think that's all I have for comment this morning.

DR. BERGFELD: All right. Halyna?

DR. BRESLAWEC: Yes, just a little editorializing, if you will permit, on this

article.

This article was a huge disappointment for us. Linda Loretz spent hours on the phone with Deborah Blum, trying to explain to her, trying to discuss with her the relevance of the issue at hand and, you know, aluminum and cadmium being thrown in the same category as metals.

So it was a very big disappointment for us. Linda is here. She is certainly available to provide some insight on this. One of her articles was quoted by the study that this article refers to, and I really -- you know, as an industry, we continue to be puzzled by the hype on the "danger in your lipstick lead" thing. It's one of the areas that has been the most studied by FDA. Over the years, FDA has stated that lipstick -- that lead levels in lipstick continue, you know, do not present a safety hazard. And that really applies to all the other trace -- very, very trace -- levels of metals that are found in lipstick, depending on who chooses to do a study at any given time.

So, it continues to frustrate me personally because, you know, this is an area where the science supports, pretty unequivocally, the safety of a product, and yet it continues to churn in the public arena.

DR. BERGFELD: Thank you. Any other comments? Well, I understand that Belsito team will be the moving team? That's what it said --

DR. SLAGA: They have less baggage.

DR. BERGFELD: They have less baggage. So, I guess we'll assimilate our teams, and move on to the 18 ingredients, and discussions on the boilerplate and priority list.

So, thank you.

DR. MARKS: Everybody's so quiet. Okay, let's begin.

In the June meeting of this year, the panel issued a safe-as-used conclusion for the tentative report of tromethamine, after adding AMPD and AEPD to the report.

So we're at the stage now to issue a final safety assessment for these cosmetic

ingredients.

Tom, Rons -- any editorial comments? Any change in the conclusion?

Nope? Safe?

DR. SLAGA: Safe as used?

DR. SHANK: Safe as used.

DR. HILL: Pardon me -- the conclusion is fine. The report's fine. Well done.

DR. MARKS: Okay.

SPEAKER: Thank you.

DR. MARKS: Any other comments?

DR. HILL: A couple of minor things on the discussion, but I don't know if they're just editorial -- I think.

DR. MARKS: Okay, Ron, we'll wait a minute. And then we have --

MR. HUGHES: Yes -- Brian Hughes, from Dow Chemical. We still have a few minor changes that we'd like incorporated in the final.

It does seem that there has been -- well, there's a 90-day rat study that was quoted for tromethamine. We think that was actually AMP.

And the use rates seemed to be a little strange to us, so we'd like that checked out.

So there are a few -- little minor comments we'd like to make before it's final.

DR. MARKS: Okay. Those sound editorial to me. So, I don't think it would change the conclusion.

Brian, did you think this had any impact on the safety of the ingredients?

MR. HUGHES: No.

DR. MARKS: No -- okay. Thank you. And then, Ron Hill, I think that Lillian can pick up your editorial comments, unless there's major that you should bring to that team, part of the panel tomorrow.

DR. HILL: I don't think so.

DR. MARKS: Okay.

DR. HILL: I suppose that -- were people puzzled, last meeting on Tuesday, when I -- because I talked about the AEPD a good bit on the Monday meeting, and I had time to reflect, over the evening, and decide that all was well, so

that's what happened there.

DR. MARKS: Okay. Good. Okay, s tomorrow I'll be moving that these ingredients be issued as a final report, with a conclusion of "safe."

Okay, as we're still, at least for me, personally, getting used to jumping between paper, electrons, and taking my eye off of the screen and looking at my team members, there may be as fluid, perhaps. Alumina.

DR. MARKS: Next is alumina. And we're also looking at these ingredients, alumina and aluminum hydroxide, at the stage now to issue a final safety assessment.

In June, we had issued a tentative conclusion of "safe," so I think we can move on with a final assessment, with a conclusion of "safe."

But there was a section on aluminum toxicity added to the report, and so I'd ask Ron, Ron, and tom -- that's page 30 of this -- if there are any significant editorial changes. And then

the other is, do you like the section, and is it relevant/

DR. SLAGA: I liked the overview. It was a nice summary. And I didn't have any substantial changes.

DR. MARKS: Rons?

DR. SHANK: I think it's fine.

DR. HILL: I thought it was great. I liked that section.

DR. MARKS: Okay.

DR. HILL: I had a small question about the -- but I think it's just -- it was on the teratogenous -- yes, I think, yes repro and developmental, its teratogenicity, its teratogenicity. There was a statement in there that said aluminum was not detected in whole fetuses, which is impossible, because we have (inaudible) aluminum in our bodies. So I wanted to make sure that I left a comment there, that we were talking about did we not see -- did they use radioactivity, and they didn't see it transferred to the fetuses? Or they didn't see an increase?

That was the only question I had.

But the statement as its written makes no sense, because we've got plenty of aluminum in our bodies.

DR. MARKS: Halyna.

DR. BRESLAWEC: Yes -- we liked the toxicity section, as well. The panel had requested it, and we think that a robust discussion of aluminum toxicity is necessary.

Our concern is that there is no discussion of the relevance of the data summarized in the toxicity section to the ingredients that are being reviewed here for safe use in cosmetics. And we would like to see that discussion developed and put in the report, and that the report be tabled so that the panel can get a chance to look at the discussion.

Our concern is, alumina is a very important ingredient in cosmetics. There are challenges to safe use of alumina. And we, in the industry, we would like to be able to use this report with confidence in the defense of alumina

as an ingredient. And, as the report stands, the relevance is missing. And we believe that the discussion in the toxicity section lacks context vis-a-vis what we're reviewing here.

DR. HILL: So, I didn't see it that way, because I thought if you read it in the context of what -- the information that was beautifully done in the toxicokinetic section earlier, about the complete lack of absorption, and why you do sometimes see a little bit of absorption with antacid consumption, for example, I thought if you viewed that section in relationship to the toxicokinetic section, there's no such quandary. But I also understand where you're coming from.

So, maybe if it's just done in such to make sure that it ties back. Because, again, what I said repeatedly the last time applies, is in any conceivable cosmetic use and exposure, you're not getting any aluminum in any form that would have an deleterious health consequences. And that's, to me, that message came loud and clear, but --

DR. BRESLAWEC: Right. I completely

agree. As an example, in the overview of aluminum toxicity, the very first, the absorption, probably belongs in the toxicokinetic section. The second, the osteomalacia discussion, what is the relevance of that toxicity to use in cosmetics? Not clear, unless, you know, you've really gotten into the area.

And the dialysis encephalopathy, what's the relevance there? That's IV and oral use.

Again, no objection to leaving that in --

DR. HILL: Just make sure that it's loud and clear what the relevance is.

DR. BRESLAWEC: -- but let's -- I mean, the discussion is supposed to be a discussion of it.

And the other thing is, you know, the breast cancer, the alumina, aluminum hydroxide as used in cosmetics as active ingredients in antiperspirant products. Well, neither are a bunch of other things.

DR. BERGFELD: Are you suggesting that

go in the discussion, that clarification?

DR. BRESLAWEC: We would like to see this document one more time before it goes, and that the data that are appropriately presented here, on toxicity, are presented in a more contextual, relevant discussion. And we'd like to take a look at it one more time.

DR. BOYER: And one of the suggestions that industry had, that I thought was (inaudible) a lot of that aluminum toxicity discussion into the introduction.

And we could easily pare it down, make it more brief and more concise, and so forth, and provide a context within an introduction section. And I think that will more or less take it away from the subsequent discussions of alumina and aluminum hydroxide, the actual ingredients that we're looking at.

And the other point that industry made is that, in fact, there is a consensus out there that there is no causal link between aluminum exposure and Alzheimer's disease, and so forth.

We more or less hedged on that, and we can also make it much more clear that, in fact, there is a consensus on that.

DR. HILL: I think you should hedge on that. There's some new -- I've been pretty deep into the Alzheimer's literature for the last couple of years, and I think the things that can be said is, there's some new and pretty suggestive information that there may be some epigenetic-related effects, and that science wasn't there heretofore to even look at.

I think when you get into using epidemiology, what that belies is that it's not just one disease, there's at least two major flavors of it. But even you get down into the disease itself, there are -- the genome-wide association studies keep spitting out new genes of relevance. And what that says is that a combination of a particular person's genetics and their environment comes into play in such a way that if you lump all those people together, and try to look for associations, you will

automatically wash it out.

So I'm not saying there is anything that definitively suggests there is a relationship. And, again, it's totally not relevant to cosmetic use of alumina, but I don't think you can completely discount it. You have said, I think, there's consensus. I think you said it pretty loud and clear. From where I sat, it was just right, in terms of, I think, the science that's known.

And I know where Halyna's coming from, but --

DR. BRESLAWEC: No, I was wondering if you had any citations, or any studies, that you can present to the panel for consideration on the subject.

DR. HILL: I didn't bring that reference, and anybody that referenced it. But it's pretty recent. And again --

DR. BRESLAWEC: Could you provide that? Well --

DR. HILL: Yes, I can. I'll have to do

the search again tonight, because I didn't write it down. But I think -- so, the point is, to completely write it off, because there is new science, based on epidemiology studies would be wrong, because we're lumping together -- it's like when you do clinical studies, if you -- for cancer chemotherapeutic, if you put together people who genetically are unable to respond, then you're going to wash out the response. And it's similar in this case.

And I don't think -- again, the point is, from any cosmetic use, by any conceivable route of exposure, you're not getting any aluminum into the system in any form that could do anything, including these epigenetic relationships.

You'd have to have a lot of systemic aluminum. And I don't think -- that's the point. And maybe we make the point even more loud and more clear that, by cosmetic use of these ingredients, you're not going to increase the amount of aluminum in anybody's body, and that's

it. Problem solved.

All is well.

DR. MARKS: So Halyna, that last paragraph in the introduction, on page 25, I thought was very clear. It begins with "Note," and then it points, I think, what you want to express very clearly, why that section's in there, and that there is not-it also talks about the extensive research has failed to support associations with Alzheimer's, breast cancer, or other health issues.

So I don't know if you want that restated in the aluminum toxicity section. But, to me, when I read it, it looked pretty clear why that was in, and that last paragraph, I thought summarized it really well.

And I guess the editorial comments -- I'd ask Rachel about this, but if they're just editorial, rather than tabling it, could they not be sent out, and then we could approve it by e-mail? But I don't know if that's proper.

I'm not sure we need to delay it just to

see a couple of editorial comments, because we're all on the same page. We're not worried about aluminum toxicity with these two ingredients.

DR. BRESLAWEC: The industry would really like a credible, robust report on this, that is clear, and does not further confuse the issue. There are a number of statements in this document -- that are really tough to deal with: "...both amorphic and crystalline alumina data on which forms are used in cosmetics were not available." Okay?

"This safety assessment does not address aluminum as a cosmetic ingredient..." -- that's true, but then there's a lot of discussion on that.

"FDA requires warning on injections that contain aluminum..." -- in the "Discussion."

I mean, it's just there are a lot of loose --

DR. MARKS: Sure.

DR. BERGFELD: Ends.

DR. BRESLAWEC: -- ends. Thank you.

You know, it's got to be cohesive, it's got to be a cohesive argument.

And especially for something that this confusing, that we really need solid toxicity and summary that needs to be presented. But it's got to be relevant, it's got to be linked up, to somebody who is not as familiar with aluminum salts toxicity as this particular group is.

DR. MARKS: So, Tom and Rons, do you like the idea of tabling, see industry suggestions? Obviously, Halyna, you'll be writing Lillian as to "these are suggested changes," and then Lillian and Lillian -- Lillian-squared -- and then we can see the next edition, with the editorial changes.

Do you want to table it, as suggested?

DR. SHANK: Is it necessary to table it? Aren't these editorial changes?

DR. MARKS: That's sort of what I --

DR. SLAGA: I think it's editorial. I --

DR. HILL: So, I would like to say it

tabled, just because, depending on how those editorial changes are made -- well, there's editorial and then there's substantive editorial. I'm sure if we get something that industry is comfortable with, it will still be fine with me. But I'd like to see that.

And I just wonder if there's any real downside to table it?

DR. MARKS: I don't see any downside. Rachel, your input, how would you, from a consumer's point of view --

MS. WEINTRAUB: Yes, well, first I want to say I thought that the addition of the section greatly improved this report. I thought it was in a context. And I thought having this note up front really explained the difference between alumina and aluminum.

But if there is a desire to further clarify, I think we should all see what industry's comments are.

The question for me is, is it possible to do that in a context that's not tabled? Or is

the only way to do that back and forth is if it's tabled?

DR. MARKS: I guess it would be if industry could give us the editorial changes tomorrow?

DR. GILL: Yes, I think I'd like to ask industry. Because what I hear is the addition of -- granted, the removal of some things that you've said are incorrect. And I think that's editorial. And I hear one or two clarification sentences, and making sure that there's no tie to these ingredients to aluminum.

Is there specific language that we could propose by tomorrow to add to this paper, to this report, that would allow it to move forward?

DR. BRESLAWEC: When we talked about it with the staff last week, there were pretty substantive changes that we would propose -- and, really, a discussion of, you know, more of the context. I think Ivan understands what our concern is.

I'm not sure we can come up with it

tomorrow, by tomorrow. That's a question.

I mean, we certainly will provide comments in whatever format, whether you table it or not. This is an important ingredient. We would like to have an opportunity to review it, and have the panel review it before it goes final.

DR. MARKS: So, what I'm going to propose tomorrow is that it actually -- since you used the word "substantive," I'm going to propose that we table it and see those substantive editorial changes. And then we'll just look at it again in the next meeting.

Is that okay, Ron? I know Ron Hill's -- Ron Shank, and Tom, is that okay?

DR. SHANK: Yes.

DR. MARKS: Okay. Thank you, Halyna. So, tomorrow I'll propose, I'll make a motion we table for industry input on editorial changes. Okay. We'll still have a "safe" conclusion. There's no question about that. But we will see these editorial changes. Okay.

Thank you, Halyna.

DR. MARKS: Next, Achilea. So, in the June meeting we had a draft final amended safety assessment of achilea millefolium -- yarrow -- and derived ingredients, with a "safe as used" conclusion.

Rons, Tom, comments?

DR. SHANK: I think the report's good as is. A minor little editorial thing --

DR. SLAGA: I agree. I think it's fine.

DR. MARKS: Halyna, can you comment on this -- or, Lillian Becker -- can you comment on this third paragraph, where it said, "comments from the CIR Science and Support Committee...suggested...safe when formulated to be non- sensitizing..."?

We had issued a draft final with "safe." We didn't feel it needed to be included "non-sensitizing," when the concentration is safe. You looked at the sensitization and the irritations study at 0.04 percent, and there was no irritation.

Is there a reason why that was added?

DR. BRESLAWEC: Yes, we thought that there are known sensitizers present in this particular botanical, and we felt that the change to "formulated to be non- sensitizing" was a safer way to go.

Carol --

MS. EISENMANN: Well, one of the issues with industry is that each botanical extract can be slightly different. And so they thought that for something like this, where you have a plant that is associated with sensitization, that maybe "safe when formulated to be non- sensitizing" would be a better conclusion, so that, you know, you're saying, industry, beware, this plant is an issue; that some extracts can be made without the sensitizing compounds, but some may have them. That's where they were coming from.

DR. HILL: To me, I thought since it's a request coming from industry that basically places a greater burden on industry, why would we not want to do that?

And I agree with their rationale, by the

way.

DR. BERGFELD: We've never done it.

DR. MARKS: Yes, that's --

DR. BERGFELD: And we've done non-irritating, but not non-sensitive.

DR. BRESLAWEC: Oh, no, I think we have. CAPB, right?

DR. HILL: We sure did.

DR. BERGFELD: Did we do it once?

DR. BRESLAWEC: Yes.

DR. BERGFELD: But not very often.

DR. HILL: Not often.

DR. MARKS: So, cocamidopropyl betaine, because of the contaminants in it, we had that "safe when formulated to be non-sensitizing."

No, I liked the rationale. Was that capture in the discussion in this? Because that caught me a little bit by surprise.

And the other question, from a procedural point of view, does this need to go back out in comment? Does this change the conclusion significantly that we perhaps need to

issue another tentative amended report, with this change and conclusion?

I think, since the 0.04 percent was safe, and that's the use, that perhaps it's not a drastic change in the conclusion. But I'm open for discussion.

So, Ron, Ron, and Tom? I heard, Ron Hill, you like the more restrictive, "when formulated to be non- sensitizing."

Now, is this going to be something you think is going to set as a precedent in all botanicals? Because we face this -- this is not the first, this may be the beginning of this is going to be the conclusion of all botanicals.

MS. EISENMANN: I don't know about all botanicals, but maybe asteraceae botanicals, for which you know -- I mean, they are known to have sensitizers, which there are others in this group today. But -- just a thought.

DR. SHANK: This ingredient has been tested for sensitization, and we have a level of use that is not sensitizing, enough to make the

argument, well maybe if the manufacturer is different, than it could be, then we're in trouble.

DR. MARKS: I agree with you, because then you say, if it's different, how about the other potential ingredients? Would they now rise to a level?

I mean, should you put "when formulated to be non- toxic?"

DR. SHANK: No, please.

DR. MARKS: I know -- but that's the extreme.

DR. HILL: But the point is, but the sensitizers act at -- can act at pretty low concentration. We're talking about a botanical here, where -- botanicals always vary in terms of -- unless you propose to make them measure the concentrations of those sensitizers, which we're not proposing, in each of these.

And so, I think -- I mean, they're coming from the industry perspective, and saying this might be a reasonable thing to do in this

case, based on the known presence of sensitizers, and the fact that botanical extracts do vary, sometimes widely, in terms of content, based on source, growing season, phase of the moon -- who knows what? I'm not even being that facetious when I say "phase of the moon."

So, I mean, I'm assuming the Belsito team will have some thoughts on this one.

DR. MARKS: Well, Don will be making a motion, but we better have our act together, too.

DR. HILL: You just heard what I think about it.

DR. MARKS: Yes, you like it. Ron Shank's a little bit on the other side of it, that we -- "safe." Tom, what do you feel?

DR. SLAGA: I'm with Ron Shank. I think it's safe the way it is. I mean, we definitely have concentrations that we can deal with, and we're below that (inaudible).

DR. MARKS: Then you would have language in the discussion, to be sure that this issue is well raised.

DR. SLAGA: Right.

DR. GILL: I was going to suggest that the language in the discussion captures what we've talked about here, and the conclusion as is.

DR. HILL: I would be okay with that, actually.

DR. MARKS: I like that, also.

DR. SHANK: Language is already in the discussion.

DR. HILL: I think it is.

DR. SHANK: About the sensitizer of these --

DR. MARKS: Is that page 26, 27? Which page are you on?

DR. SHANK: 27.

DR. MARKS: Yeah, okay.

DR. SHANK: The first complete paragraph, "The panel noted that among the constituents..." -- that's all about the sensitizers.

DR. MARKS: Right.

MS. EISENMANN: One thing to know about

the "constituent" paragraph, thujone is discussed. And in the analysis of the aqueous extract -- they did an analysis, and thujone was one of the materials they actually used. And they did not detect it a level of 300 ppm. I was thinking that that that needs to be changed to "constituents of concern in the plant," which may or may not be in the extract. If you still want to discuss thujone you can, but in the aqueous extract, which is the one that was most, there's the most data on in the report, there was no thujone at a level of 300 ppm -- which isn't a sensitizer issue, but it's in that paragraph.

DR. MARKS: So, Ron Shank, you're -- which paragraph was that again? You said 27 --

DR. HILL: It's the first full paragraph on that page, I think.

DR. SHANK: Top of the page.

DR. MARKS: Under "Discussion?"

DR. SHANK: Yes.

DR. HILL: Yes.

DR. MARKS: Yes, okay.

DR. SHANK: It starts, "The panel noted that among the constituents of these botanical ingredients..."

DR. MARKS: Oh, yes. Okay. Mm-hmm.

MS. EISENMANN: So, it shouldn't be "of these botanical ingredients," "of these plants." Because those are the constituents of the plants. I don't think, if you look back at the analytical work, those were actually in the ingredients. And I know, especially, thujone was not at a level of 300 ppm.

DR. SHANK: Yes, that's a good change.

DR. MARKS: Okay. Any other comments? So, tomorrow I'm going to move as "safe." And we've captured the non-sensitizing concern in the discussion, and it will be handled there.

DR. HILL: One follow-up comment, though, to what she just said is that I don't think we have -- one of the ingredients that's included here is the achillea millefolium flower/leaf/stem extract. And I don't think we have full data on contents of that. So that's --

that's why I think that we -- but I do agree that something needs to be changed to better reflect the situation.

DR. MARKS: Lillian? Do you have that? Captured that?

MS. BECKER: Yes, I have it. Thanks.

DR. MARKS: Okay. So, presumably, I'll move a "safe," second a "safe" conclusion tomorrow. And, if there's discussion about changing the conclusion to "formulated to be non-sensitizing, I'll present our team feels that's been captured in the discussion. And I won't even get into the issue of whether this needs to be sent out again, whether it's a significantly different conclusion. Okay.

Any other comments? Next are hair dyes. So, we have in front of us the draft final report of hydroxypropyl bis -- da, da, da, da -- hydrochloride as used in cosmetics.

The conclusion was "safe." And are there any changes in that conclusion, Rons, or Tom? And are there any editorial comments?

DR. SHANK: Again, the report is fine as is.

DR. SLAGA: I agree -- fine as is.

DR. MARKS: Great. And then we'll -- presumably, I'll be seconding a motion that this is safe. And it will be a final report.

DR. HILL: I do have something that needs to be looked into.

Under the "Impurities" section -- right? -- there was a reported range of 94.6 percent to 99.8 percent. And I grant you, built into that are analytical uncertainties.

But then they list three impurities that are below detection limits. And on the flip side, if you've got something that's 94.6 percent, then there's 5 percent sort of missing. So that just leaped out at me -- probably because that's one of the sections I focus on more than some other sections.

And I think we probably could get information as to what's up with that.

But, I mean, if it's inorganic

impurities, sodium chloride, or something like that, it probably doesn't matter. But that was something I thought needed to be addressed as the thing was finalized.

The other question I had, just tossing that out there, is we're removing any percentage cap, right? But everything's based on .28 percent maximum use (inaudible). All is well with that? When we're saying "art of use," what we're effectively doing is setting a cap at.28 percent?

DR. MARKS: And, remember, this actually is exempted by the Coal Tar Directive --

DR. HILL: I know that.

DR. MARKS: -- is that not right? That there is supposed to be pretesting?

DR. HILL: Yes, I know that. I guess what I'm asking is, are we effectively lowering the -- because it was 1 percent, right?

DR. MARKS: Yes.

DR. HILL: Are we effectively lowering it by this to .28?

DR. MARKS: Mm-hmm.

DR. HILL: Okay. This was not anything to do with the report.

DR. MARKS: Right.

DR. HILL: Just so that I know what's going on.

DR. MARKS: Any other comments?

MS. BECKER: Dr. Hill, could you re-explain what you meant with the impurities?

DR. HILL: Yes.

MS. BECKER: I'm not sure what you meant.

DR. HILL: Yes. It gives a range of impurity of 94.6 percent to 99.8 percent. So, if it's 94.6 percent that's the result, that suggests there's 5 percent impurities in there, 5.4 percent -- all right?

So -- but we've only got three things listed, and they're all below the detection limits, and that's not the complete list of things that are potentially there and of concern. So, for example, we're not capturing nitro-substituted compounds in all in that list of three

things.

MS. BECKER: Okay.

DR. HILL: So the question I'm asking is, because in the last meeting we had the discussion of why do we have, in some cases, bluish-white, or grayish-white, or what -- and I was giving some sense of there are things in there that can generate that color. It's typically some polymers, like that.

So the question is, what's accounting for the other 5 percent, since we were listing three things, and it's all below the detection limits.

And so it's, again, sort of -- I get the sense that the -- how do I put this? -- the high caliber, conscientious producers are probably producing something closer to 99.5-plus percent. But if we had a raw ingredient that's 94.6, what else is in there?

MS. BECKER: Okay.

DR. HILL: And I --

MS. BECKER: This was data provided by

industry.

DR. HILL: I know that.

MS. BECKER: If they've got any --

DR. HILL: I'm really, I'm looking at you, but I'm talking to them.

DR. BRESLAWEC: This is actually data that was provided by SCCS.

DR. HILL: Okay.

DR. BRESLAWEC: It was in their opinion. So --

DR. HILL: Okay.

MS. EISENMANN: And one thing to note about the color, references listed in the table are, like, tox studies. So it's, you know, it's like providing a sample to a lab, and they look at it and tell you what color. The opinion calls it "ivory." So I suspect it's a little interpretation of that it's similar material, but it's whoever is looking at is saying it a little bit, slightly different color.

DR. HILL: So, I've done a lot of catalytic reductions of nitro compounds in my

career, which -- this is at least part of that manufacturer, and depending on -- because one of the things that those do is tend to poison catalysts. And so, depending how well those reductions are done, and how completely, and all that, there can be both impurities that are precursors, as well as some polymeric materials generated. So that's what the question I had is.

And I guess what I'm picking up on is, if somebody's supplying material that's 94.6 percent with crud in there, it doesn't need to make its way into consumer products. Is enough attention being paid to that? That's what I'm driving out.

You all can figure out what to do with that.

DR. MARKS: Okay. Any other comments? So, "safe" for the hair dyes. And then let's move on to phytosterols. And this is the first time we've seen this report. There are 27 ingredients. So, not only Rons and Tom, any needs you have, but also are the 27 ingredients -- I'm going to refer

to page 9 -- do they look good?

And then we have a Wave 2 on these ingredients, which one particular is Stolesterol -- that's a brand name, is it?

Lillian, there was manufacturing impurities and chemical and physical properties that were -- with that -- which this initial report, I don't think, had those details in.

So, Rons, Tom, shall we start with "needs," or start with -- why don't we do it with ingredients? I'm going to look at page 9.

Do any of these 27 phytosterols and sterol alkanoates not belong in this group -- for toxicologic reasons, chemical reasons, et cetera?

And, of course, we can't use the no-brainer as an escape. This is the first report.

DR. HILL: I tried to come up with a good enough and convincing rationale for doing these one at a time, but I failed. And I knew nobody would be receptive.

DR. MARKS: So, Tom, Ron?

DR. SLAGA: I think all the ingredients look fine to me.

DR. MARKS: Ron Shank?

DR. SHANK: Yes. There's all (inaudible).

DR. MARKS: Okay, good. So, all the ingredients look good.

Let's go back to, then, what are the needs?

DR. SHANK: I had "safe as used."

DR. MARKS: Okay. So let me go to -- that's what I had, but -- Ron Hill? Tom?

DR. HILL: I'm getting there.

DR. MARKS: So --

DR. HILL: A couple of things that raise questions, so hang on.

DR. MARKS: Yep. So, this would be issuing a tentative report. Actually, the skin irritation and sensitivity was okay up to 100 percent, so -- you can't get much better than that.

DR. SLAGA: I had "safe."

DR. MARKS: "Safe." Ron Hill?

DR. HILL: The kind of issue that I want to see better looked at going forward -- because this might not be the last report in this category we see -- if you look at Table 6, which is on page 21 of the report, it's got "Total phytosterols," "Major phytosterols," "Beta-sitosterol," and then it's got a number like 49.1 --

DR. MARKS: It's what page?

DR. HILL: Yes -- page 21 of the PDF.

DR. MARKS: Oh, 21. Okay, no wonder --

DR. HILL: I may have said 27, so I apologize if I did.

DR. MARKS: 21. Okay. Yep. So, Table 6, you said?

DR. HILL: Table 6, which is short.

DR. MARKS: Yes.

DR. HILL: So you see a list of components --

DR. MARKS: Mm-hmm.

DR. HILL: -- and also a compilation. And you see a very exact number, like "49.1."

All right. So, first of all, it's not even giving any level of uncertainty for the analytical chemistry. I don't have a huge issue with that, but the fact that you have one number, whereas we know these things are going to show up in the plants in some range, suggests that this just the result of analyzing one particular lot from one particular source material, and doesn't really convey a picture of what the variation is likely to be if we get that ingredient from multiple vendors.

And that relates to -- okay, grant you, we don't have any big toxicology issues that jump out at me with these, but that relates to what material is being studied, when we get some toxicology data, how well do we really know and understand it if all we're seeing is the result of one lot, from one supplier, which, clearly, these numbers suggest to me is, in fact, the case.

So that was one. And there was something related -- as soon as I find it --

DR. MARKS: So, there are two

references, 2 and 5 in there.

DR. HILL: Yes, I looked at those.

DR. MARKS: Okay.

DR. HILL: You can look at those and see exactly what those are. I wrote a comment there that just said just use the original reference, don't reference a report that references the reference. Skip -- just reference the original data, so that people know that we have looked at that original data, and not somebody else's distillation of that data.

DR. MARKS: So, Ron Shank, any -- I hear what you're saying, Ron Hill. Does that create any concern from your perspective, Ron Shank? Those comments? Or Tom?

DR. SHANK: It didn't bother me, no.

DR. MARKS: I mean, it gives you a number which at least puts you in a ballpark of where one -- there's certainly going to be -- I agree with you, Ron Hill, there will be variation depending on the source of the botanical, but it's probably not going to be log changes.

DR. HILL: Well, we don't know.

DR. MARKS: Yes, I hear you.

DR. HILL: I mean, some components, in some particular extracts or ingredients could be 20 to 70, and this one happens to be 49.1. So if we don't get a sense of what that variation is -- which, at least, I think it was one of the other reports we had, we got a very nice and very clear sense of that. And that was a beautifully painted picture, and when we get to it, I'll point it out.

DR. MARKS: Okay. Okay. So you would like to see a range.

DR. SHANK: We always see in our reports "based on the data" --

DR. MARKS: Right.

DR. SHANK: -- "our conclusion is based on the data in this report." So if someone has an ingredient that is far afield from what is characterized in our report, then it doesn't comply to our analysis.

DR. MARKS: Thank you, Ron -- Ron Shank. Okay. Any other comments, Ron Hill? Lillian -- I

mean, Halyna, sorry.

DR. BRESLAWEC: I would draw your attention to the search strategy. I think what was searched was "phytosterols," for 35 possible hits, of which 15 were useful.

It would probably be useful to search for diosgenin and beta-sitosterol acetate, to look for toxicological data on those. I think if you just search for phytosterols, I'm not sure if you're getting everything.

DR. MARKS: Lillian.

MS. BECKER: When I "phytosterols," a lot of the stuff that came up was on those two ingredients, and just those two ingredients.

DR. BRESLAWEC: Did you search for diosgenin?

MS. BECKER: No, I didn't search for it, because it just came -- that was most of the stuff I got from my search on just phytosterols. It was diosgenin and the other one.

DR. BRESLAWEC: It would seem that if, you know, you're looking to evaluate specific

ingredients, such as diosgenin and sitosterol acetate, you'd want to search for those terms, as well.

DR. MARKS: What I -- Halyna, thank you for that suggestion. We'll be issuing a tentative report, so I think there's plenty of time to go back, search on that specific ingredient, or component, I guess. And then if there's anything different -- it sounds like, from what you found, Lillian, it probably covered everything. But I would suggest going back, as Halyna recommended, and then see what comes out, and you'll be able to give that on the next edition of this, if there are any changes.

MS. BECKER: Okay.

DR. HILL: And just a chemistry-related comment to give some attention to, and I made a note here -- is any of these phytosterols can be found as esters in any given plant, and might be extracted that way. Any of them are likely to be found as various and sundry glycosides in any given plant, and may be extracted that way -- and

we made sure that whatever's written here adequately reflects that.

DR. MARKS: Okay. So -- any other comments?

MS. BECKER: Did you put some language in for that?

DR. HILL: I put something in there.

MS. BECKER: Okay, great. Thanks.

DR. MARKS: So, tomorrow I will move that we issue a tentative report, with a "safe" conclusion.

DR. SHANK: Okay, I had just a question on the use of the term "saponification." Dr. Hill, is that really -- the alkaline hydrolysis of these sterols is a saponification?

DR. HILL: I --

DR. SHANK: I thought that saponification was an attack on a carboxyl carbon. Am I just way old? My elementary chemistry?

DR. SLAGA: No, that's what I thought, too.

DR. SHANK: Okay. If it actually mean

--

DR. HILL: Well, if you're hydrolyzing off esters, then that's exactly what you're doing.

DR. SHANK: But isn't the mechanism of saponification fairly specific?

DR. HILL: Yes -- alkaline hydrolysis.

DR. SHANK: No --

DR. HILL: I mean, typically, you use --

DR. SHANK: -- where the attack is on the carbonyl carbon?

DR. HILL: Well, it would be if you're hydrolyzing esters. That's the only way you can hydrolyze off an ester.

Well, it's not the only way. You could do it in acid, but --

DR. SHANK: So all of these are not esters, are they?

DR. HILL: The question is, whether that term is chemically appropriate if you're doing glycosides. And I have to research that.

DR. SHANK: Okay. It was more for my edification.

DR. HILL: But, I think it -- yeah, I think it just generally refers to alkaline hydrolysis. And usually that's done in sodium hydroxide.

DR. SHANK: Right. Okay. The other point was, in 2004 we reviewed wild yam, and phytosterol was looked at very carefully, because there was a question about estrogenic activity. And it might be helpful to throw in just a reference to our CIR report of 2004 on wild yam extracts. Because we went fairly deep into the analysis of did any of these sterols have estrogenic activity.

MS. BECKER: I do mention that in the introduction.

DR. SHANK: Oh, sorry.

MS. BECKER: Do you want that expanded on?

DR. SHANK: Okay.

MS. BECKER: It's the next to the last paragraph of the introduction.

DR. MARKS: What page is that, Lillian?

MS. BECKER: I'm sorry -- 9.

MS. EISENMANN: But that report did conclude a uterotrophic assay of a specific extract that had a known amount of diosgenin. That might be helpful.

DR. SHANK: And also, the structure in Table -- the diosgenin needs a double-bond. Where is that? It's a table someplace.

DR. HILL: Yes, I missed that. I think I missed that.

DR. SHANK: Table 1, page 19, between C-5 and C-6, that should be a double-bond.

DR. HILL: Yep.

DR. MARKS: Ron, was the estrogenic effect -- in the introduction, was that satisfactory, the way Lillian had it.

DR. SHANK: I'm trying to find it.

DR. MARKS: Yes, which paragraph is that, under the introduction?

MS. BECKER: It as the next to the last paragraph of the introduction.

DR. MARKS: "...were safe as used." So

that's the "safe," but it doesn't specifically -- did you want to be more specific about the estrogenic effect, there, Ron? Add another sentence or two in that paragraph?

DR. SHANK: No, I guess that's fine. I missed that. Thank you.

MS. BECKER: Thank you.

DR. MARKS: Okay. Any other comments? So, if not, then tomorrow I will be moving that these ingredients are safe, and a tentative report be issued. Okay.

Next is the botanical boilerplate. That's on the administrative section. And on page 33 of that -- so, you'll notice on that, the "Admin" cover, or title page, it's number 3, "Botanicals." So let's go to page 33.

Rons and Tom, how did you like these? And I'll say the same for anybody else who has any comments.

DR. SLAGA: I had -- I read it, and really -- it was hard to make any conclusions from what I read, because it was too hypothetical. And

it, really, it's going to be a function of each thing we looked at, how you define that summary. And I couldn't get that in here.

DR. MARKS: You give a lot of specific examples as we go down.

Rons, what did you feel? I think, because of the complexity, you have different sections you're addressing, it's really quite a thorough boilerplate.

MS. BECKER: The idea is that it's not a boilerplate boilerplate, but a guiding framework, because a lot of it is still written dependent on the data we have, and what we know. And basically, it's examples and guidance, and where to go from there.

DR. BERGFELD: Isn't that similar to the inhalation boilerplate? There are several selections you can make?

MS. BECKER: Yes.

DR. HILL: If what we're working for is strictly an internal document that can b e used by staff and by us when we need to reference it to

remind ourselves of some things, then it can continue to be a work in progress as we review botanicals, of which we have several on the plate this meeting.

And then I see there are some comments here from the Science and Support Committee, as well, too.

I guess the question is, will at some point something be released to provide guidance to industry, which would probably be something different than this? I guess there are, you know, two purposes: One is for staff and us, and one is -- if you're proposing to provide something on the website that would provide guidance -- and I don't know that you are.

I guess I'm not sure that one document should serve both purposes, because I think, in this case, unlike, maybe, inhalation, this may be more of a living, breathing, document that keeps being updated at we look at specific ingredients. And I'm not suggesting it would get longer, but that it may be refined in some sections. I don't

know.

DR. BOYER: And I think that's the way we've been looking at it so far -- basically to provide the writers with some guidance, some place to start with when they're incorporating this kind of language into their reports, and also for the panelists to take a look at if there's any question.

The bigger issue is to what guidance or what recommendations we might provide to industry for botanicals, just in general, dealing with botanicals, the kind of data that we'd like to get from them, and so on. That's also under discussion among the staff. So we're looking at that (inaudible).

DR. HILL: In that case, I assume, with the SSC, and anybody else who's interested in making sure that, you know, that they get -- if something like that emerges, that they get something useful.

DR. SLAGA: Well, one of the main points we discussed was to make sure that we understood

that multiple botanical ingredients can be in one formulation, and that we should deal with that, and how that will even also relate to stuff in the food that may, from a botanical, that we're looking at the total amount, so that you know, we don't fine something that's going to come up and bite us later.

DR. MARKS: So, I think that was captured really well in the abstract.

DR. SLAGA: Yes, that part was.

DR. MARKS: The abstract really very clearly states that concern. And then, of course, the guidance for discussion is a very -- you know, this specific example, that one, so on and so forth, how you handle it in the discussion and such.

Heavy metal -- this comes up because I got the article on lipstick sent to me by a local ABC news reporter -- what are the heavy metals?

Now, we addressed three heavy metals. Is that the only heavy metals in the boilerplate, lead -- I forget --

DR. BERGFELD: Arsenic.

DR. MARKS: -- arsenic, and -- there was one other, I thought. Is that the definition of what "heavy metals" are?

DR. BRESLAWEC: Mercury.

DR. MARKS: Yes. So, do we need to be more specific, in terms of -- or is that the only three heavy metals? Is that a definition of what a heavy metal is, those three?

SPEAKER: No.

DR. MARKS: No -- that's what I kind of thought. But, just as a -- I know it's not -- well, it is relevant to the plan boilerplate, but it kind of, when I looked back, I said, okay, what are the heavy metals that we're dealing with? And there are three. So is that --

DR. BOYER: And those are the three major ones, when you talk about environmental exposures. Cadmium is also sometimes discussed, although I think rarely in the context of personal care products.

DR. MARKS: In that article, cadmium was

mentioned.

DR. BOYER: It was mentioned?

DR. MARKS: Yes, that's why I started, "Okay, which of these metals are really the heavy metals?" And when you look at the boilerplate, there are just three that we address.

So, that opens up a whole different sort of discussion, but I don't know whether the heavy metal boilerplate, do we want to be -- it's certainly in the body of what it is, those three heavy metals.

DR. HILL: Well, at some point, it may be necessary to actually put together a document that addresses that. Because, I mean, we can in things like chromium, well, then that's highly dependent on oxidation state. But then there are possibilities of microbial transformation.

Up until recently, I would have completely written off copper from that list, but now there's a literature emerging for copper in neurodegenerative disorders. So I don't think that's much related to cosmetic ingredients --

although --

DR. MARKS: So --

DR. HILL: So the point is, at some point we may need to, somebody may -- well, somebody's bound to be reviewing. Maybe we just need a list of reviews, recent, that have addressed this nicely, and thoroughly, in the light of current science, or something like that.

DR. MARKS: So, Ivan, just -- so you're aware of it?

DR. BOYER: Yes.

DR. MARKS: Let's get back. That was a sort of a diversion from this botanical boilerplate.

So, I didn't hear any -- Tom, other than your concern that it was somewhat, perhaps, vague. I think the abstract really synthesizes what the concern is.

DR. SLAGA: Yes, that's the --

DR. MARKS: And then the rest of it is, as you have here, "guidance." And is, as you said it, the guidance really becomes very specific to

the botanical, and what's the constituent one's concerned about.

DR. SHANK: It depends. If this is a boilerplate, that's entirely different than if it's a framework guide.

DR. MARKS: Okay.

DR. SHANK: Okay? So, I read it as more a guide to us: When we handle botanicals, make sure we get these issues considered, and whatever's relevant, put into a report; that this would not be a cut-and-paste into every report.

DR. MARKS: Okay. I think as long as -- then we could change the title from "boilerplate," so the semantics are not confused, into "guidance." Although I think the abstract's going to be pretty much a cut-and-paste.

Any other comments? Halyna.

DR. BRESLAWEC: Yes, I agree with everything you all have said about "guidance" versus "boilerplate." We have some suggested modifications on the abstract -- "Because formulations may contain more than one botanical

ingredient, caution was urged to avoid reaching levels of toxicity for constituents." And what this does is try to make clear whether you're talking about botanicals themselves, and then the constituents in there.

And then "Industry should use good manufacturing practice to limit impurities."

But in terms of the discussion, I think what you did is you proposed a boilerplate, kind of a suggestion for how the discussion should handle impurities. And we think that there are three elements there. The first would be a statement of what the issue is -- you know, multiple sources of constituents from botanicals.

The second would be a discussion of the specific cases in that, or the specific circumstance, in that particular report.

And the third thing that you'd want to hit is: Was a level set. And if so, how? Did you use a TTC approach, or a different approach?

So those would be the three elements that I think would be useful, we think it would be

useful, to see in a discussion where this issue comes up.

DR. MARKS: So, there will be -- Rachel. Thank you.

MS. WEINTRAUB: I had some edits. So, I think some of the language could be edited a bit further, throughout.

DR. MARKS: Mm-hmm.

MS. WEINTRAUB: So, I'll share my edits with you about the particular sentences I'm talking about. But I think it could use another edit to make some of the language more concise. Some of it is a bit repetitive.

So, a broader edit for conciseness, I think, would be a good step.

DR. MARKS: So, my sense is that we're going to change the semantics to "this is a guiding document." And there's a number of editorial comments. And I think probably we should look at this again, in the future.

Rons, Tom, does that sound -- We'll see what the Belsito team suggests tomorrow. But, so

-- okay. So this is going to be a guiding document, and see it again.

MS. BECKER: You'll notice that the title of the document is "Botanical Abstract Discussion Framework," and not "boilerplate."

DR. MARKS: Yes.

MS. BECKER: "Boilerplate" is just a shorthand for the itinerary.

DR. MARKS: Yes. Exactly. Well, actually, in Lillian and your memo, it says "draft boilerplate." So it will be "draft guidance for botanical ingredients" in the next memo.

"Guiding document," see again with editorial -- it will be interesting tomorrow to see the Belsito's team comments, because it was Don Belsito who actually wanted to see this sort of consideration addressed. Okay.

So, we'd like to -- and we could see it again as a formal agenda item, which I think is best, rather than seeing it again when we get a botanical in the future, and then kind of go back. I think it's worthwhile just looking at the

guiding document, as I'll refer to it, as an independent agenda item.

Any other comments? Okay, if not -- the next is the PEG and PPG ethers. And this is a final report. So, there are 131 ingredients. This is the final report. And our conclusion from the June meeting, in which a draft final was issued, was that these ingredients are safe when formulated to be non-irritating.

Any comments? Ron, Ron, and Tom?

DR. SLAGA: Very nice report.

DR. MARKS: Welcome, Monice.

MS. FIUME: Thank you.

DR. MARKS: Lillian was getting tired, so she moved on. Okay.

Now, where is this? Any other comments? "Safe." Very nice report.

Doesn't sound like there's any comments at all. So, if that's the case, I presume tomorrow I'll be seconding a "safe when formulated to be non-irritating," and we'll dispense with the alkyl PEG, and PPG, proplylene glycol ethers.

Okay. That was easy, wasn't it, Monice?

Okay, next one is the sulfosuccinates. And this is a final amended report. This, again, "safe...to be non- irritating." Let me pull that up.

There are eight ingredients. This, again, we have an amended safety assessment. And the conclusion is "safe when formulated to be non-irritating." And we would be at the stage of issuing a final amended safety assessment.

Any comments?

DR. HILL: No, I don't think so. But, just a second.

DR. SHANK: Looks good as is.

DR. MARKS: Okay. Monice --

DR. HILL: Just --

DR. MARKS: "Safe when formulated to be non- irritating." So, let me find that.

DR. HILL: This is really a dictionary thing, and not a -- is that that name as written, for "diethylhexyl," it should probably be "di(ethylhexyl)," because otherwise it could be

diethylhexyl. It's really a poorly selected dictionary name -- FYI.

MS. EISENMANN: It used to be "dioctyl," so I think they've improved on that one.

DR. HILL: Maybe. Maybe. It just jumped to me, because it was really the lead ingredient for this when we reopened it.

DR. MARKS: Okay. Next are the rosemary-derived ingredients, rosmarinus oficinalis. And this is the first review of these 12 ingredients -- they're GRAS.

So, Rons and Tom, I guess, let's first -- shall we look at the ingredients? Are they all okay?

DR. SHANK: Well, I have here to remove rosmarinic acid.

DR. MARKS: Yes, that's the question that counsel -- if we look at Monice's memo, in the second paragraph, the counsel asked for explanations as to why rosmarinic acid is included.

DR. SHANK: It's a component of the

plant, but not of the cosmetic ingredient extracts. So I think that can be deleted.

MS. FIUME: Dr. Shank, it is a cosmetic ingredient --

DR. SHANK: Oh --

MS. FIUME: -- in and of itself.

DR. SHANK: By itself.

MS. FIUME: And it is also a component. So, in the past, corn acid, coconut acid, we have, there has been precedent for including the acid. But I do want to see what you think, if it fits into this family.

DR. MARKS: So, as you mentioned, Monice, there's also --

DR. SHANK: So, the other acids, we include with the extracts? Or the other acids were reviewed separately, that you're talking about?

MS. FIUME: Most of them were included with the extracts or the oils. Whatever that family was --

DR. SHANK: Was.

MS. FIUME: Whatever the corn report was, it did have corn acid in it.

DR. SHANK: Oh, in the extract report.

MS. FIUME: Let me check coconut acid.

MS. EISENMANN: But that acid is for the fatty acids from corn oil. That's not like -- rosmarinic acid is a -- I don't what the -- I think it's a triterpene?

DR. MARKS: Yes.

MS. EISENMANN: So, if it's a -- I think it's a little bit, it's not --

DR. SHANK: So when you say "corn acid," you mean "corn fatty acids."

MS. EISENMANN: That's what they are, yes.

DR. SHANK: Okay. That's different.

DR. MARKS: So the counsel (inaudible) -- are you going to talk about the diterpenes, or reviewing them first?

DR. BRESLAWEC: No, no, no. We simply want the panel to have this discussion.

DR. MARKS: Right.

DR. BRESLAWEC: You know, if you're going to review something like rosemary-derived ingredients, do you also include components -- rosmarinic acid, or solic acid.

MS. EISENMANN: Well, what struck me is that this is one of the rare times where the industry has come out and said "we normalize this to carnosic acid and carnosol. Well, carnosic acid is also a cosmetic ingredient, and it's very structurally similar to rosmarinic acid. So why pick rosmarinic and not carnosic? I don't know the answer.

So that's why I thought maybe you wanted to -- I mean, like for licorice, what you did there is you reviewed the components of licorice first, and then you reviewed the mixtures.

So I just thought maybe you should develop some kind of a policy on when do you include a component. I mean, it's getting to be more and more components are in the dictionary. When do you review a component, versus a mixture? It didn't come up until I saw that, you know, that

carnosic acid is being used to normalize these extracts.

DR. SHANK: Okay. So, let -- rosmarinic acid itself is an ingredient.

MS. FIUME: It is an ingredient. I think --

MS. EISENMANN: So is carnosic. I mean, there are other similar compounds that are in the dictionary that could be cosmetic ingredients. I don't think there's any uses of some of them, but that's -- when you pick one and not the other, I just thought you should discuss it.

DR. HILL: Right -- if rosmarinic acid is not showing up in here as a significant constituent in any of the extracts, then it doesn't, to me, make sense to be lumping it together with these extracts. On the other hand, if carnosic acid is showing up -- which it is -- as a significant constituent, and is even being used to normalize it, then we're going to put something in here that would certainly be more sensical. But whether we want to do that or not,

that seems to be a more philosophical question.

To me, if these extracts are often being standardized on that ingredient, then that ingredient should be reviewed, separately reviewed. It can go through roughly at the same time, and then you can at least reference back to that in the appropriate sports, in terms of the plant extracts.

But that's just the way I see it.

DR. MARKS: So, let's take carnosic as an example. How many different botanicals would that be found in? What would you guess? A lot?

MS. FIUME: It's hard to tell. And the problem with these botanicals is, as we go through the published information -- because, often -- now, we did get information from industry that talks specifically to carnosic acid and carnosol, but from our standpoint, we don't know if that's being standardized to that, because it's being listed as antioxidant. And is that becoming a claim information, or is that relating directly to cosmetic safety?

So that's one of the issues we have as writers, because we don't want to put claim information in the safety evaluation that needs to reflect cosmetic safety.

And as we go through these botanicals -- currently we're writing a report on citrus ingredients, and the number of constituents is incredible. It's probably about 10 pages long right now. So, if we're not getting, searching the published literature for the constituent information, it depends on where it was grown, and what time of year it was grown, how much it rained that year --

DR. HILL: Of course it does. It does.

MS. FIUME: Right. So, if we're not being given constituent information each time, on the cosmetic ingredient, it becomes very difficult for us. We start searching for a needle in the haystack in writing reports on chlorogenic acid, carnosic acid, ursolic acid. It becomes a report on constituents that may be in those botanicals, rather than the botanicals themselves.

As we go through this, we're thinking, okay, so the safety -- on many of these, because their GRAS ingredients, and they can be eaten in the ingestion isn't the concern. It's the irritation and sensitization. Is it something you look at as "Is it an irritant, is it a sensitizer, that cosmetic ingredient, as in formulation?"

So, as writers, we are also struggling with the best approach for these botanicals because of all these uncertainties.

DR. HILL: I take issue with what you just said. Just because something is GRAS, doesn't mean that that captures the toxicology if you smear it on your skin.

MS. FIUME: No, I agree.

DR. HILL: Because if you have a component that's present at relatively low levels -- I mean, our digestive tracts are engineered to respond to the -- "respond" is the wrong word, deal with the presence of some of these things.

Our skin may or may not be.

DR. SLAGA: It's one of the barriers.

DR. HILL: It's a barrier, and that's why the barrier is there. But there are some of these that can be extremely well dermally absorbed. I mean, we get poison ivy -- I mean, I can't even walk down the street from poison ivy, or I've got a problem. So that's just one example of the result of a constituent in a plant.

And what you said is exactly to the point. If somebody were going to study the toxicology of something that is fundamentally a complex mixture, we need to know, when we read across, even from things from the same plant, is that study, toxicologically relevant to the thing we're reading across to?

So, if you don't normalize to constituents of interest in terms of how much is there in the first place and, secondly, known biological effects, well, how do you base any read-across decisions?

I mean, you have to get at that issue. And I don't think it needs to be a needle in the haystack, because you're talking about things that

are present at a high concentration, or are known to be sensitizers or allergens.

And that list is much shorter. That doesn't mean there couldn't come up something that we don't know, but odds are, you know, that will be found by people using something out there, and we're having a lot of incidences. And probably nobody dies from that. And so -- but we'll become aware of a new sensitizer, the more and more these botanicals get used.

But I think it's like any clinical study for a drug use of a botanical. You've got to standardize on something. One that's on my mind, for example, is echinacea. It's probable that people have been standardizing on the wrong thing or things. There's science going on, actually, at our institution that's showing that pretty nicely.

So, I mean, just because you're standardized on something doesn't mean you know what you're doing. But at least it has some -- if you capture those major things, and you capture the known bad actors, and you capture the known

things that are doing something, then you can get a sense of if we study -- if we have a toxicological result on this particular extract, how relevant it is to those other things.

So, here we have a flower extract that's aqueous, that's clearly not going to be relevant to an oil extract. CO-2 extract, which we see in a couple of these is something different yet. We have to know.

You do a bit of toxicology results, is that relevant in the read-across? And how in the hell you should you get at that?

But in this particular case, if they're standardizing on that one component, I don't -- I think that suggests that there's at least thinking that that's important, and provide some way of getting some consistency with botanicals. That's probably about the best one can do until we are a little more sophisticated.

But the better mass-specs get, and the better we can do analytics that do pattern recognition, I think the better that will come.

I don't think "antioxidant" is a therapeutic claim, is it?

DR. SHANK: It could be a preservative --

DR. HILL: -- I mean, no, I don't think it is, you know.

DR. MARKS: So, let's get back to this report, and the specifics, whether or not we deal with, in this case, the botanical in a mixture as is, that we have -- you had suggested, Ron Shank, to take out -- we have some other acids. We talked about carnosic. There's also oleanolic, there's caffeic -- acids which Lillian Gill, the Director, mentioned in her memo to me. The counsel had concerns about that, and whether or not diterpene should be reviewed first.

So, I think the approach -- we have to make a decision, do we move ahead with botanicals mentioned in here, minus the acids, or do we do the acids separately? Do we do the acids first? The diterpene?

So, what -- team members, how would you

like to proceed? Would you like to proceed with this as the botanical, remove the acid, and then we can save the acids for another day? Because I guess the question is, what needs -- if we remove the acid, what needs do we have for this mixture of ingredients, since that's not -- mixture of components in these rosemary ingredients?

DR. SLAGA: Well, I agree with Ron Shank. I think we should take it out, because there are other acids that are extremely important in this mixture. And all we're doing is highlighting one particular acid where there's other acids that could be more -- I'll pick out ursolic acid, just for comparison. And so, you know, we're dealing with botanical extracts. And I think we should deal with the total extract, regardless what's in them.

DR. BERGFELD: So you're really talking about only mixtures here.

DR. SLAGA: Right.

DR. MARKS: So, deal only with the extracts -- botanical extracts.

DR. SLAGA: Or we should highlight other acids, since --

DR. BERGFELD: We have oils, too, and they are considered -- extracts, and also powder?

DR. MARKS: Okay. So, remove the acid, deal only with the botanical extracts, the mixtures in this report. The acids would be in a separate report.

DR. SHANK: Just, as a --

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

DR. SHANK: -- an aside, if you include specific acids, these are not GRAS ingredients necessarily. And that changes our focus.

If these are GRAS food additives, then our need for extensive systemic toxicology data -- right? -- goes away. All right? And we can focus on skin.

But now, if you add non-GRAS components, then we have to have a different data set.

So, I think it's a good idea to separate out acids which are known not to be components of

the cosmetic extract.

DR. MARKS: Ron, do I understand -- they aren't "known" to be components? Of if they are, they're not enough to rise to a toxicologic level, since they're GRAS, in the mixture? Because they are components, are they not?

It's just they are --

DR. SHANK: They're components, okay. But to include a component of the plant, which is known not to be a component of the cosmetic ingredient that we're considering, toxicologically, it's easy to separate out those components which are -- plants components which are not components of the cosmetic ingredient.

DR. MARKS: So, so far, what I -- if I hear the team correctly, we will deal just with the mixtures, in this report. We'll remove rosmarinic acid. We'll deal with the acids in a separate report in the future.

And then, now the question is this -- do we need anything else from me?

The oil was okay. That's on page 18.

But I wanted to see an HRIPT for leaf extract at 10 percent.

So I would issue an Insufficient Data Notice.

DR. HILL: So, what leapt out at me is, we have very little chronic toxicology on the leave oil. And it only is oral. And it only is three weeks' gavage in Swiss Albino mice. And there is no repro-tox. And in terms of possibility of getting something in by the dermal route, surely the things that are in the oil are much more likely than in these other extracts -- unless I'm missing something.

So, I wanted to see, really, repro-tox for the oil, delivered by a dermal route.

DR. MARKS: Ron Shank?

DR. HILL: Which is a big request, I realize.

DR. MARKS: Yes. Again, everything we say, at least at this stage, would be an Insufficient Data Notice.

But, Ron Shank, did you have -- I have

"Question pregnancy" on page 19 of the report.

DR. SHANK: Under "human," I think we need to expand that, and know why the PDR says that rosemary preparations -- that's rather general -- shouldn't be used during pregnancy. I think that needs to be expanded, as to what they had in mind.

DR. MARKS: Monice, did you have anything more?

MS. FIUME: I'm sorry -- what? On the --

DR. SHANK: On page 19 -- no, 16, at the very bottom of the "Human" -- "Reproductive and Developmental Toxicolocy," it says "Human." And then, "According to the PDR...rosemary preparations should not be used as a drug during pregnancy." And then there's no mor information.

So I think we need to know why the PDR makes that recommendation.

DR. MARKS: That's Physician Drug Reference? PDR?

DR. SHANK: Yes.

DR. HILL: But for herbal medicines. It's not the standard PDR.

DR. MARKS: Right. Well, that's still --

DR. HILL: But it's still --

DR. MARKS: Herbal.

DR. HILL: Mm-hmm.

DR. SHANK: They had something in mind.

DR. MARKS: So that would be an "insufficient data" also, "Why is that?"

So, I think Ron Hill, it reinforces your concern about pregnancy.

DR. HILL: Well, I don't know if it does or it doesn't, I guess, in this. But I did notice that, and I didn't get a chance to consult with our in-house expert on that subject --

DR. BERGFELD: It says --

DR. HILL: -- before I came.

DR. BERGFELD: -- under "Toxicology," that in the rat model, it decreases fertility.

DR. HILL: That's there.

DR. SHANK: And there is a dose-response

relationship there.

DR. BERGFELD: So, because there's no "human" on that --

DR. SHANK: Yes, that's rat data.

DR. BERGFELD: Yes.

DR. SHANK: But apparently there are human data.

DR. HILL: Something resulted in that --

DR. SHANK: Something caught to the attention of the committee that wrote that part of the PDR.

MS. FIUME: In reviewing this information -- and this is something that would be great to have guidance on from the panel -- is that the rosemary teas, or the very strong rosemary preparations, from what I found in reviewing botanical -- the folk medicine, the herbal guidelines -- is that it could be an abortifacient, and it's not recommended for pregnant women to drink rosemary teas.

Now, like I said, that is from herbal books. And that's the problem with the

botanicals, it's -- you know, you have to be very careful as to what you're discerning. I took it from these two references that that's something that you would prefer not to have in the report? Because, they're looking at drinking the herbal tea, versus what you would be putting on the skin.

I'm happy to take it out. I didn't want to not put it in, and then have someone say "You haven't talked about this."

So I'd rather put it in, and then if the panel decides that they would just prefer not to have that in there because it really does not refer to the cosmetic use of the ingredient, I'd be happy with doing that.

DR. SHANK: I think you should leave it in. Good -- it's good that you put it in. I just think it needs to be expanded. And exactly what you say, is this would be at an exposure that would be not reached in cosmetic use.

DR. HILL: And I would question whether we know that for sure, because I'm looking at leave-on concentrations of 10 percent. And,

again, I say there are components, especially in oils, that are probably going to get into the system better through the skin. I'm thinking of somebody smearing something all over their skin in a leave-on -- you know, large body surface area exposed, repeatedly, over some period of time. I'm not sure we're confident to say that the exposure would be less than drinking the strong tea, of whatever ingredients might be the cause of the abortifacient activity -- if, in fact, that's true.

DR. SLAGA: I guess I don't understand. Because it's an oil base, why it would be absorbed in the skin more than the intestine?

DR. HILL: Because oils diffuse through the skin. They're lipophilic, and they can reach the --

DR. SLAGA: Well, lipophilics can go through the digestive tract, too. I don't -- that's the point I'm getting at.

DR. HILL: But we have liver enzymes designed to --

DR. SLAGA: Or the respiratory tract.

DR. HILL: We have liver enzymes designed to take those things out, through millions of years, probably, of evolution in the digestive tract. Whereas I doubt that we've evolved to respond to things we might smear on at 10 percent, over a wide body surface area. And I just --

DR. SLAGA: If you look at all the portals of entry into the body, sure, they don't have the amount of enzymes you have in the liver, but they do have enzyme levels to help detoxify, just as the liver does.

DR. HILL: Of course they do, but it doesn't always get them. That's why transdermal delivery systems work. That's why we have numerous marketed products that make use of transdermal delivery, that really don't have anything magical in there to allow those things to penetrate the skin, it's just if you have enough potency.

And the bottom line is, we have

first-pass effect in the gut, both microbial gut wall enzymes, liver enzymes, and even digestive enzymes, that we don't have in the skin.

DR. SLAGA: But if you look at, in the digestive tract, you would have a larger volume of things --

DR. HILL: But it all goes to --

DR. SLAGA: -- oil based, to what --

DR. HILL: -- but it all goes to the liver. So, unless you give whopping, huge doses, you don't swamp those systems.

DR. MARKS: Okay. So, let's come back a bit. I would suggest an Insufficient Data Notice. What I have right now are: Why rosemary should not be used in pregnancy, that's mentioned in the PDR Herbal. And let's try and clarify that.

We would remove rosmarinic acid, deal with only the botanical extracts, in this report. The acids would be in a separate report.

And the third thing is the HRIPT for the leaf extract at 10 percent.

DR. HILL: I have one more. Okay,

that's why I wanted to summarize.

DR. MARKS: And then I also want to bring up -- so, go ahead, Ron Hill. What was the other? Is that -- team, do those three things, so far, sound good to you? Ron, Ron, and Tom -- those three things? Okay.

So, Ron Hill, what's the next thing that you --

DR. HILL: The other one was just a manufacturing question, and it goes to what things might be generated by the processes of deodorizing, which are not described. In other words, when they deodorized -- which is mentioned in at least two of these extracts -- what exactly is it that they're doing? What compounds might result, or -- if I know the process, then I can conjecture, based on what's present in the plant. But --

DR. MARKS: Interesting. Ron Shank --

DR. BRESLAWEC: I'm sorry, could you just repeat that?

DR. HILL: Yes. The question is, in the processes of preparing a couple of these abstracts

-- I can give you the specific ones, but all you have to do is search on "deodorize" -- the question is, what is the chemistry involved? What are they actually doing to deodorize in those particular extracts?

And it goes to the issue are they generating any compounds of potential toxicological concern. You know, like when you whiten paper, for example, you're generated chlorinated biphenyls. And I'm not suggesting that's what happens here, but I'd like a little more information about what that process entails -- without somebody giving away what's in their patent, you know, roughly, what are they doing -- if we can get it.

DR. MARKS: So, what page is that?

DR. HILL: Probably in a couple of the tables. I can search it if you want to know.

DR. MARKS: So, Ron Shank, Tom, was this deodorizing step in the manufacturing a concern to you? Or is there enough in this section? Where is the manufacturing section? What page is that?

DR. HILL: I'm not even sure it shows up in the "manufacturing." I think it does. But it was in a couple of the tables that describe something about the processes by which these abstracts are prepared.

I'll just search "deod," and then I should be able to find that in just a second.

DR. MARKS: Do you remember --

MS. FIUME: I'm sorry, I'm in my WORD version. Let me look -- under "Preparation and extraction" --

DR. HILL: "Preparation and extraction," it shows up three times. And then --

DR. MARKS: What page is that?

DR. HILL: PDF page 10. PDF page 10.

DR. MARKS: Okay. So --

DR. HILL: It shows up again in the "Constituents/Impurities" in the -- one, two, three -- fourth paragraph down.

DR. MARKS: That's okay, let's go back to Ron Shank and Tom. Are you equally intrigued as to what does "deodorized" mean? "Deodorized,

decolorized, and standardized using diluents and carriers that are permitted in foods," is the last sentence of that first paragraph under Preparation and Extraction."

DR. HILL: Table 6 is the other place, by the way, where this is mentioned a couple of times.

MS. EISENMANN: Those references to USP in the European Food Safety Authority. So it must be pretty standard methods.

DR. HILL: I'm assuming they're widely used processes. I have just -- I know nothing about it, and I'd like to know, in this particular case, if it's applied to these extracts, what sorts of things might be happening?

DR. SLAGA: I didn't have a concern with the deodorizing.

DR. MARKS: Okay. I'll just note that, then, under -- and, Ron Hill, I'll associate --

DR. HILL: That's fine. Put it out there.

DR. MARKS: -- your name. And I'll just

put -- we'll find out what comes out of that. But that doesn't sound like that's a deal-breaker, as far as an Insufficient Data Notice, if we don't get that data.

DR. HILL: It's also in Table 7. I said Table 6, I also see it in Table 7 several times.

DR. MARKS: Okay. "What is 'deodorized'?"

DR. HILL: It sounds like a Jeopardy question.

DR. MARKS: Any other needs? So it's used in baby -- there's baby and inhalation exposure. Does that raise any concerns? Obviously, for inhalation, we'll just put the inhalation boilerplate, I presume.

Baby exposure? Any concerns about that? No -- other than what we've put.

So does it sound -- tomorrow, again, I'll repeat myself, our team would recommend an Insufficient Data Notice, and with the HRIPT of the leaf extract why is rosemary not recommended in pregnancy? Remove the rosmarinic acid. And

then, potentially, clarify a bit on the manufacturing, what is "deodorize"?

Any other needs? Does that sound like a proper way to move forward?

DR. BERGFELD: Could I ask a question? The acid that will be deleted is mentioned all through the text.

DR. MARKS: Yes.

DR. BERGFELD: Are you taking it out, or leaving it in? Leaving it in, or taking it out?

DR. SLAGA: I would take it out.

DR. BERGFELD: And then there's mention of phototoxicity. How did you all feel about that? There were some photox testing -- the rat --

DR. SHANK: What page was that, please?

DR. HILL: I had a note that there wasn't any phototox done on the oil, but I wasn't sure, based on what's in it, that there was any need to do that. So --

DR. MARKS: Right -- which page are you, Wilma? I didn't pick out that.

DR. BERGFELD: I'm on 11, but I'm not sure how you're translating that. It has to do -- I think it's -- let me see if it's under this --

DR. SHANK: Oh, Report page 11?

DR. BERGFELD: Yes -- under the "Summary." I --

DR. MARKS: What is the PDF number? 11, for me, brings up the "steam distillation." Preparation extracts.

On the PDF, what page would that be? Let me see if I put it in --

DR. BERGFELD: It's also in the table.

DR. SHANK: It would be page 20.

MS. FIUME: 18 of the PDF. Page 18 on that is the first reference to phototoxicity (inaudible) extract.

I'm sorry -- PDF page 18.

DR. MARKS: It's the leaf -- "weak irritants," "phototoxicity" -- "None of the extracts were phototoxic." That was under was under -- that's the first study.

So I took that -- that's under 10

joules, which is a proper amount of UVA, 75 percent of the MED. So I thought that was okay. And I used that as the --

DR. BERGFELD: I saw that, too, but there was mention in the body of the document something about phototox, where it was positive -- or questionably positive.

I don't have it listed like you do.

DR. MARKS: Let me see here.

MS. FIUME: I believe it's Table 13.

DR. MARKS: And what page is that?

MS. FIUME: I'm looking.

DR. MARKS: Okay.

MS. FIUME: Is it that Adobe package you're using?

DR. MARKS: Yes.

DR. BERGFELD: Okay.

DR. MARKS: But it still should be the same page in the document. Yes, I'm using Adobe Pro, and they say --

So, which table did you say, Monice?

MS. FIUME: 13.

DR. MARKS: 13 -- so that -- let's see, where am I? Table 8 is the "Use."

DR. BERGFELD: So, you have pickled rosemary leaves. They had photo patch-testing reactions.

MS. FIUME: Page 49 of the PDF.

DR. MARKS: 49.

MS. FIUME: These are case studies.

DR. MARKS: Yes, that's --

MS. FIUME: Irritation, sensitization, and photo reactions.

DR. MARKS: Yes, I guess how I approach case studies is, if I see a cluster of a number of them, then I get really concerned. If I see one or two, it doesn't surprise me. I put much more weight on the photo-testing that was done in the body.

DR. BERGFELD: I just -- I don't know anything about the chemistry, specifically about the UV-spectra analysis of any of these. But you suspect them to have anything?

DR. MARKS: No.

DR. BERGFELD: Okay.

DR. MARKS: And it's not something that, in my mind, comes up as a phototoxic plant, in practice. So I wasn't concerned about it.

DR. BERGFELD: Okay.

DR. MARKS: From a phototoxic -- thanks.

DR. BERGFELD: It was questionable.

DR. MARKS: Thanks, Wilma. Any other comments? Okay. So we'll see, tomorrow, how the Belsito team --

So, Insufficient Data Notice. Okay. Let's see --

DR. HILL: Dr. Marks, can we have a five-minute break?

DR. MARKS: Sure. Absolutely. It's 10:21. We'll reconfigure at 10:30. That's eight minutes.

DR. HILL: That's beautiful. Thank you.

DR. MARKS: Okay. You're welcome.

(Recess)

DR. MARKS: Shall we restart? We're to the draft final report on methyl glucose

polyethers and Esters; is that correct?

SPEAKER: Uh-huh.

DR. MARKS: Â Post break, at the June meeting, we issued a tentative report with a conclusion as safe. They were some comments on this report from the counsel, this is listed on the memo, by Wilbur. Where's Wilbur?

MS. FIUME: He is still under review in the other team.

DR. MARKS: He's under review? Laughter) I'm surprised he doesn't want to come here, then.

MS. FIUME: His reports are still being reviewed with the team.

DR. MARKS: Okay. At any rate, there were 25 ingredients. Ron, Tom, actually, I think most of the comments from the counsel, Ron Shank and Ron Hill, your comments about that; is there any reason we shouldn't proceed with a final report with a safe conclusion?

DR. SHANK: No, safe.

DR. SLAGA: Safe.

DR. MARKS: Safe, okay.

DR. HILL: I think those comments happened because the weeding wasn't done after the new data came in completely enough. That was my impression, that there were gremlins left over from, what do I want to call it, things that weren't removed upon the basis of the presence of the new data, so reworded or changed.

MS. EISENMANN: One thing that still needs to be corrected is in Table 5, the Lubrizol data. They provide the percent active for all of their trade name materials, and a number of them are 100 percent, and one is 70 percent, and it's in the new comments. So that still has to be filled in, there's a blank for a number of them, and that may affect in the text when you say the material is tested undiluted, but it was 70 percent active. So that type of information might be more helpful in the text rather than referring it back to the Table.

DR. MARKS: So, Monice, you'll get, that, I look at as significant, but editorial

comments in the report. Any other comments?

DR. SHANK: Yes. We have, in the discussion, the first paragraph, and then below it a revised paragraph; I recommend we delete the first paragraph that starts with no, and use the revision as the first paragraph.

DR. HILL: Discussion?

DR. SHANK: Discussion, PDF page 35.

DR. MARKS: Right, use the revised paragraph. Okay. Any other comments?

DR. HILL: Actually, I ditto what he just said.

DR. MARKS: Okay. So, tomorrow morning, I'll move the methyl glucose, polyethers and Esters are safe in the present practices of use in concentration, and then a final report be issued with this conclusion. And, Ron Shank, do you want to mention that discussion point more, or is that -- I'll leave it up to you. Wilma will be asking if there are any discussant points if you want to mention that, that will be fine.

DR. SHANK: Okay.

DR. MARKS: A revised. Okay. Polyquats, another final report. So, in the June meeting, we issued a tentative safety assessment with a conclusion of Polyquaternium22 and 39 are safe. And are there any editorial comments, any concerns with that final conclusion? Ron Shank?

DR. SHANK: I don't have a problem with the conclusion. On page 20, PDF page 20, at the top in Figure 1, we have the acronym DADMAC, DADMAC, and I'd like the chemist to explain to me how that agrees with the name of this chemical.

DR. HILL: That would be the name of the monomer that was used.

DR. MARKS: Okay.

DR. HILL: So you don't see the diallyl anymore, because in the polymerization process, that's where the double-bonded grips on the allyl substituents on that Pyrrolidine Ring react. So it's the two wings at the top that were part of the allyl substituents, and that's the diallyl, the Dimethyl, the NN Dimethyl, and because it's quaternary, you call that an Ammonium center.

DR. SHANK: I get that, but diallyl --
DR. HILL: Yeah, it's the --
DR. SHANK: -- doesn't seem correct.
DR. HILL: So when you see the CH2s that are up there at the top, those are coming from the allyl group.
DR. SHANK: Yes.
DR. HILL: Now, whether the brackets are in the right spot --
DR. SHANK: Okay. No, it's in the first line, the Figure 1, it says DADMAC --
DR. HILL: Yeah.
DR. SHANK: -- is Diallyldimethylammonuim Chloride, and I don't think DADMAC is.
DR. HILL: DADMAC isn't diall -- that's the monomer that goes into the polymerization, isn't it? Yes. So it may be that we're not showing enough of the, the brackets are in the wrong place, this may be the problem, here, because the monomer should include two carbons.
DR. MARKS: Bart, I'm going to let you

arm wrestle with Ron Shanks, and --

DR. SHANK: Okay.

MR. HELDRETH: There should be --

DR. SHANK: You guys are chemists, you can fight it out --

DR. HILL: Are you catching what I'm saying that the brackets might not be capturing --

MR. HELDRETH: There should be an extra CH2 inside the bracket.

DR. HILL: Exactly.

MR. HELDRETH: But the monomer is correct, it's just maybe it's not represented perfectly as a residue within the polymer. But --

DR. HILL: And I --

DR. SHANK: In the structure that says DADMAC, there's no diallyl moiety.

MR. HELDRETH: Well, to the same extent, there's no acrylic acid in the other residue, it's just -- if you look to polymer nomenclature, you're always using the monomers in the name.

DR. SHANK: Okay.

MR. HELDRETH: So this is, although

maybe not accurate, but that's really acrylic acid in DADMAC, that is the traditional nomenclature behind polymers, this is the name of the monomer.

DR. SHANK: Okay. If you're happy with it, I'm happy with it.

DR. HILL: No, I'm thinking we're missing carbons in the bracket, and I kind of didn't catch that, because I knew exactly what should be there.

MR. HELDRETH: Right, that can be added in.

DR. HILL: Okay.

MR. HELDRETH: But the names for the monomers are appropriate.

DR. SHANK: Okay.

DR. MARKS: Any other comments, Ron Shank, that doesn't sub substantially change, obviously? Rachel, did you have a comment?

MS. WEINTRAUB: Yes, I did. My comment was to the panel to ask them if, in the discussion, they are satisfied with how the text explains the absence of data, and whether, since

the molecules are large, it's sufficient that there wasn't genotox, carcinogenicidian, reproductive and developmental tox data?

DR. MARKS: Which page are you on?

MS. WEINTRAUB: So this is PDF page 19, the second paragraph of the discussion.

DR. MARKS: Yeah, I think, for me, when I read that paragraph, the molecules would not be absorbed is the key issue in terms of not requiring the reproductive developmental.

DR. HILL: You could reword it to say it would not be bioavailable by any route of exposure. That would get, basically --

MR. SHANKS: So any systemic toxicology would be impossible, I guess that's --

DR. HILL: I'm overstating the case a little bit, but that's what we're trying to say.

DR. MARKS: And, Tom, does that also apply to you for the genotoxin carcinogenicity again, that it not be absorbed?

DR. SLAGA: No, no, you can have mammalian genotoxicity in cells in culture versus

also in whole animals, depending -- so it doesn't apply to mammalian cells in culture, so the sentence should be reworded, it creates a little additional work on --

DR. MARKS: How would you suggest that, Tom? Again, editorial. Maybe between now and tomorrow, Tom, Ron, could you give either Monice or Wilbur --

MS. FIUME: Can I ask -- I'm just reading this, and it's Wilbur's -- it's saying that all of the information is negative, so instead of having while and all those issues, just focus on the fact that all of that is negative, and therefore, we're not concerned because all of this is negative; is that correct?

DR. MARKS: Does that clarify that, Tom? Do you think Monice got --

DR. SLAGA: It's better than the way it is now.

DR. MARKS: Right. Okay. And then we have a sidebar -- are you still discussing chemical structure, here?

DR. HILL: We're on DADMAC again, I'm sorry. DADMAC -- we're having a sidebar on DADMAC.

DR. MARKS: Let's get back to Rachel's question, here.

DR. HILL: Maybe it needs to say from DADMAC.

DR. MARKS: So, Tom, it sounds like we clarify what -- and then you, Ron Hill, had given some other wording, as far as that second paragraph.

DR. HILL: That wasn't intended to be wording --

DR. MARKS: Right, okay.

DR. HILL: -- that was intended to sort of overstate the case, so then we could back off to get some sense of what needed to go there.

DR. MARKS: Ron Shanks --

DR. HILL: And I guess what I was driving at is, let's say we treated mammalian cells in culture, they might be able to engulf these polymeric substances and we might get some

effect, but basically, they can't reach the system by any route of exposure that we're using, here, in a way that would cause any toxicology. Even if the release low levels of monomers present, we're not going to get enough into the system in any route to cause a problem, I think.

DR. MARKS: It almost sounds, when I read the paragraph, it comes from a bunch of negatives, it should be reframed to a bunch of positives. Do we need to see that revision, Ron Shank knows.

DR. SHANK: No, I think it's perfectly clear.

DR. MARKS: Okay. Is that okay, Rachel, then?

MS. WEINTRAUB: Yes.

DR. MARKS: Thank you for bringing that up. Any other comments? So, Monice, you'll kind of tweak that a little bit.

MS. FIUME: Massage it.

DR. MARKS: Yes, massage it. Okay. So let me see, here. So, again -- and let's see who

has the polyquats tomorrow? Belsito. So, presumably, I'll be selecting a safe for these two ingredients for final report. Any other comments? So, let me see, chamomile, it's a tentative report. So, kind of context, this is the second time we've seen the report, although now what we have is Chamomilla Recutita -- how do you say that? German Chamomile split from Roman. And so, in this case, we have the Recutita -- is that how you say it?

DR. HILL: Latin, or would it be --

DR. MARKS: Any rate, we have, in June, we gave an insufficient notice, we wanted skin irritation sensitization data for the flower extract, the use concentration at 10 percent. And then, in the -- I have, in my notes, the new use concentration of the flower extract is 0.5 percent, that's page 49 --

MS. EISENMANN: Yes, that's correct.

DR. MARKS: Previously, it was 10 percent. So is this insufficient data notice incorrect, that we really don't need it for 10

percent?

MS. EISENMANN: There was, when I started going back and asking for high concentration, you know, they say we made a mistake, it's really slow. What they end up doing is giving me the concentration of the whole extract, and not just the part that's the plant, so they might be using a 10 percent of a trade name material that contains an extract.

DR. MARKS: Okay.

MS. EISENMANN: So frequently, these get revised down when they report that high.

DR. MARKS: So, the new use concentration is really 0.5 percent of the flower extract?

MS. EISENMANN: Correct. And I was able to find our IPT was in Wave 2 with 0.4 percent.

DR. MARKS: Yes. So my question is, is that going to be enough to -- it's very close, obviously. How many parts per million does that work out to be, the difference between -- what is 0.1 percent in parts per million, is that like

100, or what? Did you do the math on that, I didn't.

MR. HELDRETH: 1000.

DR. MARKS: 1000 ppm. So now the question is, certainly, if we were dealing with, like, methylisothiazolone, methylchloroisothiazolinone, a thousand ppm would be really significant. Is it with this extract with components of it which would be quite diluted. So, for me, the issue was do we issue a tentative report limiting it to 0.4 percent, which is the HRIPT, or do we just issue a safe, since it's so close to the 0.5? I could go either way. I don't think there's, even though it's a thousand ppm, I don't think it's going to make that much difference with a botanical extract.

DR. BERGFELD: You can put it in discussion.

DR. MARKS: Yeah, okay. So --

MR. HELDRETH: There is one concentration that's higher for the Chamomile Recutita extract that is not plant part specific,

it's 0.61, just to say.

DR. MARKS: Thank you. Which, you're on page, let me see, page 49?

MR. HELDRETH: Correct.

DR. MARKS: And let me take a look -- where are you looking, Bart, on that, because somehow I've got --

MR. HELDRETH: It's on --

DR. MARKS: It's probably --

MR. HELDRETH: Table 6.

DR. MARKS: It's --

MR. HELDRETH: 0.61 for dermal contact --

DR. MARKS: Oh, yes, I guess it's because it was just six uses, I tended to focus on the 966 uses of the flower extract, 0.5. So, again, I don't think, now we're talking about 2000 ppm, probably doesn't -- now, it is being used in baby products, I just wanted to, on that same page, 49, you see 26 baby products at a very low concentration, 0.0097, but I just wanted to be sure we had noted that as a team.

DR. BRESLAWEC: Yes, and that's a rinse-off.

DR. MARKS: Yeah, a rinse-off. Let me see, inhalation, there's some inhalation, so we can put that boilerplate. Discussion, okay, any other needs? I think we can move forward with a safe, then, to me, unless Ron, Ron or Tom, you'd have any other -- and I wanted to bring up azelene also, which is found on page 39 in the discussion.

DR. HILL: My comment, I guess it indirectly addresses that, which is that we have no chronic tox data on most of these, and only oral on the flower and flower extract chronic tox. So the whole thing, I still don't have a problem with the conclusion, but I think the discussion needs to be very clear, and we're getting there the way it is now, that the whole thing rests on the fact that the concentrations, in general, of use or low, the leave on concentrations of use are quite low, and that's what provides with plenty margin of safety. I haven't stated that in a way that, I wouldn't want it captured directly that

way, but that's the jist of it, the assessment of safety rests on the fact that overall use concentrations are quite low, leave on concentrations are even lower.

DR. BRESLAWEC: Dr.Â Marks, Dr.Â Hill, I would just like to elaborate that this follows the approach that the panel seems to have adopted for botanicals, not because there's so little, but because, initially, you're looking at products that are used in foods and are often grass. And as a result, you don't need to concern yourself with systemic toxicity unless you have dermal penetration, and so you're focusing more on sensitization and irritation --

DR. HILL: And, again --

DR. BRESLAWEC: As opposed to just de facto because they're used as very low --

DR. HILL: And, again, I say I'm not in full agreement with that for the reasons I stated earlier in that, just because something's grass doesn't mean it's perfectly safe when you wear it on your skin. It's just that, in this particular

case, we've got low concentrations particularly, and notably so in the leave on, and so things like azulene, which are raised, why it might be a problem if the concentrations in the final product were a whole lot higher. But it would have to be a whole lot higher before we'd even begin to talk about it, so that's what I'm hoping that we will somehow capture. Otherwise, somebody says, well, gee, there's this stuff and that stuff and that stuff in there, isn't this a problem. And I think it needs to be very clear it would be a problem if we had these things being used at very high concentrations. But the fact that we are giving our assessment safe as used in cosmetic ingredients, we need to be sure that somebody who reads this knows that it rests on the art, the current art based on what we see in those tables. And that's important, very important.

DR. MARKS: Any other comments? So that's just a discussant point.

DR. SLAGA: What is the conclusion, safe?

DR. MARKS: Safe.

DR. SLAGA: No concentration limit?

DR. MARKS: I don't think so.

DR. SLAGA: We don't need to set concentration limits because --

DR. MARKS: No, no, we're talking about sensitization.

DR. SLAGA: No, the sensitization data is good up to 0.4.

DR. MARKS: 0.4.

DR. SLAGA: So anything I would say --

DR. MARKS: Limit.

DR. SLAGA: -- say that, safe as used up to 0.4 percent, because there are some uses for leave ons above that.

DR. MARKS: Tom, that's fine. If you could tell, Ron I was wavering as to whether to set a limit or not. You're being, holding, being pure, which I like.

DR. BERGFELD: May I ask a question?

DR. MARKS: Yes.

DR. BERGFELD: If it were a higher

concentration, you're worried about sensitization?

DR. MARKS: Well, we don't have data that support --

DR. BERGFELD: I know, I was asking what --

DR. SHANK: That would be --

DR. BERGFELD: That would be your primary irritation and sensitization, or more sensitization?

DR. SLAGA: Sensitization.

DR. BERGFELD: Then you could put in your discussion what you did earlier that it should be compounded to be (inaudible) formula.

DR. SHANK: I just think we're tending to go to this limitation when formulated to not. First, it was, would be irritating, and that seemed to be okay, now irritation is quite different -- I'm preaching to the choir, here -- irritation and sensitization, which is two different things, and --

DR. BERGFELD: But there is a threshold of sensitization.

DR. SHANK: Okay.

DR. BERGFELD: I'm just --

DR. SHANK: If the dermatologists are fine with saying --

DR. BERGFELD: Well, they were fine before --

DR. MARKS: Well --

DR. SHANK: One case, only one case.

DR. BERGFELD: Well, I was reminded there was one other case.

DR. SHANK: Just one, yeah.

DR. BERGFELD: Two, now.

DR. SHANK: Two now.

DR. MARKS: Now, I'm fine with setting a limit, I don't think that's -- because we know it's definitely safe, using the HRIPT in Wave 2 up to 0.4 percent, and that's, as I mentioned in the beginning, I was struggling, wavering whether or not, since now, Bart, you have it up to 0.6 percent, I was looking at the flower extract at 0.5 percent. Let's set it to 0.4 percent. This is going to go out as a tentative report, industry

has one at 0.6 or 0.5, then we can put safe as used.

DR. SHANK: Well, Table 6 lists the flower at 1.2 percent in leave on.

MS. EISENMANN: That's a mistake, though.

DR. SHANK: Okay. It's kind of hard, then, to --

MS. EISENMANN: Well, if you look --

DR. SHANK: So what are the real numbers, then?

MS. EISENMANN: Well, it's 0.5 there, too, if I remember --

DR. SHANK: There?

MS. EISENMANN: Correct. Yes, if you look at the Table that came from me, it's 0.5 there.

DR. SHANK: 0.5.

DR. BRESLAWEC: This is in a permanent wave product?

MS. EISENMANN: Uh-huh.

DR. MARKS: Safe up to 0.4 percent.

And, let me see, I think I'm the one, and that's what I'll make a motion tomorrow, and we'll see where it goes with the Belsito team. Halyna, yes?

DR. BRESLAWEC: Yes. Again with the search strategy. It would be perhaps useful to search for some of the components, especially as it relates to the toxicokinetics, the flavins, the epogenic and luteolin.

MS. EISENMANN: I was just concerned about the statements in the pharmacokinetics section that it says the data were not found in the published literature, and I did a quick look on chamomile and kinetics and found three references. I mean, this is a highly used ingredient, there's going to be a lot of, I think, German data on the components under kinetics. And I'm not sure it necessarily needs to be in here, but the statement that says there's no data just doesn't seem appropriate. There's got to be a different way to state that there may be data on the components, but we didn't look for it, or -- I don't know how you want to state it, but just

saying there's no data I don't think is the right -- and I'm not saying you necessarily need to put all the data in there, but the way it is written, to me, was troubling.

DR. MARKS: So you'll communicate that with Monice to Wilbur. Perhaps -- well, first of all, I think, as with the previous botanical, doing individual searches, although we don't have Wilbur here to directly comment that, apparently, a number of those individual components came up. But I think that's to be heeded in the future as to when there are important components, that should be part of the search strategy, and mentioned when it's under the search strategy. Ron Hill?

DR. HILL: And then Bart. But we had this discussion, I think, the last time or the time before, and I've made note of it in several of these reports. I mean, the concept of toxicokinetics with these botanical extracts is not even an appropriate concept. So, I mean, if you know what components you ought to be looking

for, that would be one thing. So I react exactly the same way you do to that in the sense of toxicokinetics, N/A, because that's what I'd kind of like to see. I mean, I don't know if we just not have that section in there or we deal with it in some other manner, but if you want to talk kinetics, then you have to talk about particular components, particular compounds, and that will be different for each one of those compounds based on their biohandleing. So --

DR. MARKS: So let's get back on page 39 in the draft discussion, the second -- no, the third sentence is azulene has been identified as a component. The panel previously concluded there's insufficient to support the safety of azulene for use in cosmetic products, then it says the panel agreed that the component should be present at levels that are below the threshold of toxicologic concern. To me, there's a contradiction there, if you said there's insufficient data on azulene, and then you say the levels are below the toxicological concern. How can you say that if

you have insufficient data? Bart?

MR. HELDRETH: I think it's, maybe it's useful to say that, okay, there's azulene out there and it has a certain toxicity in certain situations, but I think we're failing to get to the point of there's not complete chemical characterization of these ingredients. And if we don't know what concentration azulene is in each of these ingredients, what do we really know about how that's going to be effective at all. So maybe there's data on azulene, but we don't have data on how much azulene is in each one of these ingredients. And I think that's what Wilbur was going towards when he said there's no data, because nobody's given us characterization data on these ingredients, and it's not in the literature that we've seen.

DR. MARKS: So, Rons, Tom, how would you -- to me, if I read this discussion as it is right now, I'm a little bit concerned. Halyna?

DR. BRESLAWEC: Look at Table 5.

DR. MARKS: And what page is that?

DR. BRESLAWEC: Jeez, I don't know.

DR. HILL: 32, 31.

DR. MARKS: No, Tables would be after 39.

DR. HILL: I'm on, sorry, I've got the advance report, that's why.

SPEAKER: Page 25?

DR. MARKS: 45.

DR. BRESLAWEC: In the flower oil, there is data, there's characterization.

DR. MARKS: Oh, yes, 0.4 percent, am I reading that correctly, in the flower oil? Carol, you have a look like you want to say something. Nonverbally, you're communicating to me, that isn't captured in this mic.

MS. EISENMANN: Yes, for at least the oils and for chamomile there are probably plenty of data. I mean, there's a lot of botanicals where there are not data, but for the oil of this one, I think there's probably enough data.

DR. SHANK: I think we have to keep in mind that these are, the plant and the oil are

grass food ingredients, so the concern is the skin, not systemic toxicity. So we need skin data, and we have some.

DR. MARKS: Okay. So, again, Ron Shank, you feel we can move forward with a safe?

DR. SHANK: Yeah, I say safe up to 0.4 percent.

DR. MARKS: Yes, right, that's based on --

DR. SHANK: Based on the skin sensitization.

DR. MARKS: Right.

DR. BERGFELD: 0.4 or 4?

DR. MARKS: 0.4 percent.

DR. SHANK: Now, in your experience, clinical experience, is there much difference between 0.5 percent and 0.4 percent? Is there that kind of a cut off?

DR. MARKS: Well, that's why I asked it be transposed to parts per million, because I always -- and when you talk, it depends on the chemical, a thousand parts per million is really a

lot for Formaldehyde or MCIMI. So, in this botanical, is there a difference? I don't know. I'm perfectly happy presenting it, as you suggest, Ron Shank, setting the limit at 0.1 percent, and then we'll see where theÂ Belsito -- 0.4 percent, I mean -- and see what the Belsito team has to say. And we can have that discussion tomorrow. I was, I could go either way, to tell you the truth, because chamomile hasn't come up in my clinical experience as a big sensitizer, and it's in lots of botanicals now. Lots, what was it, the use was like 700, or something? It was a lot. So I'll propose that limit tomorrow. I think the important thing is, we're moving forward with a tentative report safe, and then the discussion, perhaps, will revolve around the we set a limit of 0.4 percent, which is the HRIPT results in Wave 2. Monice?

MS. FIUME: I just want to ask for clarification so I can report back to Wilbur. The whole azulene started because of wording in the discussion? Do you have any suggestions for him

on the wording of that first paragraph of the discussion? Because that's, I think, what started it.

DR. MARKS: So, again, that's page 39 in the PDF.

DR. HILL: I think you follow with a sentence that says, well, now we're setting a limit, but in the arts of use, the concentrations are low. I mean, 0.4 percent would be low. If you then look at the percentage of azulene that's in the, what you're putting in there, so it would be whatever modest percentage of it is azulene of the 0.4 percent you're putting in the product, so you just say the concentrations of use are low. Azulene would be kept well below the threshold of any toxicological concern. That's true of any of the ingredients in there that have potential toxicological issues.

DR. MARKS: Yeah.

DR. HILL: If you were proposing to uses at 40 percent, we might look again at if it's 40 percent and we smear it over our entire body, what

would be the potential for systemic tox. But that's not the case here, and that's my point. And that, regardless of grass, because, I mean, the PDR for herbals says don't use it if you're pregnant, so there's something. This is one, right?

MS. WEINTRAUB: No, that's rosemary.

DR. HILL: Okay. Sorry. But this is the one with bazabalol, right? And so we have reduced numbers of fetuses, and so forth. I mean, it isn't written in here, but potentially, we have the same concern.

DR. MARKS: Well, I think the last sentence of that first paragraph is fine, the components are present below the threshold of toxicologic concern. For me, the contradiction was you have a component which you previously said there was insufficient data that support the safety. How, then, can you say it's below the toxicologic concern? Ron Shank, did you have that, or is that just me, looking at the way this paragraph was constructed? To me, there was a

contradiction.

DR. SHANK: I don't see a contradiction.

DR. MARKS: Okay.

DR. SHANK: I've always been tentative about saying everything's fine, so long as there's no toxicological concern. That, to me, is a dodge. In the context of this particular paragraph, it's okay, but --

DR. MARKS: Okay. So you didn't like the last sentence, particularly?

DR. SHANK: Not particularly.

DR. MARKS: So how would you rephrase that, or would you leave that sentence out? I'll let you think about it, and you can give Wilbur feedback.

DR. SHANK: Well, a possible alternative would be to delete that sentence and just say the levels of these toxic components in cosmetic ingredients is sufficiently low to be not of toxicological concern.

DR. MARKS: Okay.

DR. SHANK: It's a little bit different.

DR. MARKS: Right. I think that's what you said, Tom.

DR. SLAGA: It's in the extract and not the pure compound. The pure compounds are a concern, but not (inaudible).

DR. HILL: If it's there, it's there. I mean, we can suggest that one compound might be antagonizing the effects of the other, because we were about to come back to azulene. Do we not have some information that tells us if this much gets into the system, we have a problem, and if it's below that, it's fine? We have no toxicology on azulene? Because then we do have a problem, we're missing something.

DR. MARKS: Well, we're referring back to that, our previous conclusion of insufficient -- but I think the way you state it, Ron, and you implied, Tom, is the way to go with that paragraph, that last sentence. So, Monice, if you would give that feedback for Wilbur, and we're going to see this again, obviously, this is a tentative report, and the counsel can weigh in,

also, on this. Okay. Any other comments? Tomorrow I'm going to move that a tentative report be issued with a conclusion of safe up to 0.4 percent for the Chamomilla Recutita, or however that's pronounced -- who had Latin?

DR. BERGFELD: I did, but it was too many years ago. (Laughter)

DR. MARKS: I hesitate to use the common German chamomile, but I may resort to that tomorrow, just so there's a Latin linguist in the audience. Unfortunately, Belsito is going to be coming after, I'll ask him. Okay. So safe up to 0.4 percent, and we'll massage the discussion, we'll see the next rendition in the tentative report. And, in the second half, Anthemis Nobilis. So, let me see --

DR. BERGFELD: (Inaudible) concentration in this one, because they were together.

DR. MARKS: So this is the second time seeing this report, we now have the Roman chamomile split out, we issued a tentative, the oil is safe, insufficient for other ingredients.

We wanted composition, we wanted the HRIPT for the floral extract, we got that in Wave 2, 3 percent HRIPT of the flower water. HRIPT at 3 percent, flower water was 4 percent in a leave on, 10 percent in a rinse-off, so I still thought that's probably going to be okay. It's used in baby's, also there's inhalation. So, comments, Rons, Tom?

DR. SHANK: I had --

DR. MARKS: I think it was Don that wanted a composition. But, at any rate, we still didn't get the composition, right?

SPEAKER: Here it is, Table 3.

DR. SHANK: I had we still needed HRIPT on the water extract at 10 percent.

DR. MARKS: Percent.

DR. BERGFELD: Doctor?

DR. SHANK: Did we get that?

DR. BERGFELD: No, and you will not.

DR. SHANK: And we will not?

DR. BERGFELD: No.

DR. SLAGA: I said we need that, too, but they have sufficient for the oil.

DR. BERGFELD: There's no change in the concentration, Carol, this one because it was split off from the other.

MS. EISENMANN: No, that one, there is no change with the water, and I haven't been able to get the data on it, but there's still a possibility that I could get lower concentrations on the extract. I have to keep going lower to see if I can rattle up some data, but the water, I'm not going to get any data on it. So you could go insufficient, safe for the oil and insufficient for the other two.

DR. MARKS: Okay. So we still need the composition, correct?

DR. SLAGA: Uh-huh. Well, I doubt if we get it.

DR. MARKS: So if we -- how do you feel, Ron and Tom, in terms of composition? Should we have, now, an insufficient, a tentative report with an insufficient data (inaudible) composition?

DR. SLAGA: To me, if we have the one thing that Ron wanted, we wouldn't need the

composition because we could say that the oil is already sufficient data, and if we have that for the extract, then I think it's sufficient without composition.

DR. MARKS: Ron Shank?

DR. SHANK: I'm still trying to find just what are grass, so just as the spice is grass, so I guess that's the whole thing. So, again, we're down to skin data, and the oil/skin data, the skin data on oil seems to be okay, but not on the water extract.

DR. SLAGA: Yeah.

DR. SHANK: So we could split it, the oil is safe as used and the water extract is insufficient with a need for human sensitization data if you use concentration.

DR. MARKS: How about the flower powder and the flower extract? We don't have data on that. Let's see, the flower extract, we got 3 percent HRIPT was okay. Flower -- so, Ron Hill, what we were discussing earlier is, we have the composition for the oil. Do we want to move

forward with a tentative report that the oil is safe and the others are insufficient?

DR. HILL: That's what I was expecting to see.

DR. BERGFELD: For a non chemist, what's the difference between the oil and the water in penetration? I would think the oil would penetrate easier.

DR. HILL: Yes, I would expect components of the oil to be more penetrable but to be different, so I just, this is a case where I think, personally, the absence of data isn't the same as data that shows the absence of effect, that's all. I mean, it would be sensitization that actually, to me, would be about the only concern in this case. And if that's not a concern with these guys, then --

DR. MARKS: No, I think that's exactly right. We do have the flower extract up to 3 percent, we could put a limit on flower extract, if we wanted to. Oil is safe, we could say the others are insufficient and need for

sensitization, or we could say the flower extract up to 3 percent -- what was the use concentration of flower extract?

DR. BRESLAWEC: I think it was 0.1 percent.

DR. MARKS: 0.1, okay. So then that would mean the flower extract should be okay, am I interpreting that correctly? I think that's what I had, here, the extract was okay, but we don't have composition, so is that necessary for the flower extract?

DR. HILL: I was sort of assuming that Dr.Â Belsito was wanting that to assess the possibility of additive effects when this is used with other botanicals in the same formulations. And so, without that compositional ingredient, he could -- I don't know, I highlighted a bunch of stuff on the transcript, I could have a look, but that was my general sense is that enough information to know the additivity issue.

DR. BERGFELD: I have another question on the penetration. If it's in water, it's

trapped in the stratum corneum, so all of your chemical ingredients articles would be at the outer layer of the skin. The oil would penetrate supposedly a little deeper, so the affects of absorption, you would think, would be much less with the water, if it is the same plant part.

DR. HILL: I --

DR. BERGFELD: That's a different vehicle.

DR. HILL: Well, because you're going to get, with that water extract, you're going to get a different array of components, and the sorts of things that would be penetrable should be there at much lesser concentrations, probably even negligible. So I think it's a matter of what's going to be present in what amounts based on having oil versus having water extract. And then, yes, in general, I think the things that would show up in the water extract --

MS. EISENMANN: What -- water, I mean, it's not a water extract, it's when you --

DR. HILL: I know --

MS. EISENMANN: -- fill it. I mean, it can be a water extract, but when, in key names, things that are named as water is part of distillation process, and, again, you might know better once you take off the oil soluble part or, and then the water part comes up. I mean, it's all in that distillation process.

DR. HILL: All right, okay. So you do a steam distillation --

MS. EISENMANN: So it's not an extract -- right --

DR. HILL: This was probably the second organic lab I did in college, and you get oils, but then, yes, they come to where you can easily remove the oils and you're left with whatever's there in the water, and that's what I'm assuming we're assessing, here.

MS. EISENMANN: Right, right. And so it's not water --

DR. HILL: That's --

MS. EISENMANN: -- I mean, than the other extract, if you put some plant material and

put water in it and stir it around --

DR. HILL: I misstated --

MS. EISENMANN: -- that's a water extract.

DR. HILL: I misstated when I said water extract, but effectively, that's what you get, because once you do a steam distillation, cool everything down, then you have oil and you're going pull that off and you'll have whatever stays in the water, which would be why it would be awfully nice to have some composition database I think that would come out loud and clear, and we don't have that. But --

DR. MARKS: So let's get back, do we need the composition? We have it for oil, we don't have it for the flower, for the water, for the flower extract, the water. And then what was the last one, it was powder.

DR. HILL: And I'm putting words in Don's mouth that shouldn't be put --

DR. MARKS: Well, we'll find out what Don has to say tomorrow. What I want to get

straight is --

DR. HILL: I just --

DR. MARKS: -- what our team is saying.

DR. HILL: I was just going by a sense of what I read in the transcripts from the other group.

DR. MARKS: So, do we need composition?

DR. SLAGA: No.

DR. MARKS: No, okay. So we can move forward without composition. I have the oil and the flower extract safe, water and the powder insufficient --

DR. SHANK: Yes.

DR. MARKS: -- based on sensitization.

DR. SLAGA: Right.

DR. MARKS: Water and powder insufficient, need sensitization. Okay. So we'll see how this works tomorrow, but we'll be issuing a suspect tentative report, and at least our team feels the report's conclusion is going to be the oil and flower extract safe, the water and powder insufficient, and the insufficiency that's the

need for sensitization data. Any other comments? There was, did -- Rons and Tom in the Wilbur's one, two, three, four -- one, two, third paragraph in Wilbur's memo, the August 16th memo, panel needs to consider whether these studies should remain in the report. And that was the trade case reports on pages 5 and 6 and two epidemiological studies relating to reproductive and developmental toxicity page 7 in his memo. How did you feel, did you want to keep these studies in or delete those?

DR. SHANK: Which page is this?

DR. MARKS: Wilbur, do you want to -- I'm looking at Wilbur's memo dated August 16th right in the beginning, and it's -- are the pages the PDF pages, or is it the pages of --

MR. JOHNSON: No, they aren't, I'll check from here.

DR. MARKS: So it's page 5, 6 and 7. I assume that's under the repro and development, there were two cases, and you said two epidemiologic studies were all done to repro and

development. And you were wondering -- what was the question, why were you wondering whether they should remain in, Wilbur?

MR. JOHNSON: Because we didn't know whether or not they were Anthemis Nobilis or Chamomilla Recutita derived, that's the reason why.

DR. MARKS: Okay, now I understand.

DR. HILL: To me, if you don't know the source, at most you leave them in at a footnote of some sort.

DR. MARKS: I guess it gets back to, even if you leave them in, it did not --

DR. SLAGA: The report separate the three, you can't interpret the data, right?

DR. MARKS: That's what I would think. But it gets back with these, does it raise any toxicological concern for repro and development. I know, I can't overlook Wilbur's --

MR. JOHNSON: And that's starting on page 24 on the case reports.

DR. MARKS: Is that in the separated, is

that also in the German chamomile report, these three cases and the two epidemiological studies?

MR. JOHNSON: Yes.

DR. MARKS: Yes. So we left it in that, okay, we leave it in since we can't separate it. Again, Ron and Ron, does this change or influence your conclusion at all?

DR. HILL: I don't think we had the discussion whether we left it in the chamomile report, did we? We just skipped right over that.

DR. MARKS: That's why I asked Wilbur that, because I think it's very important, if we leave it in, do we have to -- it seems to me we have to at least mention it in the discussion and explain why this is not of concern.

DR. HILL: What I would like to see in both of them is, this is my, I'm just tossing this out there, is have it summarized in a table, much the same way some of our other tox summaries show up, and then reference in the discussion, at most, or else we just take it out. I mean, which I'm fine with, I think we've lost some data, we don't

know the source. We've lost some data if we just totally take it out, but yet, if you keep it in chamomile, you don't know if it's contributing to that, because you don't know if it's been done with the Recutita. If you keep it in the other one, you don't know if it's contributing to that assessment because you don't know if it's been done with Nobilis.

DR. MARKS: I've got to say, I'll ask Rachel, but I don't like the idea of leaving it out, I think it has to be addressed. And we can say we don't know which one of the chamomiles, whether it's German or Roman, but it gets back to, this, to me, is a hazard alert, how do we deal with this.

MS. WEINTRAUB: I agree, I think that's a better way to address it.

MS. EISENMANN: For the epidemiology side, I believe most commercial chamomile teas, if that's what they were drinking, are German, I don't think that make much of the Roman chamomile, I think it's German that's sold as the tea. So I

think it's more likely to be German than Roman, but I can't say that for sure, I haven't actually looked at the studies.

DR. MARKS: So what would we -- I mean, we've gotten to the point of saying safe, we've set some limits on sensitization, but going back, there's, presumably, there were no other alerts, as far as repro and development, so can we --

DR. HILL: Well, let me back up one step, then, because -- I'm sorry, I tend to make the mistake of over relying on the data table that you guys put at the beginning of the reports, because sometimes those don't get updated when we have additional data come in. But just looking at the data table, and you're familiar with this, so you could -- it's on page 4 of the PDF -- there's no chronic tox on any of the Anthemis Nobilis ingredients reported in here, there's no repro developmental toxicity on any of the Anthemis Nobilis ingredients listed in here. We have a genotox result on the flower oil, and that's all. Actually, we don't have any acute tox except for

the flower oil, oral and dermal, but that's one of the reasons we'd like to have the composition, because then you at least have a better chance of thinking about read-across. Without that, you have zero chance, from where I sit.

DR. MARKS: Ron Shank, I think he made the comment earlier, well, this is grass. So even though these things are reported, it's a grass.

DR. SHANK: Correct.

DR. MARKS: So --

DR. SHANK: So this focuses on skin, not systemic toxicity.

DR. MARKS: How should Wilbur incorporate that in there, then? These studies should remain, should we just say it's a grass ingredient and it's not relevant? And that's for you, I know Ron Hill has a little different take about the skin exposure, but any rate, I think that's why we went right over the systemic tox, because it's a grass.

DR. HILL: We didn't know if Anthemis Nobilis was grass, I thought that was what was

captured in the transcript.

DR. SHANK: It says it's grass now in the use part.

DR. HILL: Okay.

DR. SHANK: As far as case reports --

DR. HILL: Okay, they are, they both are.

DR. SHANK: To me, they're not helpful at all.

DR. MARKS: Yeah, your approach is the same as --

DR. SHANK: So, if you want to be inclusive, put them in, sometimes they're entertaining reading, but they certainly don't help me as a toxicologist. Because you really don't know what the case is, what else they were exposed to, a single person responding to whatever just doesn't help me. I have no objection to taking them out --

DR. MARKS: Interesting.

DR. SHANK: The only reason to include them is to be inclusive and show that we have

looked at all the data.

DR. MARKS: How about the epidemiological studies? Well, I could let you off the hook on the case studies, I agree with you.

DR. SHANK: Oh, dear, I was hoping -- well, again, in most cases -- well, the epidemiology here did not help me, either.

DR. MARKS: Okay. And you would leave them out, Ron Shank.

DR. SHANK: As I said, it makes no difference to me, really.

DR. MARKS: Okay.

DR. SHANK: I don't object to them being in.

DR. MARKS: Perhaps this --

DR. SHANK: And it does show that we are aware of the literature, but it didn't help me.

DR. MARKS: And would you -- it didn't help you because? Again, these are grass substances, and --

DR. SHANK: Well, that, for sure, and

then these case, someone developed rhinitis when smelling this.

DR. MARKS: Okay. Does that give you some direction, Wilbur? We're going to see this, we'll see this gun, and, Wilbur, don't hesitate to bring that up again in a memo. So, tomorrow, let me see, am I the one -- no, this is Belsito. So a tentative report, as you know, I have no hesitation in representing our team, so, tomorrow, I'm going to perhaps second a tentative report with a conclusion --

DR. SLAGA: Perhaps?

DR. MARKS: Well, I haven't seen the motion yet, so that's why I say perhaps. A motion that the oil and flower extracts are safe, that the water and powder are insufficient because of the need for sensitization data use concentration. Any other comments -- and, Wilbur, we'll let you deal with the case reports and the epidemiologic studies based on what Dr.Â Shank has said here. Any other comments? Next one is formic acid. So, in the June 2012, I'll highlight the year, so

it wasn't last June, it was the June before the last June, we reopened these ingredients, the formic acid, and now we're at the stage of showing a tentative amended report on formic acid and sodium formate, safe when formulated to be nonirritated, and then we need the skin, and particularly the respiratory concerns on irritation in the discussion. So we added sodium formate, there was a new function as a preservative, also as a fragrance, but we don't deal with fragrances in our evaluations. So, Ron, Tom, does that sound like a reasonable move forward with a tentative amended report with a safe when formulated to be nonirritating and handle the skin and respiratory issues in the discussion?

DR. SHANK: Yes.

DR. SLAGA: Same here, yes.

DR. HILL: Yes.

DR. MARKS: Okay. Any other comments? Okay. Again, presumably, I will be selecting a motion to that effect. Next, butylcarbamate,

rereview.

DR. HILL: Is that in the admin book, I don't see it.

DR. MARKS: Is that the admin?

DR. HILL: I think so.

DR. MARKS: Should be. Yes, that's under the rereview --

DR. HILL: No, that's a separate file.

DR. MARKS: Yes, it is. Butylcarbamate --

DR. HILL: (off mic)

DR. MARKS: Yeah, the rereviews are in the admin, you're right. I have a lot of notes, here. So, in 1996, the panel issued a final safety assessment, iodopropynyl butylcarbamate safe as a cosmetic ingredient, less than 0.1 percent, should not be used in products intended to be aerosolized. The second paragraph of Wilbur's memo summarizes the European Union's recommendations, which are significantly different.

DR. SLAGA: How did they come up with

those numbers?

DR. MARKS: Well, that's what, based on iodine -- it says in, I have in Wave 2 --

DR. SLAGA: In the past report?

DR. MARKS: Iodine levels, correct?

MR. JOHNSON: There's a panel report that was included in Wave 2, but then, you know, just based upon the other team's review, it doesn't seem to be a sufficient basis for some of the limitations that are being, you know, proposed, here. But it's that, supposedly, it's based upon that particular document in Wave 2.

MS. EISENMANN: Based on iodine exposure?

MR. JOHNSON: Yeah, uh-huh.

MS. EISENMANN: Is there a concern with iodine exposure, or was it not considered at all?

DR. MARKS: In our original?

MS. EISENMANN: Correct, right. I mean, they're saying it should only be a certain percentage of the daily intake, the amount of iodine that is in cosmetics.

DR. SHANK: This is not iodine, and this compound is not likely to be dehalogenated in formulation or in use, so I don't see this as an issue at all. It's a matter of reopening, is it not, and I don't think --

DR. MARKS: Yes.

DR. SHANK: I don't think we need to reopen it. And, if necessary, in the rereview summary, you can mention the European concern.

DR. MARKS: So --

DR. SHANK: And our response is that this is not a source of iodine or iodide ion. And then the quantitative argument is based on rat, and rat is a very poor model for thyroid in, for a human.

DR. MARKS: So not reopen. David, so we have a guest, come find a microphone and identify yourself, David.

DR. STEINBERG: David Steinberg. Ron, just one comment; iodopropynyl butylcarbamate will hydrolyze and release the iodine molecule at pHs above 7. It's a very slow, it's temperature, pH,

time dependent, and you notice it immediately because you get the characteristic iodine color, which is why we don't use it. Its principal use, it is purely an antifungal preservative, and it is used principally because of its action, and that's in water. So it's used in emulsions, creams, lotions, cleansing products, things like this, and you've just got to keep the pH below 7, or else you're going to fail your stability testing because your product will turn yellow or purplish. So it does hydrolyze, it can release that iodine molecule, but we just don't use it in that type of action.

DR. SHANK: Thank you. Is it antifungal because of iodide ion?

DR. STEINBERG: No.

DR. SHANK: Okay.

DR. STEINBERG: No, it's -- actually, if you remove the iodine completely and just started with the intermediate, it's strongly antifungal, but it's also strongly irritating, so the iodine calms the molecule down.

DR. MARKS: So let's, David, don't leave quite yet.

DR. STEINBERG: Okay.

DR. MARKS: I want you to address, because if we do not reopen, then there needs to be a robust discussion about the use concern about iodine and our lack of concern. And so I hear Ron talking about it, it's, iodine doesn't, isn't released by the compound, but that's in the caveat if it's below 7, the pH, it isn't.

DR. STEINBERG: Basically, we use it, I've seen it in formulations as high as, like, 7.2, 7.5, but then as soon as you put it in accelerated ageing testing at 40 degrees Celsius, you start getting that yellow color, and that's not very popular with consumers. So if you use, you're keeping the pH below 7, and it is not the release of the iodine which has anything to do with its antifungal properties. It's been -- the molecule was invented around 1950, '52, used almost exclusively in the industrial marketplace for paint as an antifungal agent. It was in the

late '80s that we came up with a refined grade for cosmetic use. It was originally offered as a cocktail, a mixture, that's one of the reasons why the levels are higher, because of the cocktail mixture was a 95/5 ratio, 95 percent of an antibacterial agent, 5 percent of the IPBC.

It's overkill, its maximum solubility in water has been reported to be anywhere between 150 and 175 parts per million. If you exceed that 175 parts per million, you do not get any better antifungal activity, so it's a waste of money to go up to 0.05, when 0.02 is about the max it's going to work.

DR. SHANK: Thank you.

DR. MARKS: So you're, Ron Shank, still, do not reopen and incorporate your discussant points. And, David's, the two to address the EU limits. Because we --

DR. STEINBERG: The EU has dealt or has -- this came up in the EU principally through Denmark, and this goes back probably, I'm going to say 12, 13 years ago, when they were concerned

with exposure to iodine in any way, shape or form. So they banned sodium iodate, for example, which no one ever used as a preservative anyhow. They questioned the colors that hide iodine in them, they questioned this and came up with their reports based on ingestion of iodine. It doesn't apply, we don't use this in lipsticks, lipsticks don't need an antifungal agent.

DR. MARKS: It's interesting, because they specifically ban it on lipsticks, oral hygiene and lip care products. I don't know if lipstick is called a lip care product, but any rate --

DR. STEINBERG: But they're anhydrous, they don't use water based products for that purpose.

DR. MARKS: Okay. And then, how about the, so it is, the uses have gone up dramatically since it was, since 1996, from 122 to 942 in the present report. It was used in baby products, the EU, not to be used for children under 3 years of age. Again, this is the iodine concern?

DR. STEINBERG: That was what was the concern back 13, 14, years ago when this came up. Its increased use in the United States is because of the decreased use of parabens, it's the best antifungal replacement, and if you're going to be without parabens because of marketing concerns, we'll put it that way, as opposed to scientific concern. Where do you turn to? And the two principal antifungal agents that we have available to us are the IPBC and ascorbic acid, which is why you saw dramatic growth. And you will continue to see the growth in the United States because of the diminished use of parabens.

DR. MARKS: Any other comments about that?

DR. SHANK: We have, in the original report, chronic oral exposure in experimental animals, and there was no reported thyroid effect, even in rodents, which are much more sensitive to iodine levels. And, in this country, we use iodate as a nutritional supplement, so I don't think this is an issue.

DR. MARKS: Okay.

DR. STEINBERG: Remember the ingestion studies, I think, go back to its use in paint, and they were always concerned with children eating paint.

DR. MARKS: Okay. Ron Shank and David Steinberg. Okay, so it seems like the EU restrictions that are mentioned in paragraph 2, we've addressed those, there's no reason to reopen it because of concern with iodine toxicity. Interestingly, when I went back and looked at the original report, although I don't think it needs to be changed, is that the limit of 0.1 percent was really based on a comedone assay, not on sensitization. And that was, actually, Don Belsito was concerned about that when you read the minutes, but it's not being used, its maximum is 0.05 percent on leave ons, so it's way below, so that doesn't seem to be an issue. So don't reopen, Ron Hill, Tom?

DR. HILL: (Nodding)

DR. SLAGA: I agree.

DR. MARKS: Okay. And, Wilbur, you got --

MR. JOHNSON: We need to capture all of that in the discussion.

DR. MARKS: Yes.

DR. HILL: I have a question, it's a dermatology question, I guess. There was a statement in here that said continued, it was a publication by Adreshe and Marks, was that you?

DR. MARKS: What year --

DR. HILL: I've got a 2002 paper that continued surveillance would be prudent with increased use. The uses clearly have increased, are we -- I mean, we're not seeing any increased sense -- I assume not --

DR. MARKS: Right. That's from, and that was in here, the North American Group Data, so, yes. So that's what we're doing right this morning, is continuing surveillance, and it hasn't raised any issues since --

DR. HILL: We haven't seen issues come --

DR. MARKS: When I wrote that article, yes. Thank you, Ron, for bringing that up. (Laughter).

DR. BERGFELD: Has it hit the top ten in your list?

DR. MARKS: I don't believe so.

DR. HILL: That's what I was driving at is, have the incidences increased in the ensuing ten years.

DR. MARKS: There may have been, I'd have to go back. I didn't put that page --

DR. BERGFELD: Well when you searched, you searched in (inaudible)Â --

DR. MARKS: Oh, yeah.

DR. BERGFELD: -- annual reviews of the contact sensitize.

MR. JOHNSON: Uh-huh, yes.

DR. MARKS: I think, if I remember one of these, there was a statistical increase, but the frequency of reaction was still low compared to things like Quaternium. Okay, so, not reopen.

DR. HILL: My, this is going to go out,

right? This is going to go out, I mean, this rereview will go out and will be published, or --

DR. MARKS: Yeah. Remember, Ron, what we do is, tomorrow, we'll come to a conclusion whether to reopen or not reopen. If we don't reopen, then there's a discussant, and we actually, that's why we had the rereview summaries are in the administrative folder --

DR. HILL: Okay, that's what I thought we were doing here, so that's why I asked the question about has it gone up in the ensuing ten years, because, sort of, as a reader, that statement sort of leaves you hanging. Continued surveillance was suggested, but then we never did find out has it gone up or not.

DR. MARKS: Not reopen. And, to my -- no, if it's gone up, it's been minimal, nothing alarming.

DR. HILL: It's like reading a novel, but having to stop right before, you know, everything is resolved. That's what I'm getting at.

DR. MARKS: Okay. It is 10 of, shall we do the rereview summaries in the administrative section?

(Chorus of ayes)

DR. MARKS: Okay. So, tomorrow, I will move that this not be reopened, and that, in the discussant points, we'll talk about iodine and why we're not concerned about it. Okay, admin. And, under page 38 of the Admin Section, the rereview summaries of polyvinylpyrrolidone and retinol and retinyl palmitate. Any editorial comments, Ron, Ron or Tom?

DR. SLAGA: Not here.

DR. MARKS: Okay. Wilbur, it looks like --

MS. WEINTRAUB: I had one.

DR. MARKS: Yes, Rachel?

MS. WEINTRAUB: There's a minor typo on Footnote 80 for retinol and retinyl.

DR. HILL: I thought we were still on, I thought we were just still talking about PVP.

DR. MARKS: No, I put them together. So

Rachel's first --

DR. HILL: That's fine, I'm good with that. I thought we were strictly on PVP at this point.

DR. MARKS: Yeah, we're doing, since it seems like there were only footnote corrections --

MS. WEINTRAUB: Which one is it, Footnote 80 --

DR. MARKS: -- so, do you have that, Wilbur?

MR. JOHNSON: Reference No. 80?

MS. WEINTRAUB: Yeah, there were two periods after the name of the publication.

MR. JOHNSON: I got it, thank you.

DR. SHANK: What's the PDF page, please?

DR. MARKS: Any other comments? It sounds like we need to leave.

(Interruption)

DR. MARKS: Okay. We are going to start shortly, when Dr.Â Bergfeld arrives, or else we can start -- there she is. See, I knew she would arrive as soon as -- take your time, Wilma. So

the first ingredient I have from after this morning is the isethionates, and at the June meeting, we issued a conclusion that it was safe when formulated to be nonirritating. We're at the point now of issuing a final amended safety assessment, are there any comments in the discussion, any concerns with a conclusion safe when formulated to be nonirritating.

SPEAKER: I think the report is good as it is.

DR. MARKS: Okay. So, Monice, you have transformed into Christina now.

MS. FIUME: I am now Christina.

DR. MARKS: Okay. At least we have the same gender, we don't have to -- go ahead, Ron.

DR. HILL: I did have a general comment, it wasn't just pertaining to this one, because I encountered it somewhere else. On the last full paragraph of the discussion, let's see, it's an inhalation, it says, panel believes that the assays is blah, blah, blah, larger than the risk viable range and/or aggregate or agglomerate to

form larger particles. I can see how that might apply to a powder or a spray powder like a deodorant, for example, that's squirting fine powder out, I'm not sure how we think aggregate or agglomerate applies to liquids. I wish Ivan were here, because he is the guru on that, so we don't need to discuss it right now, but I'm just tossing that out there.

DR. MARKS: Okay. Any other comments? So, Monice, you'll -- thank you, Christina, very nice report.

MS. FIUME: Thank you. (Inaudible) interesting to see what day two was, see if there were any issues in that. I don't think so.

DR. MARKS: I didn't have any --

MS. FIUME: I thought there was a Wave 2 on this, I was just trying to quickly --

MS. EISENMANN: There is, it was a correction to the use of baby products, it was not a powder, it's a wipe, and the concentrations were just a --

MS. FIUME: Thank you, Carol.

DR. MARKS: Okay. So, presumably, I'll be seconding a motion with a safe, nonirritating conclusion. This will be issued as a final amended. Next is the alkylamides. So, what we have in June, an insufficient data announcement was issued, and the data needs are listed in Christina's memo, dermal irritation sensitization for two-lead comments, or two-lead ingredients, I should say, for Lauroyl Lysine and Sodium Lauroyl Glutamate.

DR. HILL: Can we start with the category is named wrong and fix it?

DR. MARKS: Well --

DR. HILL: I made strong comments last time, but nothing changed, so I don't know if that was just the administrative convenience or if I was being blown off. I guess it doesn't matter, practically.

DR. MARKS: Well, it does if you have a concern for the --

DR. HILL: Yeah, but --

DR. MARKS: Are you talking about the

nomenclature?

DR. HILL: Amino acid alkylamides does not describe these ingredients.

DR. MARKS: What was your suggested change, because this is a tentative report, so --

DR. HILL: Right.

DR. MARKS: -- it certainly can be changed easily at this stage. And let's see who presents this tomorrow.

DR. HILL: I didn't write anything down again, I had a note to go back and remind myself what I said last time. So we don't need to do that right now.

DR. MARKS: Well, just bring it up tomorrow, there will be discussion tomorrow.

DR. HILL: Yes.

DR. MARKS: And Bart will be here. So, Rons and Tom, my notes, issue tentative report safe, formulate nonirritating, limit the sodium la -- how do you say that -- lauroyl?

DR. STEINBERG: Lauroyl.

DR. MARKS: Lauroyl.

DR. HILL: Lauroyl, okay, glutamate to 2.5 percent possibly. I had mainly relevant to, and as in the memo, it's to the skin issues.

MS. EISENMANN: In Wave 2, there's a, you see the data in Wave 2, there's Guinea pig sensitization studies and there's some HRIPT, and there's one on the Lauroyl Lysine at 12.5 in 600 subjects.

DR. MARKS: Right. The Wave 2, the max was 50 percent non sensitizing in Lauroyl Lysine, so I had no problems with that. And then, for the SLG, I'm going to say Wave 2, the max was okay at 2.5 percent, so that's why I said do we want to limit that to 2.5. What I have Don's team, limit question mark. Use in a leave on is 4 percent, max, 40 percent in a rinse-off, so that's why I felt set a limit for the SLG, the sodium lauroyl glutamate. I'm going to have to practice that a few times. How was that, Ron Hill?

DR. HILL: Lauroyl.

DR. MARKS: Lauroyl, okay. So, Rons, Tom, what do you think about that, setting a --

move on to a tentative report with the Lauroyl Lysine as safe, and a sodium lauroyl glutamate, a max at 2.5 percent, or that concentration is safe, since we have max data to support that concentration. Carol, am I summarizing that correctly? That's what I saw when I reviewed Wave 2. I can go about 2.5. You had mentioned some other -- yeah. Does that sound --

MS. EISENMANN: But I'm wondering how you're going to apply it to the rest of the ingredients.

DR. HILL: Yeah, I was getting to that, but I was waiting until everybody else --

DR. MARKS: I think we chose those as the sort of lead. We oftentimes don't have sensitization data for a number of ingredients when you have them grouped together. That's, it was actually the Belsito team who wanted to set the limit for the sodium lauroyl glutamate.

DR. HILL: So none of those are grass this time, right? I don't have to --

MS. EISENMANN: My other question is

what about rinse-off products for the sodium lauroyl, SLG? That is used at higher levels.

DR. MARKS: Right, 40 percent, I think I had noted; is that right, Carol? Up to 40 percent? That's the way I set a limit.

MS. EISENMANN: Yeah, yes, I think so. And I've gotten some HRIPTs, but there are ones at 0.2 and ones at 3, but they're tested as diluted --

DR. MARKS: Exactly.

MS. EISENMANN: The rinse-off, they're tested diluted. So if you set a limit at, it doesn't, your limit for leave on products only. I mean, they're mostly used, this ingredient is mostly used in rinse-offs.

DR. MARKS: Yeah, well, when I took 10 percent of 30 percent, that's 3 percent, which is close to that 2.5 percent limit from the max earlier, so that's why I just chose 2.5 percent.

MS. EISENMANN: So, it's okay at 30 percent in rinse-offs?

DR. MARKS: It should be. But, now, how

to word it to include that. Could put a limit on the leave on, and the use as it is is okay -- well, 30 percent, as you say. So, let's get back to Tom, I think you raised, or maybe Ron Hill, read-across on this. And then you brought up, you went back to, our main concern was really the skin tox with these, non systemic; is that correct, Ron, Ron, Tom?

DR. HILL: Well, as you recall, I had a problem lumping the Nacetyl with these others for exactly that reason. But, yes, I think that's probably still applicable for those, as well. Right. And, so, if you look at toxicology, I don't have any information, nor was I able to find any information that strongly suggested that these amino acid long-chainÂ aceoeal compounds. I don't have any information to suggest that they would be cleaved to a parent amino acid than the long chain fatty acid in the skin. Because amidases in the skin are usually pretty specific, and I don't know any compounds that look a lot like this biochemically that would traffic that way. So

what (inaudible) will do is hang in the skin, and I think it will get into the membrane.

So my concern is repeatedly, over long periods of time, are we doing something odd in the skin because of build up. We've only got toxicology data on two amino acid, alpha amino acid long-chain amides, and now we find out one of them isn't even at the alpha nitrogen, it's at the epsilon nitrogen of the lysines. So we've only got one amino acid long chain amide, which is a glutamate.

DR. MARKS: Uh-huh.

DR. HILL: So I made myself a list to see what other amino acids were there, most of them are there, there's various and sundry long chain amides, I just have concern that we have no data about what these things might or might not do biochemically in the skin.

DR. MARKS: So let's get Ron and Tom, Ron Shank, Tom. Again, do you have any concerns other than the skin tox at this point? Because I think we have to decide how we're going to handle

that. It wasn't raised in June of this year, in that meeting.

DR. HILL: I think I raised it in low-key fashion, I can go find the transcript, but. But we did not have information that the lysine -- I mean, it still doesn't cover a lot of those other amino acids, but we did not have that piece of information that's nepsilon rather than nalpha amidated.

DR. MARKS: Ron Shank?

DR. SHANK: I can't find any concerns I have with these compounds other than sensitization. And we got the data for Lauroyl Lysine, not for the glutamate. And I thought the amides would be hydrolyzed, so if that's not the case -- not amides, it's amides.

DR. HILL: That's a perfectly acceptable way to say it.

DR. SHANK: Amides?

DR. HILL: Amides, amides.

DR. SHANK: Okay.

DR. SLAGA: I didn't have that concern,

just the original concern. I'm satisfied.

DR. MARKS: So, would you move forward, then, we would issue a tentative report with safe formulate the non irritating. That the, the only limit we would put is sodium, this SLG, sodium lauroyl glutamate, to 2.5 percent leave on and 30 percent on rinse-off.

DR. SLAGA: Yes.

DR. SHANK: The use table says 40 percent on my document, has that been reduced?

DR. MARKS: No, that's 40 percent is what I have is the use.

DR. SHANK: The rinse-off.

DR. MARKS: But when you look at the HRIPT, which Christina mentions in her memo, and Carol points out, we have safe, we have a 30 percent concentration. But, again, that was diluted. But that's, again, presumably diluted the way it's going to actually be used.

DR. SHANK: I don't know --

DR. MARKS: So I'm kind of picking the 30 percent rate.

DR. SHANK: How do we get these condensed use tables? We used to get a breakdown, I know it's very hard --

MS. EISENMANN: I still do it.

DR. SHANK: You still do that?

MS. EISENMANN: I still can provide those if you want to look them up. I don't --

DR. SHANK: Well, on this one, if this is used in what, say, a shampoo --

MS. EISENMANN: I don't know --

DR. SHANK: -- bath -- we consider rinsing creams rinse-offs, don't we? Would you rub that into your skin, so --

DR. BRESLAWEC: I think we're okay with the 30 percent rinse-off, even though there's 40 percent usage reported, because there's day to support the 30 percent rinse-off.

DR. MARKS: Right.

DR. SHANK: Skin sensitization?

DR. MARKS: Yes, that was in the memo, Ron.

DR. SHANK: That was in Wave 2?

DR. MARKS: That's actually in the memo of Christine, so if you look at the memo, it's in the third paragraph.

DR. SHANK: Okay.

DR. MARKS: Since the announcement, we received HRIPT data on SLG in products at concentration of 22 percent and 30 percent, then it was tested at 1 and 10 percent dilutions, which presumably would be similar to how it's actually being used.

DR. SHANK: We know that.

DR. MARKS: Yeah.

DR. SHANK: That the 1 and 10 percent dilutions are how this is used, or do we --

MS. EISENMANN: I don't know for sure, what I know is rinse-off products, when you do an HRIPT, they usually test the dilution of some sort, they don't ever test the full strength, because it's not used in a manner that would require that.

DR. MARKS: Plus, full strength would be irritating in and of itself.

MS. EISENMANN: Right, that's probably the reason for the irritation. So, but I have to look back and see what the -- because Reference 59 and 60, let's see what it says.

DR. MARKS: We could certainly move forward with a tentative report with that limit. And I have no problem -- the others that we don't have the data, presumably, it's going to be used similar concentration and uses as in the report. So what do you think, should we move forward with a tentative report and safe when formulated to be nonirritating, and then we put a limit on the sodium lauroyl glutamate, with the data we have now from the max and the HRIPT, 2.5 percent max, maximum concentration on leave ons and 30 percent in rinse-off.

DR. HILL: Because the disodium stearoyl glutamate goes up to 6 in leave ons, according to this table.

DR. MARKS: Yeah. If we go to the, if we go back to the parent of Lauroyl Lysine, it's used 50 percent with non sensitizing in a max

test, it's really a high concentration there.

DR. HILL: But, again, I say as soon as you move -- I mean, I'm not going read-across lysine to any of the others except maybe Arginine anyway.

DR. MARKS: Yeah.

DR. HILL: But as soon as you switch from lysine substituted at the terminal, the epsilon nitrogen as opposed to the alpha, then structurally, that's quite different. I'm not reading across from that lysine data to any of the rest of them on that basis.

DR. MARKS: Okay. How do you, do you want to move forward with a safe, and then the limits on the SLG? Ron?

DR. SHANK: Well, haven't we been using the Lauroyl Lysine to read-across for all of these?

DR. MARKS: Uh-huh.

DR. SHANK: Well --

DR. MARKS: I think, actually, at the last meeting, the sodium lauroyl glutamate was

chosen to read-across for the other.

MS. EISENMANN: You also have some data on the sodium lauroyl silk amino acids, 20 percent is the highest, it's in LLNA. And silk is, I keep forgetting, primarily glycine, serine, abilene and threonine.

DR. HILL: All we have on that is the LLNA.

MS. EISENMANN: I'd have to look through it, I think they provide a little bit more data on that, too, but --

DR. HILL: That was in Wave 2 that we just --

MS. EISENMANN: No, no, it's been in the report, the silk.

DR. HILL: Okay.

DR. MARKS: Do you know what page that is?

MS. EISENMANN: Well, the Table 9 has the dermal, all the dermal sensitization data that was in the original report.

DR. MARKS: And that's page, Table 9?

MS. EISENMANN: I don't have a PDF file, it's page 33 of the report.

DR. HILL: So that is PDF page 58, maybe -- page what? 33, you said?

MS. EISENMANN: Yes.

DR. HILL: It's page 62 of the report, ish. Sodium lauroyl silk --

DR. MARKS: Which Table did you say? I'm at 5A and I'm on 57.

DR. SHANK: The sensitization studies.

DR. HILL: Table 9.

DR. SHANK: Table 9 on PDF 62.

DR. MARKS: 62, okay, I just found that. Not only did I note that, I had those highlighted, but I think it was just because of the LLNA.

DR. SHANK: I'm still confused by this dilution business, it says a facial cream containing 30 percent ingredient, and it was tested at a 10 percent dilution. What's applied to the skin, the facial cream or the facial cream diluted 10 times?

DR. MARKS: I think if we set a limit

for leave ons, and it was 2.5 percent. If this is diluted down, and they're actually testing with 3 percent, essentially, a 10 percent dilution of 30 percent test material, I think it covers that, if this cream is meant to be a leave on. It seems like it should be a leave on, but it is --

MS. EISENMANN: It's a cleansing cream rather than just a cream that needs, that should be corrected in the Table. The title of it says cleansing cream, so it's --

DR. MARKS: Okay. So, in the Table, it's a facial cleansing --

MS. EISENMANN: It's not left on for very long, and that's why don't do a, it would become irritating if they leave it on.

DR. HILL: So what we --

DR. MARKS: We have --

DR. HILL: -- sorry.

DR. MARKS: So we have the cocoyl glutamate, which is non sensitizing --

DR. HILL: What were the primary amino acids in silk that you listed? You said serine,

thaline, because we don't have that anywhere in here.

MS. EISENMANN: Glycine, threonine --

DR. HILL: Glycine, serine, thaline and threonine?

MS. EISENMANN: Yes.

DR. HILL: Okay. There's one LLNA.

DR. MARKS: And there are a lot of HRIPTs.

DR. HILL: But at high concentrations. Yeah, but they're all acetyl and then the rest are glutamate.

DR. MARKS: Uh-huh.

DR. HILL: And I don't buy any of the acetyl data for read-across, that's my point. You can't make me and you can't convince me.

DR. BERGFELD: I'm having trouble finding out why you have concentration limitations when you could use as in use, because of your sensitizing testing.

COURT REPORTER: Dr.Â Bergfeld, could you keep your voice up because of the jack hammering?

DR. BERGFELD: Okay. I just said I'm having trouble trying to establish a limiting restricting concentration rather than just concentrations of use.

DR. MARKS: Because the highest concentration reported an SLG, that's the real, when we're getting the specific ingredients. We'll get back to read-across in a minute, but the highest use concentration is 40 percent, and we have a max at 2.5 percent, so the leave on, that's, the concentration is higher than the use -- the use concentration are higher than either the max or the HRIPT that we have up to 30 percent, presumably when they're diluted. It's what would be the typical exposure diluted, so that's why I think we set limits on that particular ingredient.

DR. HILL: Meanwhile, I remembered why I didn't like the LLNA, because we had that extended discussion of the AP paper where, if something was tested at less than 80 percent purity in the LLNA. We had questioned whether that was valid,

although, then, there were lots of provisos. So this is 20 percent of, 25, 50 or 100 percent solution of butanone in a mouse.

DR. MARKS: Don brought up that objection.

DR. HILL: I know.

DR. MARKS: And that because in a botanical.

DR. HILL: I know.

DR. BERGFELD: Mixture.

DR. HILL: But this is a mixture, too, silk amino acids nacylated.

DR. MARKS: So shall we, Ron Hill, I'll ask you tomorrow to bring up that discussant point, which is fine. Ron.

DR. HILL: Who's making a motion on this, is it them or us?

DR. MARKS: I think I am.

DR. HILL: Okay.

DR. MARKS: Not I think, I am.

DR. HILL: Maybe you could let them do the discussion first.

DR. MARKS: No, no (laughter). No, that's not the way --

DR. HILL: So that I don't have to say anything if they have a chance to come up with the same issues that I have.

DR. MARKS: We have to have a motion, and motion is presumably going to be issue a tentative report. The question is, what is the conclusion of that tentative report going to be? I don't think there's any question that the sodium -- I mean, it's kind of interesting, if you don't do read-across, you really are left with sodium lauroyl -- I mean, the Lauroyl Lysine is safe, and then limit -- so how do you want to proceed, Ron Shank or Tom? Make that motion along with the limits, and then we'll see how the discussion evolves from there?

DR. SHANK: Well, if I remember correctly, I didn't see anything to suggest sensitization anyway in the report.

DR. MARKS: Right.

DR. SHANK: So I am troubled because I

did use the lysine compound as the read-across.

DR. MARKS: Uh-huh. I think it may have been, I'd have to go back and look at the minutes, it was Don's team and Dan Liebler who wanted to use the SLG as another read-across.

DR. SLAGA: Read-across, and that's why those two were picked.

DR. MARKS: Right. But the problem with the second one is, I think if you use that logic and you set a limit for SLG, then does that mean everything, if that's another one, what do you read-across with that? Well, shall we just make it safe and then we'll see how it evolves tomorrow, that would be very interesting.

DR. HILL: I'm on board with those two ingredients, that's perfectly fine.

DR. SLAGA: I would make that motion.

DR. MARKS: I have a little problem with safe for both, because the 2.5 percent on leave ons we know is safe, but its use is up to 4 percent, and we know 30 percent on rinse-offs is safe, and it's used up to 40 percent on rinse-off.

So I'd still want to set limits for those two, what do you --

DR. SHANK: Well, we have, in Table 9, we have sodium lauroyl glutamate tested at 5 percent active matter, 5 percent, by this end chamber in humans.

DR. MARKS: Yeah. Which page are you on, Ron?

DR. SHANK: PDF62.

DR. MARKS: 62, okay.

DR. SHANK: Table 9.

DR. MARKS: Table 9, so at the bottom, 5 percent active matter, that's just with 20 volunteers. Oh, yeah, so that, to me, that's just -- no, that's just a patch test, a single, that's not really an HRIPT.

DR. SHANK: So it's not a sensitization --

DR. MARKS: No, to me --

DR. SHANK: -- it shouldn't be here.

DR. MARKS: -- that's more of a diagnostic and more, non sensitizing,

nonirritating, but it doesn't help me in terms of sensitization. That's why --

DR. SHANK: How can you say it's not sensitizing if it's just a single application?

DR. MARKS: Carol, can you help with that, because I didn't -- they had a thing in HRIPT. I guess you could say it was non sensitizing in that particular instance, but it's not significant for me to --

DR. SHANK: Not a valid test for it.

DR. MARKS: Yeah.

MS. EISENMANN: My guess is it shouldn't be in this table, it should be on the irritation table, right?

DR. SHANK: Okay.

DR. MARKS: Yep. So, going back to what am I going to move tomorrow --

DR. SLAGA: Set the limits.

DR. MARKS: Set the limits. So safe other than a limit for SLG of 2.5 percent, and then we'll see how it evolves, how does that sound?

MS. EISENMANN: Now, what other compounds would be appropriate for reading across to -- you know, I asked for data on those two compounds. Well, maybe there's data on another compound I haven't asked for yet, is there another compound that would be better for reading across for the rest of these than what you've got data on?

DR. SHANK: Okay. What are the highest uses, I'll have to find that.

DR. HILL: In terms of concentration or in terms of number of uses?

DR. SHANK: Number of uses. Sodium stearoyl glutamate has 120 uses.

DR. MARKS: What page is that?

DR. SHANK: 57.

DR. MARKS: 57, okay.

DR. HILL: So other than getting higher concentrations, I'm good with glutamate. I have difficulties reading across a number of these other amino acids based on either glutamate or lysine data, that's the point.

DR. BERGFELD: I thought you took out the lysine ingredient.

DR. HILL: Lysine's there, that's --

DR. BERGFELD: I thought you said because of the --

DR. SHANK: You said that --

DR. HILL: I just said I wouldn't use it for read-across because the amide is on the other nitrogen, so it's not an alpha amido acid like the rest of them are.

DR. MARKS: Yeah, there's a number, I have sodium stearoyl glutamate is 120 uses TEA, cocoyl glutamate 65, so there's a fair number. I think the Lauroyl Lysine, it had 649, so that stood out as just having lots of uses.

DR. HILL: I think that was part of the reason why those two were selected is there were just tons of uses.

DR. MARKS: Right.

DR. SHANK: And the other high uses are glutamates, too. I think we can use sodium lauroyl glutamate as a read-across, but then you,

Ron, you said the acetyls are a whole other can of --

DR. HILL: No, I'm not really worried about those --

DR. SHANK: Okay.

DR. HILL: Because those could be hydrolyzed, I think even in skin.

DR. SHANK: Okay. So then I would say the sodium Lauroyl Lysine is safe as used, and the sodium lauroyl glutamate is safe up to --

DR. MARKS: The 2.5 --

DR. SHANK: 2.5 percent --

DR. MARKS: -- leave on --

DR. SHANK: -- leave on --

DR. MARKS: -- and 30 percent rinse-off, the data we have. It should be an interesting discussion. Any other comments, Halyna, Carol? Okay. So that's what I'll move to tomorrow is that, and then you like the non irritating, correct, with these? I think, are these, a lot of these are subtract and serve diluted, so we need to have the non irritating.

Okay.

DR. BERGFELD: But do you need it in the conclusion?

DR. MARKS: I think so, formulate to be non irritating. Any other comments? Okay. Next are the alkyl betaines. There's a draft report, and, of course, this is going to -- so this is the first review, 11 ingredients, I'm sure we'll go back to the betaine as 459 uses, so a lot of uses. The lauroyl betaine has 338. Rons, Tom, the 11 ingredients okay, and then we need, what are our needs to move forward?

DR. SHANK: Well, I have for needs, we need HRIPT sensitization data on one of the alkyl betaines, lauroyl betaine is used in mud packs at 0.06 percent, and then there are several alkyl betaines that are used in cleansing preparations at 8 or higher percent.

DR. MARKS: So you wouldn't take the betaine alone with the HRIPT and say that can be read-across with the others?

DR. SHANK: Correct. And the other need

I had was more data on the reproductive development toxicity studies on page 12 PDF. It says there were toxic effects in the fetuses and newborns, but I don't know what they are. I think that's important. I have to find page 12.

DR. MARKS: And let's go -- so, Ron, let me just be sure I have this right. So you want sensitization --

DR. SHANK: Well, that's me, yeah.

DR. MARKS: Yeah, that's okay. I've got sensitization data --

DR. SHANK: On at least one of the alkyl betaines.

DR. MARKS: Alkyl betaines. And then two was the reproductive developmental or just re --

DR. SHANK: Yeah, on page 12, at the very top, you get a little bit on the bottom -- well, actually, at the bottom of page 11, it says there were fetal malformations that weren't significant from the controls, that's fine. Some bone, skeletal changes.

MR. HELDRETH: I'd also like to remind of the extra data that Christina submitted today, there is a dermal sensitization there on the last page for lauroyl betaine, there may be some other ones there.

DR. SLAGA: I thought we can't use this to put it in the report, but you looked at it, right?

DR. MARKS: Well, it will go on a report in the next edition of the report, right?

DR. BERGFELD: You mean the European --

DR. SLAGA: Yeah.

DR. MARKS: Pardon? I'm sorry, Tom, repeat?

MR. HELDRETH: Legal actually cleared us to use this data. We have the summaries here, we don't actually have what the consortium has for the actual report, but we can use this.

DR. SLAGA: You can?

MR. HELDRETH: You can.

DR. HILL: That means that we have to digest it.

DR. MARKS: Let's take a couple minutes and look over this, because I really didn't. So, Ron --

DR. SHANK: I'm still looking.

DR. MARKS: Bart, it's this page to your -- well, we'll come back to the sensitization.

(Pause)

DR. MARKS: Ron, are you --

DR. SHANK: Okay, I found it, I had them marked in the wrong place, it's PDF page 11, the top. There's a dermal developmental toxicity study in rabbit, and I guess this was used as a dose finding range study, and it says near the bottom of the first paragraph that there were changes in the fetuses and newborns, but it doesn't say what they are. And this was used as a basis for an oral study in the rat, presumably, and I was wondering if the authors described the effects in fetuses or not, and I didn't have access to the journal for some reason. So if there's more information there, we should get that. And that was a dermal study, the rest of

the studies are oral, and they showed no problem, so, to me, that's confusing.

DR. MARKS: What study is that, can I --

DR. SHANK: Okay, yes.

DR. MARKS: Who is the lead author, I guess?

DR. SHANK: I have to find the references, now.

DR. BRESLAWEC: What page is that?

DR. MARKS: Page 11, Halyna. Because that, in the ECHA website, this summary, here, Bart, you mentioned there's a number of repro and developmental toxicity studies on this, so obviously, do you -- and then there's actually -- Ron, you probably didn't get to look at this, I just pointed out there are a number of alkyl betaines that wereÂ tested in animals -- right. And then, as Bart mentioned, this one with lauroyl in an HRIPT. Small number of volunteers but everything would indicate it's not sensitizing, so I think we could probably eliminate that insufficient data.

DR. SHANK: Okay. The reproductive toxicity studies are EPA reports, and I couldn't get ahold of those.

DR. MARKS: Okay. So that's an EPA report.

DR. SHANK: And then you say we, the sensitization data we have now?

DR. MARKS: Yes. If you look on, it would be the third sheet, third page at the top, you'll see betaine C12 to 14, or three studies there in Guinea pigs, and they were all not sensitizing. And then we comb to cocoyl betaine --

DR. SHANK: Right here.

DR. MARKS: -- that's non sensitizing. And, as Bart mentioned earlier, the lauroyl betaine in HRIPT was non sensitizing, so I think we can eliminate that.

DR. SHANK: Okay, fine. I didn't know it could --

DR. MARKS: Yeah, neither did I, I hadn't looked at that, either.

DR. SHANK: Okay, good.

DR. MARKS: So, do we want to -- I'm not sure it really would be an insufficient data notice, because we're trying to clarify the reproductive -- Tom, were you able to look through this? And, Ron, obviously, you haven't, how should we handle this? Should we take another five minutes and kind of scan these, or do you want to do that overnight, and then tomorrow in the discussion?

DR. SLAGA: I think we need to study it.

DR. MARKS: Okay.

DR. HILL: Can we at least talk about why we've got betaine lumped with all the rest of these? That was raised by somebody in industry, and I totally agreed with them. I had that in my reading it when I encountered that memo, I think this is the one. Yeah, it's page 58 right at the bottom in the memo from Halyna to, it was actually Dr.Â Anderson. Actually, it just says please include a rationale as to why it is appropriate to review these ingredients in one report. The only

outlier seems to be betaine itself, I don't know why it's in the same report.

DR. BRESLAWEC: I think we could live with it in the same report, it's the question of to what extent you can read across between it.

DR. HILL: None, zero, zilch, none. So without this data that came from the ECHA, I was ready to say you don't have anything. That, we've got plenty of information to conclude, I just --

DR. MARKS: So, Ron, you're going back, Ron Hill, you're going back to my original question, here, the 11 ingredients, okay.

DR. HILL: Yes. If you asked that, I missed it, because I was on a tangent right at that moment.

DR. MARKS: So we're going to look over this. Rons and Tom, I had questionable, do we need more robust manufacturer and impurities.

DR. HILL: I have that as a need.

DR. MARKS: Okay. Sufficient --

DR. HILL: Method of manufacture, not impurities.

DR. MARKS: Method of -- well, I had a question with impurities. Is DMAP or amino amine found in these?

DR. HILL: No. At least I can't see how that would arise.

DR. MARKS: Okay, so that shouldn't be an issue. And the manufacturing of these DMAP or amino amine is not used in the manufacture or these betaines? Because that was the problem with cocamidopropyl betaine was these were used in the manufacture or it could be residual.

DR. HILL: If the methylation were to be done at the end, and doubt that's the way it's done, because I suspect it's reaction of dimethylglycine with an alkylating agent that has the long chain on it. I wouldn't say I'd bet my life on it, but I'd come somewhere into that. So the only issue is, if there's dimethylglycine in there, which I highly doubt for these lipophilic ones, which is, again, another why we have betaine lumped with these surfactants. And do we have any concern about making sure it's all out so we don't

have nitrosation problems, or we have -- And if we had just sketchy information about the method of manufacture, which I think is going to tell us react dimethylglycine with a long chain alkylating agent. We know how to reach conclusions on a lot of that.

DR. MARKS: So method of manufacture is insufficient, correct?

DR. HILL: I would like to see it, because I don't think anybody has to collect anything, nobody has to generate any data, they just need to supply it.

DR. MARKS: Impurities, not an issue. And then the second issue is reproduction and development, that page 11, that EPA report; and then we're going to review these tonight, Tom and Ron and Ron, and if there are more things --

DR. HILL: There are only two repro tox that is listed on here, so that makes that, for you, fairly quick, and it's right at the very bottom of the last page.

DR. MARKS: That's okay, I don't want to

rush it, although we do --

DR. HILL: Okay, fair enough.

DR. MARKS: -- certainly have the time now, but I got the sense from Tom that he would like to spend more time to look over these.

DR. HILL: I have written composition, here, but I have no idea why, but I suspect it was related to some of the plant source fatty acids, but I'm not all that fired up consumed about it. I think I was, what's in hydrogenated tallow and tallow, I think that was it, and coco, but that's kind of, I don't think I have to have that.

DR. MARKS: Okay. So, so I'm going to be the one who is making a motion tomorrow, this gives us plenty of time, actually, if this turns out to be the way we go. At this point, our team and Ron, Ron and Tom, does this sound reasonable, an insufficient data notice, and what we would like is method of manufacture. And then, two, clarification of the reproductive and the development issue on page 11, the EPA report. And then, after reviewing these ECHA sheets, we'll add

anything more to that. Does that sound reasonable?

DR. SHANK: Yes.

DR. HILL: And, on the composition, I think the reason I didn't, in terms of moving forward, I didn't have any issue is because we have that information from, I think it's the vegetable orals report for those; it's coconut oil, hydrogenated tallow, and tallow. Maybe we could just capture that data and roll it over.

DR. MARKS: Okay. Any other comments?

DR. BERGFELD: Do you think you want, in your discussion, to make a declaration of the betaine versus the surfactants?

DR. HILL: I still think we should separate report.

DR. BERGFELD: Well, you haven't got anything in here about it.

DR. HILL: The betaine --

DR. BERGFELD: Well, you have, you don't discuss the lipophilic portion versus the surfactant portion of this group anywhere in here,

I just went back to read it. You discuss each one individually, but you're talking about studies, absorption, enhancement, penetration. You don't discuss that they may act differently. I would this is the place to put it.

DR. HILL: In which place are you think --

DR. BERGFELD: In discussion.

DR. HILL: In discussion?

DR. BERGFELD: Maybe in chemistry.

DR. HILL: Yeah, up in chemistry, I think there's, I thought there was enough, but maybe I need to look at that. I'll look at it again.

DR. BERGFELD: Well, you feel very strongly about it, you mentioned it here --

DR. HILL: Just, no, what I felt strongly about was that we didn't need to have betaine itself in with these, the rest of them are all long chain behaving as surfactants, whereas betaine would not. Betaine is small, water soluble, very different from the other substances,

that's what I was driving at. I would have liked to have seen that in a separate report all its own.

DR. MARKS: Okay.

DR. HILL: Because I think it just obfuscates when you mix together things that are so different and put all that data in one report. Because there's no reason to read-across, no basis for using that as read-across.

DR. MARKS: Okay. Any other comments? Wilma, any? Okay. So, tomorrow, I will move that we issue an insufficient data notice. One, we need the method of manufacture, two, we want to clarify that reproductive and the development issue from an EPA report document on page 11 of this draft safety assessment. And then we'll also, I'd huddle with the team before the meeting and ask about the review of this ECHA and whether that, if there brings anything else of concern. Or if you want to spend, do you want -- Tom, I just got the sense that five minutes isn't an adequate amount of time. I mean, weÂ could do --

DR. SLAGA: Well, we can go over it in the morning before we start.

DR. MARKS: Okay. Sounds good. Because it will come out, obviously, in the discussion tomorrow if there are any concerns, I just don't want to do this too quickly.

DR. SLAGA: It says in our thing that we can't use this without permission, and we do have permission now?

DR. MARKS: Yes, that's what Bart said, we just can't --

DR. BERGFELD: We can use the summaries, we can't use the specifics.

DR. SLAGA: You can use the summary.

MR. HELDRETH: You can use what's in front of you, you don't even have access to the full document.

DR. MARKS: So if there are concerns raised, then we have -- okay. We'll deal with that, then, tomorrow morning. And the next one is not going to be any easier. This is the last, is this the last one, are we.

DR. SHANK: It is.

DR. MARKS: Okay. The hydrolyzed wheat protein -- where is that on here, is that under hydrolyzed -- yeah, here we go. So, at the March 2013 meeting, we tabled it? The discussion of these, we wanted more information concerning the reports, particularly from Japan of Type 1 allergic reactions. These would be anaphylactictype reactions to the hydrolyzed wheat protein in soap products, so we issued an insufficient data announcement on: One; method of manufacturing data for the hydrolyzed wheat protein; and, two, composition and characterization. Also from the minutes, we decided to split out wheat from other plant proteins such as soy or silk, so it looks like we're going to proceed with doing the plant proteins individually. So, in this report, on the hydrolyzed wheat protein and the hydrolyzed wheat gluten, Rons and Tom, what are the needs? My first question is what's the difference between wheat protein and wheat gluten? Was that

mentioned in this report?

DR. BERGFELD: Somewhere, I think.

DR. MARKS: I didn't get a good sense. And why --

DR. SHANK: Wheat gluten would be a protein, and wheat proteins would be a mixture of proteins.

DR. MARKS: Right. So is wheat gluten one protein.

DR. SHANK: That's how I read it.

DR. MARKS: Okay. So, Tom, Rons, needs at that point? The manufacture still, the composition? Method and manufacture, the composition?

MS. EISENMANN: There is some information on, in Table 2. That's what I presume is the ingredient that the industry would like you to assess, the information in Table 2, plus there's information on what the protein, hydrolyzed protein that was causing problems in Japan, with a 40 to 50 kD protein produced by acid hydrolysis over a certain length of time. So you

have that information on a bad actor, and then you have the information on the protein from certain suppliers. I think you should assess the safety of the protein that's listed in Table 2.

DR. SLAGA: So we don't need anything.

DR. MARKS: Table 2, what page is that?

MS. BURNETT: Page 30.

DR. MARKS: Pardon?

DR. SLAGA: Page 30.

DR. BRESLAWEC: So I think the point is that we'd like you to focus on size as opposed to specific product.

DR. MARKS: Size. What do you mean by that?

DR. BRESLAWEC: The protein.

DR. SLAGA: Molecular weight?

DR. BRESLAWEC: Molecular --

DR. SLAGA: Range?

DR. BRESLAWEC: Yes.

MS. EISENMANN: Yes.

DR. MARKS: So I see, so, Tom and Rons, does Table 1 suffice for manufacturing? Is that

what you're saying, Carol?

MS. BURNETT: Table 2, it's the Table right under it.

DR. MARKS: Table 2. Oh, yeah, here we go. Was that also in written form in the body, did I miss that? Because, normally, we don't, when we read the report, we don't jump to a table and say this is a method of manufacture, there's actual text.

DR. HILL: I think there is. I was just there, I jumped down to the tables, method of manufacturing is on -- sorry, thank you -- PDF page 22.

DR. MARKS: Okay.

DR. HILL: And then you have to, because there's sort of preamble information in the chemistry section, you have to use that together with the method of manufacturing side of the section, and probably Table 2 to get the full picture.

DR. MARKS: So this is where you were saying, that's where you got to 40 or 50 kD in the

second paragraph of the method and manufacturing. I had that highlighted.

DR. HILL: So your suggestion to concentrate --

DR. MARKS: Larger than the main band in gluten. So how, that was my conundrum is how do you, there are, what, over 1,000 products that contain wheat protein? It's a large number, or 900, whatever it is. How do you make, how do you assure a safe product?

MS. EISENMANN: One suggestion is you limit the molecular weight size of the protein that could be used. Exactly what the limit should be, I mean, there is, one suggestion is it has to be greater than 30 kDs to bind to IgE. But I think some of the industry is using a cut off more of 3 kDs.

DR. MARKS: Three?

MS. EISENMANN: Three.

DR. BRESLAWEC: So anything below 3 is safe?

MS. EISENMANN: Right.

DR. HILL: So the real question is, they started with, does one come from gluten. It doesn't say that -- yes --

DR. MARKS: Yeah.

DR. HILL: -- from gluten by partial hydrolysis, means you shouldn't have anything in there in the first place bigger than gluten, assuming that whatever that was that was larger than gluten and went through the partial hydrolysis, it's hard to imagine why that wouldn't have been -- so, then, it's almost like it might have been a contaminative microbial growth after the fact, after it was produced, I don't know. The real issue is how did it get in there. It's unlikely to have been something that survived the hydrolysis process, to my way of thinking. I don't know what protein would survive the hydrolysis that they're using for gluten and still end up with a 50, 40 to 50 kD molecular size -- molecular weight, excuse me.

MS. EISENMANN: I don't --

DR. HILL: I know you don't know, I

can't even conjecture, but I'm thinking the microbial growth happened after manufacture and then it somehow got -- I mean, it's just a guess, this is something that wouldn't normally appear in any of these. An anomaly.

DR. MARKS: Carol, where is the data that support the idea that about 3 kDs, that this is the protein, this is the molecular weight of the presumed allergen, or is that just a theoretical, if it's above 3 kDs, it doesn't bind IgE? Because I don't, there was a similar issue with natural rubber protein, and when the natural rubber protein gloves were manufactured, there was a limit of, like, 230, I think, and once that limit was in place, the Type 1 reactions to natural rubber lay text gloves disappeared, we just don't see it anymore. So that's where I was hoping there would be something, like you say, set a limit, I just couldn't find anything to help me in arriving at that.

MS. EISENMANN: The discussion is in the report under Type 1 hypersensitivity.

DR. MARKS: Yeah, it's on --

MS. BURNETT: Page 25 of the PDF, there's --

DR. MARKS: 25.

MS. BURNETT: -- about midway, there's a few paragraphs about --

DR. MARKS: Yeah, the most IgE epitopes in UWP -- what's the U stand for? The WP is whip. Wheat protein. There's a U on that page.

MS. BURNETT: Unmodified wheat protein.

DR. MARKS: And then what's the H again?

DR. HILL: Hydrolyzed wheat protein.

DR. MARKS: Hydrolyzed.

MS. BURNETT: Starting with the paragraph that says binding patterns of serum IgE.

DR. MARKS: I'm looking at the one, overall, the authors concluded binding pattern. So the one above that. So, in no cases, did the IgE bind to the hydrolyzed wheat protein less than 30 kDs, I see what you're saying.

MS. BURNETT: And then the paragraph starting with, in a Japanese study, which is below

that, the last sentence, there arises the size.

DR. MARKS: So you would suggest put the limit of hydrolyzed protein polypeptides less, should be greater than 30 kDs.

MS. BURNETT: Less.

DR. SHANK: Less.

MS. EISENMANN: Less. Or you might choose another one, the 3. I mean, 3, I think, is --

DR. BRESLAWEC: It's the one that your --

MS. EISENMANN: Right, the Japanese study, that's the one they were doing.

DR. MARKS: Where did the 3 come from? You're doing a margin of safety times 10? Onetenth of that is 3.

MS. EISENMANN: It's 3 kD.

DR. BRESLAWEC: 3,000 Daltons, 3 kDs.

DR. HILL: So if you read, if you're on page 25 of the PDF, and you ignore that very last three lines, just above that talks about, it's theorized that limiting the size of the proteins

or polypeptides. And what comes before that is, they're hypothesizing, probably with some evidence, that they're getting higher molecular weight aggregates from smaller molecular weight fragments by things like disulfide coupling, which is certainly going to happen if you free cystines --

DR. MARKS: Do you feel comfortable, Ron, Ron and Tom, that using maybe that, to me, theorized, if I'm at risk for having an anaphylactic reaction -- I'm not sure theorized, that's just a word, but this 3,000 Dalton, 30 amino acid -- how difficult is this for industry to, are they going to be looking at their ingredients and say, okay, we're going to have no residuals less than 3,000 Daltons.

DR. SLAGA: More.

MS. EISENMANN: I think more and more, they are becoming more concerned about it because of this incident in Japan and other incidents like it. But this is an area where the industry would like you to research this. You may need more time

to look at, and we can try to find more references for you, and maybe someone to come in and speak on this issue, if you'd like. This is a concern for the industry right now.

DR. MARKS: I actually like the idea having an allergist, somebody who is an expert in Type 1 allergy come in and speak to this.

DR. SHANK: I would.

DR. SLAGA: Yeah, definitely.

DR. MARKS: Because I don't feel --

DR. SHANK: This is a weak one for me, I'm sorry to say.

DR. HILL: Well, and the reality is that the molecular level understanding of this sort of thing has been coming up very rapidly in the last several years on that. It would make a difference in terms of how one -- I mean, reaction is reaction, but it makes a difference in terms of how one makes predictions and interprets data, I think.

DR. MARKS: So, with that in mind, should we table this and ask that we have an

expert in Type 1 allergy come in and discuss it? And it obviously is going to be an allergist who understands not only the molecular biology of this, somebody that's got a basic science background, just not somebody who sort of comes in who, you know, say, a clinician who doesn't understand, perhaps, the basic mechanism and molecular biology. So, we're at the stage now of having a tentative safety assessment of hydrolyzed wheat protein and hydrolyzed wheat gluten. One option would be to table it and ask that an expert come in and address this, does that sound like a reasonable way to proceed? Let's see, who's -- tomorrow, it will be, where is it, hydrolyzed wheat protein -- it's Belsito, but that doesn't matter, we can (laughter) -- so, do you like that idea of tabling?

DR. SLAGA: Table.

DR. SHANK: I do. This is an important issue.

DR. MARKS: Yeah, absolutely. I'm wondering --

DR. SHANK: I think we need to fully understand what's going on, here.

DR. BERGFELD: Do you think that the literature has been searched deeply enough on this subject? Because if there's an expert, he's certainly written on it, and we should probably see that, as well. He or she, excuse me.

DR. HILL: You've got a pretty good series of references, here, but yes.

DR. MARKS: Okay. So I'm going to suggest tomorrow we table it, because I have, I don't feel -- I'm amazed that there's a thousand uses, and it hasn't been seen. You had suggested that it's possibly some manufacturing process in Japan that resulted in this, and that's the same with the -- I mean, it's reproducible in terms of the natural rubber latex in gloves when we had them manufactured in the U.S., we didn't see the problem. Once the HIV epidemic occurred and the demand for gloves outstripped what we could manufacture in the U.S., it was Pacific Rim, they weren't rinsed properly, they weren't processed,

and then we had a lot of residual natural rubber protein, and, bammo, then we had the contact urticaria and Type 1 reactions to gloves. So I like the idea of getting an expert in, because, you know, a great majority, it's not an issue with a thousand uses, but we need to understand, in my mind, better what guidance we need to give to industry of how to proceed with this.

DR. SHANK: I agree.

DR. BERGFELD: Does industry have a cap on it currently of 3 kDs?

MS. EISENMANN: Each company has different caps.

DR. BERGFELD: I mean, but what is the highest?

MS. EISENMANN: I don't know that answer, but it's variable.

DR. BRESLAWEC: Probably between 3 to 30.

MS. EISENMANN: Well, I know one goes down to 2.5, too.

DR. MARKS: Yes.

MR. HELDRETH: Just so this isn't something that goes off into table land indefinitely, should we set a time frame on when we expect to have this back in front of you?

DR. MARKS: Yeah, my feeling would be is, if we had the expert at the beginning of the next meeting, we could then have it on the agenda in either the next meeting or the following meeting, then we could proceed with a tentative safety assessment, with the recommendations in terms of dealing with a Type 1. So I should think within one or two meetings, we should be able to do it, I guess, but it depends on the availability of the expert.

DR. BRESLAWEC: Well, we will certainly search an expert out and recommend for CIR to make a decision on which expert they'd like to speak. But my understanding is, when you table something, you don't rewrite the report, you don't redraft the report, it is as stands.

DR. MARKS: Right.

DR. BRESLAWEC: We happen to think that

the discussion of the Type 1 allergy is pretty thorough, so we just work from this document and then consider the expertise of the speaker, and then see if you want to amend it at that point.

MS. EISENMANN: Do you have any suggestions for speakers? I mean, we would be also interested, you don't have to say now, but if you have, we would always be interested in your suggestions.

DR. SHANK: Okay. I do, but I'll let you know.

MS. EISENMANN: Okay.

DR. MARKS: Okay. So I'm going to -- depending on what the motion is, let's table. It will be easy, I'll second the motion. If it isn't, I'll make that suggestion, and then we'll see where the panel decides to go with this. Any other comments about the hydrolyzed wheat protein and hydrolyzed wheat gluten? Okay, table. This is the end of the ingredients I have on the agenda, is there anything else, Ron, Ron, Tom, we should cover, Rachel, Halyna, Wilma? If not, I

think we can adjourn, then, and we'll read over the ECHA, and then we'll huddle in the morning in terms of how to deal with that. Thank you, everyone.

(Whereupon, the PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

I, Christine Allen, 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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