124th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

MAIN SESSION

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P R O C E E D I N G S

(8:30 a.m.)

DR. BERGFELD: Welcome. Alan has prompted me that we should get started.

Again, here we are gathered and it's so nice to see everyone here, especially some of us that had a little difficulty getting in last night, Ron in particular. Ron Shank.

We have -- this is our 124th CIR meeting, unbelievable. And today we're going to be looking at 17 ingredients, 10 of which to go final, 3 tentative final, and 2 new drafts. We were to have a visitation from PCPC but they're unable to make it today. And so hopefully in the near future that will happen..

The other thing though I wished to mention was I was quite struck, and I think maybe all of you were with the consistency of the reports this time. They were beautifully done, very easy to read and interpret. The tables and certainly the addition of the chemical structures were excellent. My personal opinion was that they were markedly improved, and I want to thank the CIR staff for that. I'm sure that the editors of

the Journal will be very pleased as well.

Alan, do you have anything to say before we break up into the teams?

DR. ANDERSEN: It's about as nice a thing as you'd want to hear. It's difficult to go beyond that, but I'm sure that the effort that everyone has been putting into this to get to a level of consistency is not something that we do just in isolation. It's been awful (inaudible) steady feedback from the panel that we've tried to incorporate into it. The Personal Care Products Council, CIR Science and Support Committee has been ever diligent to make sure that if there are issues we hear about it. So the process is indeed working to produce the best product that we know how. Is it going to be perfect until we go back and forth with the panel for a few times? Probably not, but that's science.

DR. BERGFELD: Was there anyone else who would like to make a comment? I forgot to mention I was most impressed also with the discussions. They were thoughtful. They raised the issues and told the answers as best we could tell them, more

so than in the past somehow. They were more readable. I don't know about anyone else's comment upon that but I thought they were excellent.

DR. ANDERSEN: Great.

DR. BERGFELD: So, shall we proceed?

DR. ANDERSEN: I think so. Let's see. My notes say that Belsito is out of dodge, so to speak. I do want to make a comment that you have some additional materials that have been provided. You certainly received Wave 2 electronically. I think we have copies of the Wave 2 information but blessedly, I think it was like 50 pages. It was just not much additional stuff. But you received an additional copy of an analysis that BASF did on triclosan, parabens questions that will be in front of you.

I also wanted to, for everybody's benefit, make a comment about the one study on triclosan of effects on muscle that was published in PNAS. It was really tough for us to deal with that. We have an agreement with the Copyright Clearance Center to allow us, for a fee for being part of this, to distribute information that's

published to the panel for review. PNAS is not included in that agreement. So when it came to receiving this new publication, wanting to send it out to you, legally we couldn't do that. PNAS does not grant that distribution right. You can use it individually. Any one of you that wanted to look at it could have gotten it and looked at it but we're not allowed to distribute it, which really gets in the way of doing our business.

Now, having said that, I have copies of it here today, so if anybody wants to look at it I have it if you haven't already looked at it. And I've got copies of all of the other studies that are in this -- triclosans, parabens, new data, milleau. So when we get to that I have them. Any other interested party during the team meeting and team discussions of that, I'll have all of the copies so you can feel free to look at them. I also brought copies of the final safety assessment of triclosan and the final safety assessment on parabens just in case you needed to refresh your memory about what's in those.

But just in both of those studies there were a lot -- that's very unquantified -- there

were repeated dose toxicity studies, none of which raised any endpoint, any question about muscle effects. So all of the studies that have been done to date have not flagged that that is an endpoint that anyone is actually seeing in testing. So.

D: Just in terms of those studies, Alan, I know it's frustrating that you can't provide them to the panel, but I think most of us through our libraries can easily get them. So just giving us the name of the author or even the ISN number, within five seconds I had that paper up. And if someone from industry is really interested, you can also purchase it online when it comes up. So, you know, if that's the case in the future, just alert us to the publications. I think most of us can easily download them.

DR. ANDERSEN: Okay. Great. Not to put Stan on the spot, but Stan Milstein has joined us. He'll be sitting in as the FDA liaison today. And welcome. And now it's time to kind of pack up and move to the other room, which I'm not really sure where it is but hopefully you can find it.

DR. MARKS: Are we ready?

DR. HILL: More or less.

DR. MARKS: Okay. So the first report we're going to review is the safety assessment of tin oxide as used in cosmetics. That's in the Green Book. As you'll recall, in the June meeting of this year this report was tabled. We decided to delete tin and focus on tin oxide. And one of the questions came as to whether or not this would be absorbed. If not, then obviously the toxicologic data needs would be reduced.

So Rons and Toms, how did you find this report as it stands now? Do we need anything more or could we proceed with a tentative report?

DR. SLAGA: Safe.

DR. MARKS: Safe?

DR. SHANK: Safe.

DR. MARKS: Ron, safe? Okay. So I will move that we issue a tentative report on tin oxide that it's safe in its present practice of use and concentration in cosmetics. Are there any discussant points that anyone has concerning this ingredient?

Ron Shank?

DR. SHANK: There's still reference to

elemental tin in the report, in the abstract, in the summary, and in a table. I recommend those be deleted. And in two cases there are concentrations of tin oxide listed. I have it written down here without the valence. So I'm pretty sure the valence, the oxidation date of the tin is known. So if that could just be clarified. It's on page -- Panel Book 17 under ocular irritation and report page 4 there's 1.3 percent tin oxide but no valence state. So if we could just put down that it's either Tin 2 or Tin 4, that would be helpful. That's all.

DR. MARKS: And we're dealing primarily with Tin 4 here. Is that correct, Ron Shank?

DR. SHANK: Yes.

DR. MARKS: So delete tin in the report and clarify the valence in several parts, Wilbur.

Any other comments? Actually, that's not the discussion; that's more editorial.

DR. SHANK: Editorial.

DR. MARKS: Yeah. Anything else? Okay. Do we need to say anything about absorption or just that it isn't?

DR. SLAGA: It could be mentioned in the

discussion.

DR. MARKS: The discussion.

DR. BERGFELD: Could I ask a question? A number of years ago the FDA had some proceedings dealing with sunscreens and titanium oxide and zinc oxide. And I have -- I attended that. It was at a CIR meeting and we went over to hear some of the dissertations. And one of the things that held up those physical blockers was the fact that the industry was micro pulverizing them. So they were putting them in a state that they could be absorbed. And when absorbed, they were toxic. And they have just now approved titanium oxide and zinc oxide, and I'm not sure what they did with the micro pulverized because the products available are micro pulverized because you cannot see them. You know, it used to be that when you put them on they were opaque and you could see the opaqueness. So my question really is falling into this particular chemical, does it change if the chemistry changes and the physical properties change?

DR. SHANK: If the physical properties change, yes, it will change the absorption rate.

MS. BRESLAWEC: We are not aware of this chemical being nanoscaled.

DR. HILL: Even if it was, what would be the absorption mechanism? I mean, incidental oral ingestion but solubility in this case is so low that I don't know how it would get in. I mean, I suppose it could work its way down into sweat glands or something but it should just sit there.

DR. BERGFELD: Well, this had systemic toxicity to kidneys and other organ systems when absorbed, but it was a different, obviously, element.

DR. HILL: Yeah.

DR. SLAGA: I doubt if it was even made in smaller particles that it's (inaudible) stratum corneum.

DR. MARKS: Rachel.

SPEAKER: Two points. One on this, and that is something that I've been thinking about actually. I wonder if it would be useful for our purposes to know whether a particular ingredient is formulated in a nano form, because I think if it is then there's different considerations that the panel would need to consider. So that would

be, I think, very useful if that information were to be included in reports.

The second thing is more specific to this report, and I want to make sure that the panel is comfortable with the fact that there's no reproductive and development toxicity data here, no carcinogenicity data here, and while the summary mentions that data on absorption distribution metabolism and excretion of Tin 4 oxide were not found, I want to make sure that the panel is comfortable with the summary and the discussion and the analysis of this ingredient without carcinogenicity and reproductive and developed mental toxicity information.

DR. MARKS: Yeah. I think that was why I wanted to reiterate the absorption here. And you could hear the panel without it being absorbed and there's not concerns.

Now, carcinogenicity, Tom, did you have any --

DR. SLAGA: No. I mean, first of all, I would have to get down inside the epidermis, down to the basal cells.

DR. SHANK: The last paragraph of the

discussion handles that and says we're not worried about the systemic toxicity because of poor absorption rate.

DR. HILL: Maybe it should say exceedingly poor or something to make it clear. And maybe this is partly a consequence of the last version of the report there was some status fluoride data in there where there would be enough solubility and there was some systemic data. At least I urged that that be taken out, which I think it was. So I believed that that was completely irrelevant and included the issues, but --

DR. MARKS: Any other comments? So again, tomorrow, I'm going to make a motion that a tentative report be issued on tin oxide with a conclusion of safe. These discussant points actually are already in particularly the absorption.

Wilbur.

MR. JOHNSON: I have one question, Dr. Marks. I know that with respect to the data that were provided by industry we sort of assume that the data are on Tin 4 oxide and in the text it states likely Tin 4 oxide. Can we confirm that

the data provided by industry are actually on Tin 4 oxide so I can amend the report?

DR. EISENMANN: Yes. Since that's the cosmetic ingredient, it's Tin 4 oxide.

MR. JOHNSON: Tin 4 oxide. Thank you.

DR. MARKS: Okay. Let's move on to the next ingredient in the Green Book, methyl glucose polyethers and esters.

So this is the first time we've seen this report so it's the first time we'll review the methyl glucose polyethers and esters. And there's always two things that I ask. One are the ingredients listed? And that's in Panel Page Book 17- 22. Do those look okay? And then obviously, what are the needs for this?

So I'm looking at Table 1 on Panel Book 17. Is that a good place to look over the ingredients Rons and Toms? And are there any that stand out that shouldn't be included in this group?

DR. HILL: The only thing I noticed and it doesn't pertain to what ingredients are listed is that there was a small selection where there seemed to be a conflict between -- I'm trying to

find Table 2 now because here is one and here is -- okay, two is the structures, right?

DR. MARKS: Correct.

DR. HILL: Right. There seemed to be a conflict between -- what did I write down? Conflict on Table 1 with definitions as compared to what's there in Table 2. And it's -- I'm on Panel Book 18. It has to do with -- sorry, this is one of the first ones I looked at. I'm trying to remember what I wrote now.

DR. MARKS: So essentially, you want to be sure that the chemical name matches the structure.

DR. HILL: Right. And I think these are dictionary definitions, but the structures don't seem to correspond and so one of them may not be correct. It could be the dictionary. And I assume the definitions in Table 1 are copied straight out of the dictionary. Is that correct?

MR. JOHNSON: No, Dr. Hill. In some cases I guess the italicized text would really include that portion of the definition provided by the CIR staff.

DR. HILL: These are not italicized on

any of these. I'm on the last page of Table 1.

MR. JOHNSON: Okay.

DR. HILL: And it's the one --

DR. MARKS: Well, there's -- if you look at the top of page -- Panel Book Page 18, actually, there is some italicized on the first one. Methyl --

DR. HILL: That wasn't one of the ones I was concerned with.

DR. MARKS: Okay.

DR. HILL: It's actually the third, fourth, fifth, sixth, and seventh one on that page starting with PEG-20 methyl glucose distearate. This would be a conflict between what's there and what we have in the structural information on Table 2. So we can look at that later.

DR. MARKS: Right.

DR. HILL: It doesn't affect my assessment of the --

DR. MARKS: But that's an alert, yes. So the PEG-20, the PEG-80, the PEG-20 again, if you would confirm, Wilbur, that his structures match.

DR. HILL: That the structures

correspond to the definitions in proper form.

DR. MARKS: Right.

MR. JOHNSON: So the PEG-20 methyl glucose distearate and the next two?

DR. HILL: And the next four..

MR. JOHNSON: Next four?

DR. MARKS: Yeah.

DR. HILL: So PEG-20, dimethylglucose distearate and then the four after that down through the sesquistearate?

MR. JOHNSON: Okay.

DR. HILL: But otherwise, in terms of the list of ingredients, I was comfortable with what we had.

DR. MARKS: Ron Shank, listed ingredients, anything to be deleted? Anything to be added?

DR. SHANK: No. I have no change in what's listed.

DR. MARKS: Tom?

DR. SLAGA: No, I don't have anything to add or take out.

DR. MARKS: Okay. So we'll proceed with the ingredients as listed in Table 1. And now the

next question, what are the needs that we have to move this report on?

DR. SHANK: Well, for the esters, I separated the esters and the ethers. For the esters, their use of very low concentrations and they're likely to be hydrolyzed in the skin. We don't have systemic toxicity for those. But because it's unlikely that any appreciable amount of the ester would get into the circulation, and I don't think we need the systemic toxicity. We've already reviewed the hydro -- the products of hydrolysis, the PEGs and the fatty acids.

We have irritation and sensitization data at 100 percent for one of them, PEG-20 methyl glucose sesquistearate. I have 100 percent. Its maximum use is 10 percent. And that was negative. The only possible concern I could see would be that methyl glucose would be a hydrolysis product and that has a potential to compete with glucose metabolism, but the concentration would be so low I don't think that's a problem. We could handle that in the discussion. So I'm content with what's available on the esters.

The ethers, I don't know anything about

their absorption. If they are absorbed, then we would need to know genotox and reproductive developmental tox.

DR. HILL: I had a question, and I guess this is probably for Wilbur. At least it indicates that methyl glucoside coconut oil ester is listed as proof for direct addition to food for human consumption. If that approval being the case, I would think that we'd have toxicology data on which that decision was based. I didn't research this myself, but we're not picking up much of anything on that score. So I'm wondering if somehow we missed something in the search.

DR. BERGFELD: I have a question. I also have a question and that is on page -- Panel Book 13 through 14. And the Lubrizol entries of testing, they're lacking details of those test systems and concentrations, et cetera, which I would think would be needed to make these valid rather than just a summary statement.

DR. MARKS: I had the same question. What are the RIPT details? Are they in humans? Number of subjects? So I would have liked that.

DR. BERGFELD: And it looks to be all

the Lubrizol materials which reference 22 to 28.

DR. SLAGA: Yeah, I had the same concern. It was very meager data.

DR. MARKS: So we're going to put that as a need also.

DR. HILL: Yeah, because while I certainly agreed with Dr. Shan's comments, I mean, if you look at the table that's not in the report but in the book as prepared, for the whole list of ingredients there's no systemic toxicity for any of them listed at all. I mean, and so, but it surprised me partly because the direct food additive used for the one and then also it's restricted, the sequi -- method of glucose sequistearate is restricted to uses in indirect food -- what's the term? Indirect food additive, which means you can use it during processing and so forth. So it seems like if they made that restriction, there may have been a basis why they made it. That's not picked up in here either.

MR. JOHNSON: No information was revealed in a search.

DR. HILL: You couldn't find it. Yeah. I'm just saying somewhere along the line the FDA

looked at these and they agreed this could be direct, this one was indirect, and information has to be out. I mean, I would think how they made those decisions and because of the ability for read across, that would be an extremely valuable set of data, if it's there.

DR. SLAGA: The only need I had was genotoxicity. It would be nice to have a little.

DR. MARKS: Genotox?

DR. SLAGA: Yeah. Ron mentioned that, too. So.

DR. MARKS: And is that for just the ethers or the esters, too?

DR. SLAGA: Well, I'd ask for both right now.

DR. MARKS: Genotox for both. Okay. Now, I also had a concern about the methyl glucose dioleate. There were case reports of allergy to that. The use concentration was 2 percent, and we didn't have any RIPT data on that. So I would like to see an RIPT on methyl glucose dioleate to confirm that it's safe with the use concentration.

How about impurities?

DR. SHANK: The problem with the case reports is that someone reports that there was a clinical response and they mentioned a particular ingredient, but there are other ingredients as well. So why do we necessarily say it's the oleate/dioleate? I'm not trying to defend it.

DR. MARKS: Yeah.

DR. SHANK: I'm just trying to look at it objectively. And you pick out one out of several chemicals and say -- you imply at least that the allergenicity is due to that one chemical.

DR. MARKS: They actually --

DR. SHANK: There were several other chemicals in the formulation.

DR. MARKS: They actually in a couple of the cases had positive patch test reactions to methyl glucose dioleate. So they dissected that out from the final product. If you look in the second paragraph, patch testing with methyl glucose dioleate, this was 10 percent (inaudible) revealed a positive reaction. And the last one, the last paragraph under that case reports again, patch testing with methyl glucose dioleate 5

percent (inaudible) positive reaction.

So I agree with you, Ron. When it's the total product and they haven't sorted it, separated it out, then I don't put a lot of stock in that. But when they've actually got the ingredient with positive patch tests, then that raises a red flag for me. And that's why I wanted to see what the RIPT was with the methyl glucose dioleate.

DR. BERGFELD: On page 13, they have an animal study, a rabbit study that lacks data but it's negative.

DR. MARKS: Yeah.

DR. BERGFELD: Nonirritating, nonsensitizer as they've stated but we don't know the concentration of that.

DR. MARKS: Correct. That's why I wanted to see an RIPT. At 2 percent it would be desirable since that's the use concentration.

How about going back to the impurities? Were you happy with that section? Do we need that?

DR. SLAGA: I had it listed, too, but --

DR. MARKS: So if we're going to go forward with insufficient data, I mean, we

normally don't go through with ingredients unless we have some sense.

DR. EISENMANN: There is more information on Lubrizol's website on impurities and physical chemical properties. You just need to click through. I mean, they went to the first page of this group of ingredients and there's more spec sheets. So there is more information on that that can be added that's available on the website..

DR. MARKS: Okay. And was the -- was the ingredient very pure in this or was it --

DR. EISENMANN: They're given information about the material as they sell it, which is -- generally is a mixture. They did have heavy metals, levels and ash and the standard information you'd find for this type of ingredients are there.

DR. MARKS: So presumably we have that data. That wouldn't be insufficient but we'd like to see it in the next rendition.

DR. HILL: Well, and of course, we're all -- where we have polyethers we always have the concern about the monomers, but -- and we keep

being assured that processing -- they take heroic measures to get rid of any residual ethylene oxide or propylene oxide. So I would assume that applies but maybe we need to put that in the discussion.

The other thing I was going to ask, I remember we discussed a couple of meetings back -- I think it was a couple of meetings back -- material safety data sheets. And this came into my head not in terms of the toxicity but it did come in terms of physical chemical properties because really don't have anything captured here. And then there was another report -- it's not this one -- where everything listed was calculated and it bothered me that that was the case. Did we say we can't reference material safety data sheets at all? I'm trying to remember what our philosophical stance on that was because what you're talking about on the website, I don't know if those are data sheets for the products.

DR. EISENMANN: They have specification sheets and technical data sheets and they have MSDS because I was suggesting some of the same

information is on all three.

DR. HILL: And, of course, the caveat, and this has come up in some of the writing I've seen, is that, you know, we have some specs that say not more than thus and such. And if it's from a particular vendor, that's the particular vendor's spec. So unless you have a compendial spec, it has to be written in such a way that we realize that's that vendor's specification and is it always in some of these reports? And so we have to keep in mind that yes, many of these ingredients may have only one vendor but it doesn't necessarily stay that way for the next 10 years. So.

MS. BRESLAWEC: I think the report refers to certain specs and then that becomes the current conditions of use. Is that correct?

DR. HILL: I agree, but it isn't always written so that's clear, and that was just really saying that for the staff members in the room, that when it's coming from a spec from a particular vendor, we need to make sure it's written that way. Clearly written that way.

DR. MARKS: Okay.

DR. BERGFELD: Read through what you have?

DR. MARKS: Right. I was going to go -- I think we'll move forward with an insufficient data announcement, would be the appropriate next step. And if the needs that I've gathered are one, we need the penetration data, absorption data of the ethers, so that we can decide whether we need the systemic toxicity if it's observed. Two, we want the RIPT details with the methyl glucose sequistearate. We want genotoxicity data for both. We specifically want a RIPT on methyl glucose dioleate. And then five, we'll get in the report the impurity data that we have already and perhaps then also what are the monomers and ethers, and are they of concern. Is that correct, Ron?

DR. HILL: No, I wasn't saying monomers because the only monomers that I would worry about in this case are the ethylene propylene oxide. And again, I think --

DR. MARKS: That would be in the impurities.

DR. HILL: Yeah. But I would add to the list that in those five ingredients that I flagged

where the definition seemed to conflict with what we had in structure, that we make sure we have information that tells us really what those compounds are. I'm sure -- well, they should be mixtures but what actually are we looking at those -- what are the nature of those molecules for sure?

DR. MARKS: Okay. Any other data needs?

DR. BERGFELD: You need the Lubrizol data. You need the Lubrizol details of those studies, animal studies on page 13.

DR. MARKS: Yeah, I mentioned that. The MG sequistearate. I mentioned getting those data studies in here.

MR. JOHNSON: Can you run through that list one more time, please, Dr. Marks?

DR. MARKS: Okay. One is what is the penetration absorption data of the ethers? I'll go as we discussed them, not necessarily in the way they are in the book. The RIPT details with the MG sequistearate. Three is genotox data on both. Four is RIPT on methyl glucose dioleate. And then five, the impurities are going to be clarified in the next report. Next iteration of

this report.

Any other comments? Okay. So presumably tomorrow I will be seconding an insufficient data announcement and I'm sure the Belsito team's data needs will be similar to ours.

Okay. So the next is chlorphenesin. It's in the Blue Book. In June, we issued a tentative report that it was safe, and as you recall, the reason we reviewed this ingredient, there was some confusion as to what chlorphenesin and we've clarified that as far as the cosmetic ingredient. Chlorphenesin, not the drug chlorphenesin. And so we're at the stage now that we should be issuing a final report on chlorphenesin that it's safe as used.

Are there any comments?

DR. HILL: Well, I would just say pursuant to the comments I made at the last meeting, I went to the primary literature to try to determine, because in most cases when you have a primary carbomate -- or maybe I should put it this way -- a carbon made of a primary alcohol and a drug, it will be bio-transformed to that alcohol. So in that case, if you gave chlorphenesin

carbomate, it would be bio-transformed to chlorphenesin and then that toxicology would have been applicable. What I determined -- that drug's been off the market for a long while and looking back at some of the studies, they really didn't do -- I think they showed the major root of biotransformation was actually glucuronidation that comes out in urine. They really didn't do definitive blood levels of chlorphenesin itself and so I couldn't come up with anything, at least so far, that suggested that we could rely on that toxicology in any way, which is what I was hoping for. So I thought I should follow up because of the comments I made last meeting. I don't want to say I came up empty, but I didn't come up with anything I'd like to hang my hat on in toxicology.

DR. MARKS: Okay. Any other comments other than -- is that the correct pronunciation, Ron Hill?

DR. HILL: Potato, potato. Chlorphenesin, chlorphenesin, one of those. I think I always heard chlorphenesin.

MR. STEINBERG: Chlorphenesin.

DR. HILL: Chlorphenesin? I've never

heard it that way.

DR. MARKS: That's the way I say it. So chlorphenesin..

DR. HILL: I will collapse to chlorphenesin and we'll go from there.

DR. MARKS: I kind of like chlorphenesin, but -- at any rate, we have in front of us -- we'll see which way I say it tomorrow -- tomato or tomato. But at any rate, any comments about the discussion? I think we want to thank you, staff. Well written.

MS. BRESLAWEC: The introduction and the summary currently contain the following statement: Based on the use concentration, chlorphenesin in cosmetics and the dermal root of exposure, serum concentrations would never reach levels that are needed to cause muscle relaxation. And we're concerned that that continues to confuse the issue since we are not aware of any data and apparently neither is the panel about potential muscle relaxation with chlorphenesin.

DR. SLAGA: That should be deleted.

DR. HILL: When I was teaching this drug, the information I had was that the muscle relaxant effects were probably due to chlorphenesin, not

the carbomate. So that's a cloudiness that I was trying to resolve in the literature search and I never got there.

MS. BRESLAWEC: Right. So our position is if there are any data that suggests that there are muscle relaxation properties, then let's see them and discuss them. If there are not, then we shouldn't be attributing that to this ingredient because it continues the confusion and perpetuates.

DR. MARKS: Again, so our team members agree and this sentence can be deleted. Where was that Halyna?

MS. BRESLAWEC: It was in the introduction, page 1 and page 10 of the Panel Book. That's the summery, I think, statement. The first paragraph of the Discussion on Panel Book 27. And in the introduction.

DR. MARKS: Hold a second. The last --

MS. BRESLAWEC: CIR Panel Book 18.

DR. HILL: I guess my question is do we know for certain that this ingredient at a high enough concentration can't cause them? Have those studies been done in such a way that we know

it?

MS. BRESLAWEC: The question I have is are we aware of any studies that suggest that there is muscle relaxation? If there is, let's see them. Let's discuss them. We're not aware of any and I'm not sure that you all are either.

MR. STEINBERG: I think that the statement in the discussion is an indication of why FDA asked us to take this on. It may not be the result --

MS. BRESLAWEC: I think they made a mistake.

MR. STEINBERG: That's correct. Because they had asked us because of that concern, and if we need to clarify that there is a difference between this an (inaudible) or to eliminate it we will. But I think that's the reason and that statement should probably stay but be clarified.

MS. BRESLAWEC: As long as it doesn't suggest that there's muscle relaxers --

MR. STEINBERG: Yes, agreed.

MS. BRESLAWEC: Properties associated with chlorphenesin, which we are not aware of and

I don't think the panel is aware of either.

DR. BERGFELD: So you're suggesting that the whole statement be changed but the impact is that they're two different --

MS. BRESLAWEC: Absolutely.

MR. STEINBERG: Right.

MS. BRESLAWEC: And one of them, there is no data suggesting that there's a muscle relaxant process. That's the difference.

DR. BERGFELD: So you'd have to change both sides, the introductory remarks and this one.

MS. BRESLAWEC: Thank you.

DR. MARKS: Well, Lillian, I think the first paragraph on page 27 in the Discussion clarifies that. It makes it very clear why the CIR considered this ingredient. It was driven by the FDA.

DR. HILL: Except when you get to the last sentence.

DR. MARKS: Yes. And I think the last sentence -- I would agree with you. I think the last sentence in this -- the first paragraph, the discussion, in the last sentence in the

introduction I agree could be eliminated. Team members, Ron Shank, I see you shaking your head. Ron Hill and Tom?

DR. SHANK: I agree.

DR. BERGFELD: May I make a comment? I think that there's a problem but such effects are not expected for the cosmetic ingredient. And I think you should change that. Somehow not expected means it could happen to me.

DR. MARKS: Correct.

DR. HILL: I mean, I think the introduction -- these paragraphs were written with the intent to show that there's difference and they're different chemicals and I'm just not -- I don't think it quite got there.

DR. MARKS: David.

MR. STEINBERG: David Steinberg. There was one case of a newborn baby dying from the cosmetic use of chlorphenesin and it goes back probably 20 years ago. I can probably find the exact date. It was a newborn baby. The mother was nursing the baby. The mother used a nipple cream to soothe her nipples and the cream was preserved with chlorphenesin. She did not wash

her breasts before feeding. The baby ingested very small amounts and died. That was the only case that had ever come up and the FDA has it on their website, I believe, and they did the background to see that this was --

DR. MARKS: Dave, we would need to verify that and we ask whether the material you're referring to was chlorphenesin as we understand it in the cosmetic context or chlorphenesin carbomate.

MR. STEINBERG: It's chlorphenesin. It was used to preserve the cream, just as it's used as its own use in cosmetics as a preservative.

MS. BRESLAWEC: And my recollection from the last meeting was that the statement FDA made was that it was not chlorphenesin; it was chlorphenesin carbomate and they erred -- they erred in asking for information on chlorphenesin.

MR. STEINBERG: I know the formulation. It was -- what they said -- I know what went into it. It was the mixture that was sold by Collaborative Laboratories, which uses straight chlorphenesin.

DR. HILL: Well, and I will say, and

these are very high doses, but if you look at both the acute and the chronic toxicology, there are effects on rats that suggest, I mean, loss of gait, lethargy, the sorts of things that one might get if you did have -- I mean, there are multiple possible explanations. They could be central, they could be peripheral, but they're not inconsistent with the muscle relaxant effect. The point is preservative use now, the current use, the percentages are so low that the chances of exposure -- I mean, I flagged that statement that you want to remove and said it's almost certainly false because, again, back when I was teaching that drug, which was back at the beginning of my career, at least the folklore was that the result traced at least in part to the hydrolyzed carbomate. In other words, chlorphenesin. And I couldn't find work where they'd done the analytical chemistry on systemic blood levels to really support or refute that one way or another, and I'm not sure the in vitro work has been done to determine one way or another does it have muscle relaxant effects or not. I couldn't find those data one way or another, which means you

don't know for sure but you don't know for sure that it isn't. And that's the bothersome part here for me.

DR. MARKS: But the statement that Halyna is questioning is true, is it not?

DR. HILL: I think it can come out of the introduction. I agree with her and I agree with those who would like to do that.

DR. MARKS: How about --

DR. HILL: The tangential mentions in the introduction, I'm going to continue my search when I go back because I didn't quite finish --

DR. MARKS: How about for the discussion because that's where it's actually elicited. And in fact, the sentence before refers to muscle relaxant effects but such effects are not expected for the cosmetic ingredient chlorphenesin.

DR. HILL: I think if the definitive science had ever been done and again, I'll try to finish my search to know one way or another do the effects trace strictly to the carbomate or do they trace to that metabolite, or both.

DR. MARKS: But the reason we're finding

this ingredient safe is because even if it did have, even though there's some question and you've raised with this animal study is whether it may have muscle --

DR. HILL: But the doses were huge, you know. That's the thing.

DR. MARKS: Yes. So would you like -- so one way of dealing with this is eliminate that sentence in the introduction but keep it in that paragraph which is more robust in the discussion? So that would be an alternative.

DR. HILL: If we could get wording that the Science Support Committee is comfortable with then, yeah, sure. And meanwhile, I'll continue my search to see if I can find anything.

DR. MARKS: Ron Shank, would you like the sentence left in or deleted as suggested? It says both effects are not expected for the cosmetic ingredient chlorphenesin. So it does refer to we're not concerned about this happening with the cosmetic ingredient.

DR. SHANK: I understand why the sentence is there but when I read the report it stuck out in the introduction and again the

discussion that that last sentence is confusing.

DR. MARKS: Right. Oka.

DR. SHANK: Bringing in the discussion on the cosmetic ingredient and muscle relaxation when we had said the muscle relaxant effect was due to a drug, not the cosmetic ingredient.

DR. MARKS: Okay. So you would continue to support deleting the sentence in both sections, both the introduction and the discussion?

DR. SHANK: Yes, I would.

DR. MARKS: Okay. Comments? Ron? Tom? We had said yes, delete.

DR. SLAGA: I said delete, too.

DR. MARKS: Yeah. Okay. So again, I will move tomorrow that we issue a final report with chlorphenesin or chlorphenesin is safe and that there will be editorial comment and we'll see what the discussion brings tomorrow with the Belsito team. But those two sentences deleted. Panel Book page 18 and 27 delete sentence.

Any other comments? Yes.

MS. WEINTRAUB: Dr. Marks --

DR. MARKS: Rachel.

MS. WEINTRAUB: -- I just wanted to make

sure that -- I understand the concerns about these sentences, but I think it's still important that the distinction be made between the ingredient and the drug, and I'm afraid that if these sentences are taken out that that concept may be lost. So I just think we need to make sure that that distinction is made.

MS. BRESLAWEC: That's our objective as well, to make sure that there's a clear distinction between the drug and the cosmetic ingredient.

DR. MARKS: And I think that actually is quite clear in the second sentence of the discussion right at the top there. It says that opining -- the CIR panel opined that the drug chlorphenesin carbomate, also known as chlorphenesin, is known to have muscle relaxant effects, but such effects are not expected from the cosmetic ingredient, chlorphenesin. So I think that's very clear that there's a difference. One is a carbomate; one is not.

DR. BERGFELD: Maybe you should add because of the low concentration --

MS. BRESLAWEC: That's where we have a

problem.

DR. MARKS: Yeah, that's the follow-up sentence we're deleting.

MS. BRESLAWEC: Because of the low concentration, the suggestion is that in fact it could, and we're just not aware of any such data.

DR. BERGFELD: I still think as stated it could. Would not be expected to me means there is somebody it could be expected in.

MS. BRESLAWEC: That's up to the panel to decide. It's just a concern. We really would like to make a clear distinction, as clear a distinction as possible between the drug and the cosmetic.

DR. HILL: And that is what made the literature searching so difficult. I mean, basically, it means you have to read each paper and decide to keep or toss because at one point in time the generic name for that drug was chlorphenesin. We referred to the carbomate, so when you do the search, if it just says chlorphenesin, in many cases you don't know which compound unless it had the CA numbers or unless it's clearly written, then, you know, research

done with chlorphenesin and you don't know for sure. And that means you have to read everything, every primary piece if you think there's an issue. And I'm not sure we've come to that level and, like I say, the folklore in the teaching materials I had way back at the beginning was the muscle relaxant effects were in part traceable to the parent compound. In other words, the carbomate was removed and attributable to chlorphenesin itself. And I just can't find definitive research that says one way or another, yes, it really is that or yes, it really is that. The major root of metabolism in humans, most normal humans, is glucoronidation, which suggests that most of the activity would be attributable to the carbomate and not the metabolite, but you just can't rule it out definitively based on everything I've looked at so far. You don't know. And I guess absence of data is absence of data, but I'm not even sure it's absence yet because I haven't finished what I was looking for.

MR. STEINBERG: Would you be comfortable with saying that data suggests that there is no data to suggest?

DR. HILL: Yeah, if we wrote it that way that would be fine. Because that way if somebody comes up with some, we can go back and amend.

DR. MARKS: I think if you want to add, Lillian, another sentence in the discussion, we can -- you can certainly do that. Show that to Dr. Hill -- Drs. Hill and Shank, and then tomorrow, as we discuss this ingredient for the final safety, this is editorial but also we'll have the input of the Belsito team.

Okay. Any other comments? For now, when it comes to comments after the motion has been made I'm going to propose that those two sentences be deleted but we'll see how that discussion evolves tomorrow, and if there's an alternative way of stating the safety, we will certainly support that. What we want to do is be clear.

Next in the Buff Book is Retinol and retinyl palmitate.

So this is -- these ingredients are to be looked again and considered whether or not we're going to open the document for review. In 1987, the CIR declared that these ingredients

were safe. In 2005, it these were re-reviewed as safe but then we noted in that re-review that there was an NTP study ongoing and when that occurred and we had the results we would review those results and decide whether to reopen. So the first question is should we reopen based on the National Toxicology Program Data, which we got a wave on that. And obviously, I'm going to ask Tom about that. And then there is also the question of whether we should open to add seven more retinol esters.

So there are two issues. One, is there concern about the photocarcinogenesis of these ingredients? And based on the NTP study and reopen because of that? And is it a no- brainer to add -- reopen and add seven retinol esters? So Tom, do you want to start with the interpretation?

DR. SLAGA: Yeah, I would reopen it on both accounts.

DR. SHANK: So would I.

DR. MARKS: Okay.

MS. BRESLAWEC: I just want to point out that this is not a final study. It's still a draft study. It has not been issued in its final form.

DR. SLAGA: It's also the longest existing study in NTP's history.

MS. BRESLAWEC: Which could cause people to wonder why it hasn't been finalized. Just pointing that out.

DR. SHANK: But we also received several studies on photomutagenicity which were positive.

DR. SLAGA: Right. Right.

DR. SHANK: So my concern causing me to suggest we reopen it isn't based only on the NTP study but also the several photomutagenicity studies.

DR. SLAGA: And for clarification, it's really a photo co-carcinogenicity study, not a (inaudible).

DR. BERGFELD: Could you comment on the NTP study at all? The draft that you reviewed?

DR. SLAGA: Yeah, it's, actually, if Alan was here -- back in 2009, Alan Connie published a paper on creams the SKH-1 mouse as a vehicle, and all the vehicles from industry that he tried -- I'm giving a pre to the NTP. All of them increased UV or acted like a co- carcinogen

to photocarcinogenicity. So there is a strong database which we don't even mention in here. We need to pull Alan Connie's paper 2009. I believe the first author is Lu, L-U.

MR. JOHNSON: Is it L-I-U?

DR. SLAGA: Because he did reformulate and took out a few things and made a cream that was not photo co- carcinogenic. Related to the NTP studies that obviously one of the big questions is that the cream control gave an enhancing effect but when they added the retinyl palmitate with it, it gave additional effects. And you could argue that it's possible the cream did something to the retinyl palmitate that gave a further effect, but it definitely, to me, there is a hint that there is something happening, and that is why I'd like to see, you know, more discussion of this. As Ron brought out, there is other data that actually says there is effect here. So I have some concerns.

DR. HILL: Do we know if any other those other retinol esters are in use? We don't -- we didn't try to --

MS. BRESLAWEC: We haven't looked..

DR. HILL: Okay.

DR. MARKS: So reopen. And the primary reason is to review the carcinogenicity of this mutagenicity of these ingredients?

DR. SLAGA: Well, to re-review all data since we looked at it back in 2005, be it photomutagenicity, photo co- carcinogenicity. It should be photo co-mutagenicity. To review because there is some other data that suggests that UV can actually change the structure and lead to oxides with some of these compounds.

DR. MARKS: So, Tom, again, to review the photomutagenicity and the photo co-carcinogenicity?

DR. HILL: Do we have to reopen if we think we're missing key pieces of information? Or can we actually table because we haven't done anything and find the additional data that we think we might not have captured and make sure it gets considered? And then meanwhile, we can survey and find out are these other esters being used. I mean, I don't know the rules of order here because I'm relatively new.

DR. SLAGA: Well, based on all the

criticism of this study, it can be another year or two before all the dust settles before a peer review states precisely what happened.

DR. HILL: Because I know the environmental working group, you know, it's clear what their stance is, this surgeon, and we need to work on it. But for me the science here is extremely complex partly because these are endogenously present compounds and so we have binding proteins and endogenous processing and then there's the issue of, okay, if a particular individual is taking a high dose supplementation of Vitamin A already and then they add these on dermally, that might be a different circumstance than if they're not. So I was left with -- and I know Peter Fu personally, actually. He's a first rate guy in some of the chemistry parts of this, but to me the complexity was such that I couldn't reach a conclusion within the timeframe I had to do it and that's why I'm asking. I agree that the NTP study suggests there's a signal here but, gee, you're getting positive results on an ingredient that we looked at and saw no such before. It's a little strange.

DR. MARKS: So Ron, procedurally we can reopen, and after we review the data, decide we aren't going to reopen it and just handle the discussion. So this would be considered a re-review, updated information, but one in which we aren't reopening unless we decide to do it for the seven -- adding the seven retinol esters would warrant reopening that alone. If we had these ingredients, we'd reopen.

And so going on, Panel Book page 1, it's the one on the back side of the initial memo, are there any of these -- you notice Wilbur in red has put "no-brainer, add on; no- brainer, add on." So do these seven meet the retinol acetate, the propionate, the linoleate, the oleate, the rice brand. So now we have rice. Rice branate, soyate, which I assume is from soy but I'm not sure. And talate. Are these all no- brainers? Yes. Okay. So we would do those.

So Ron Hill, from a procedural point of view we would reopen this and just add those seven.

DR. BERGFELD: Could I add something?

DR. SHANK: I think there's a potential

here that we may change the conclusion; therefore, that's why we should reopen. Adding on other ingredients is fine, but I think we really need to look at our conclusion based on what is new now.

DR. BERGFELD: I'd like to add on a practical point, in dermatology and cosmetics for photo aging and rejuvenation of skin, this group of chemicals are widely used in just over- the-counter products, not prescription products. And growing, is it very effective? And retinol is in almost everything now.

DR. MARKS: Well, I was struck on retinyl palmitate, when you look at the current frequency and concentration of use, there are over 2,000 uses. That's all on Panel Book 32.

MS. BRESLAWEC: A request that as part of the reopening it for re-review, that the CIR staff attempt to determine whether NTP is, in fact, repeating the study as has been rumored. Or what the status is of the draft.

DR. MARKS: Wilbur, did you hear that request?

MR. JOHNSON: I'm sorry.

DR. MARKS: Halyna, would you --

MS. BRESLAWEC: A request that the CIR staff determine, (1) when and if the draft will be finalized; and (2) if, in fact NTP is planning on redoing the study.

DR. MARKS: So we not only have that but we'll capture as Ron Shank mentioned, there are some photo mutagenicity.

DR. SHANK: There are several, and I think if only those studies were presented to the panel without the NTP study, we would ask to look at those studies and then if we find -- if we agree with their results, they are all positive for photomutagenicity, photo genotoxicity, we would then ask for a photocarcinogenicity study and we already have that. It may be flawed but before us it is also positive. So I think we really need to look at this very, very carefully.

DR. SLAGA: Just for a note, one of the reasons this study was extended so long is after Alan Connie found his results, he talked to NTP because those studies were underway and they had some confusion. So his cream showing an enhancing effect on photocarcinogenicity was one of the reasons. And NTP did not evaluate

histopathologically the controls which I don't understand why they didn't do that.

MS. BRESLAWEC: It is essentially a study where the control -- a flawed study. I agree it may be the only study out there but it was significantly flawed.

DR. BERGFELD: I'd like to add that they did not read the dermatological literature before they did this study and created their control because --

DR. SLAGA: Alan Connie's study was published in 2009. This was started many years before that.

DR. BERGFELD: Well, I was just going to say anything that adds a lubricant to the top of the skin does enhance the UV excitement. We do that with psoriasis all the time to enhance the phototherapy.

DR. MARKS: So I'm not sure there if your conclusion is that when you add the retinol that you increase the carcinogenesis that indeed having a control showing some increase is expected. Now your end point is is there an enhancement of that or not? And this would

suggest there's potentially an enhancement with these Retinols.

DR. SHANK: Well, there are. I have not read them myself but in our books, reference to studies where the retinol or retinyl palmitate actually reduced the UV-induced finding dimmers, which is the usual mechanism we think of inducing skin cancer by UV light. But, and that's a good thing. But the UV light also produced oxidate -- reactive oxidate -- reactive oxygen species, et cetera, which were, they suggest, pro-carcinogenic and mutagenic. So I think we really need to look at this very carefully.

DR. MARKS: Any other comments? So presumably tomorrow I will second a motion to reopen these ingredients to explore and clarify the more recent studies, including the NTP study on carcinogenicity of these ingredients or mutagenicity or genotoxicity, all of that, along with adding seven retinol esters, which are a bit of an aside. That's the lesser of the important issues.

DR. SHANK: Okay. Is this the time where we would ask for more data needs or do we wait

until it's officially reopened?

DR. MARKS: Why don't we get it for the record now and then Ron Shank, I'll ask you tomorrow to note that.

DR. SHANK: Okay. I think if it's known, I'd like to know what the residual levels of retinol and retinyl palmitate were in the epidermis? What were those levels in the NTP study? Did they look at that? It was the UV -- the UV exposure was in the morning. The retinyl palmitate was applied in the afternoon. So if it's UV-induced photocarcinogenicity, the retinyl palmitate applied in the afternoon would still have to be there in the next morning's exposure. If they have any information on that, I would appreciate it.

And then I'd also like to know what are the normal levels of retinol in human epidermis. Is that known? And how much does cosmetic use of these compounds change that?

DR. MARKS: Any other comments? Thanks, Ron.

(Recess)

DR. MARKS: We'll resume after that

previous break we just took.

Okay. The next is Blue Book -- Panel Blue Book bis- diglyceryl polyacyladipate-2 and -1. And we should be at the stage now of issuing a final safety assessment for these two ingredients that they are safe as used. Any comments?

DR. SHANK: Conclusion's good as is.

DR. SLAGA: Yep. Particularly good conclusion.

DR. HILL: I thought they did a particularly good job with the inhalation write-up on this one. This was one -- in a couple of the others where I was less satisfied, this was one of the couple that I pointed them to to compare with.

DR. MARKS: Yes, Halyna.

MS. BRESLAWEC: I would like to point out that this was a report that we had no comments on. That doesn't happen.

DR. HILL: Of course, anything I say here is going to carry even less weight than usual because I'm Mr. Hill according to the transcript. So I got demoted..

DR. MARKS: So tomorrow I will second

a motion that this ingredient be -- the safety assessment have a conclusion of safe. Okay.

Next are the microbial polysaccharide gums. You will recall from the last meeting we had a discussion concerning how we would name this report. So I'm going to assume that our panel members like this final naming. And we're at the point now of again issuing a final safety assessment with a conclusion that these gums are safe. Any comments?

DR. SHANK: The report's good as is.

SPEAKER: Dr. Marks, there's actually a comment from the Council, and being that it's final you wouldn't have seen it otherwise. They had a comment, and I'll read it as is, "Other than listing the three hydroxyl propyltrimonium chloride compounds, this report includes no information about these ingredients or the hydroxyl propyltrimonium group. Perhaps the previous report on the trimonium ingredients should be mentioned in the introduction. In the discussion section, the CIR expert panel should then indicate that based on the safety data on the polysaccharide gums and the data on trimonium

ingredients included in the previous report, the CIR expert panel considers trimonium polysaccharide gum compounds to be safe." Which would just strengthen the discussion if you agree to put it in, but it seems as it would be an editorial change.

DR. SHANK: I'm okay with that.

DR. SLAGA: Same here.

DR. MARKS: Okay. Monice, do you want me to ask you tomorrow when we say are there any editorial comments, you will bring that up?

MS. FLUME: That will be fine..

DR. MARKS: Okay.

DR. HILL: I really liked the use of the color in showing the structure of these multi-component polymers at the beginning. I'm sure that's out of the routine but I really liked that.

DR. SLAGA: Yeah, I mean, that kind of color uses in organic chemistry presentations has been out there for a while and I certainly use it when I teach, but I liked it even though it requires then color copies, which I imagine increases the cost substantially. But it's still

nice.

MS. FLUME: Thank you.

DR. MARKS: You're talking about Panel Book page 18?

DR. HILL: Page 18, yeah. I wouldn't think we'd need to see them on tables and such, but this use in this particular instance was really valuable and nice. I liked it and I just wanted to point that out.

DR. MARKS: So, Ron, you liked it from a scientific point of view or an aesthetic point of view?

DR. HILL: No, from a reader. From a reader point. Well, both, but I mean, from a reader point of view. A readability point of view.

DR. MARKS: Gotcha. So tomorrow I'll move that we issue a safety assessment of the microbial polysaccharide gums as used in cosmetics are safe. And then Monice, I'll ask for you to read that editorial comment from the Council. And I assume the Belsito team will hear that editorial comment before tomorrow. But if not, that's okay. You can surprise them.

Next, we're with the vitis vinifera aka grape- derived ingredients. It's in the Blue Book. And we're running a string now of final safety assessments. We're at the point now that we can issue a final assessment for these ingredients with a conclusion they're safe. Comments from the panel?

DR. SLAGA: Great report again.

DR. SHANK: I do have a comment. The leaf extract is used on leave-on concentrations up to three percent. We have no biological activity on the leaf extract. It is highly colored, but we don't have any phototoxicity data on that. It is used in suntan preparations. Some of the other ingredients are also color but they're used at very low concentrations. Can this be handled in the discussion? The concentration of the leaf extract in the suntan preparations Is not three percent; it's lower. I have to look it up. I didn't write it down, but I thought that was a concern that we did not address in the discussion.

DR. HILL: I had a concern about -- and this should be editorial in the discussion. While I would agree that we would not expect glycosides

of phytosterols to be absorbed across the skin, many of the plain old phytosterols which we might get in hydrolyzed products, for example, which we've now added are comparable to hydrocortisone and numerous of the other dermally-applied sterols. So to say they don't penetrate the skin seems absurd. And that doesn't change any conclusion, but I'm just pointing it out in terms of changing the way that that particular -- it's the third paragraph of the discussion section reads. So if you just struck out that clause or sentence, what I wrote was, "For those that potentially could be," and then I crossed out everything down to "extensive data are available." Because some of the sterols, if the glycosides are removed most certainly can be, at least penetrate the skin, if not show up heavily in the system.

DR. MARKS: What page was that, Ron?

DR. HILL: It's where the discussion is, page 27. So if you want me to repeat what I just said I would do it if it were up to me. It says, "Also, although no dermal absorption data were available," what I did then was added, "For those

that potentially could be." And then I crossed out everything down to "extensive data are available showing that these phytosterol constituents are not estrogenic," blah blah blah. It just bothered me to say they wouldn't be absorbed because particularly in the hydrolyzed and some of them they're there as free stole anyway, there should be at least skin penetration. And I think we continue to not make the distinction between skin penetration versus systemic availability.

DR. MARKS: Ron Shank?

DR. SHANK: The only concern I had was the one I mentioned.

DR. MARKS: Right.

DR. SHANK: Phototoxicity.

DR. MARKS: And I was looking at my notes from our previous meeting in June, and I hadn't -- we hadn't picked that out. I have irritation, sensitization, all the skin toxes being okay.

DR. SHANK: I missed that the last time we went around on this, but this time I saw that the leaf extract is highly colored.

DR. HILL: The percentages are high.

DR. SHANK: And at 3 percent I thought we should have phototoxicity data on that.

DR. MARKS: I guess my clinical reaction would be that it's unlikely to be a photo-irritant or a photo-allergen because to my knowledge, and we didn't capture anything here in terms of workers and vineyards who obviously all the time are brushing up against broken leaves, getting material from grape leaves on their skin, to my knowledge there's no reports of vineyard workers having phototoxic or photo-allergic reactions to their skin. And normally, if that were a significant problem, and obviously there the extract, whatever it is they're getting on their skin, I would think it would be obvious. It certainly occurs in other settings. So I think from a clinical perspective I'm not concerned about it, but I hear you in terms of we don't have that data point.

DR. SHANK: If the clinical experience is cleared up this is not a problem, then let's put that in the discussion as to why we don't need experimental data.

DR. HILL: And I'm not sure I buy the vineyard exposure argument because I think there's a difference between that kind of exposure versus putting it in a cream that might enhance dermal penetration and then smearing it on. So I guess I wasn't so concerned based on the nature of the compounds we're probably talking about. I guess we have a definitive characterization of those colored components and they're polymeric like that, but I missed that last time, too.

DR. MARKS: Monice, so did I obviously.

MS. FLUME: Just, I actually have two questions/comments. The 3 percent is used in a perfume, so I don't know if that would play a role. The actual skin us concentrations as in skin preparation products are under 1 percent. I think under a 1/2 percent actually. And then on CIR Panel Book, page 25, does have one occupational exposure referenced in a vineyard and then a case report. And it is only one case report, but they did test a crushed leaf extract with UVA. I don't know if that's useful at all.

DR. MARKS: It's under the sectional

Occupational Exposure. Yeah, that's a different immunologic reaction they're testing for, but again, it's looking at vineyard workers.

DR. HILL: Yes, but at least in that case they did prepare an extract, an ethanol extract of the leaf. I don't know if we have details of exactly how they did it.

DR. SHANK: But you don't know the role of light, sunlight.

DR. MARKS: Correct.

DR. SHANK: In that report.

DR. HILL: Right. They just used UVA and UVB light mixture according to that. Did I read that correctly that they treated with the extracts and then hit with UV light?

DR. MARKS: That's under the case report, I think.

DR. HILL: Yeah, it's under the case report, which --

DR. MARKS: That's different than the occupational above.

DR. HILL: Oh, okay. All right, okay.

DR. MARKS: Where they were looking for type one reactions. They were doing prick testing.

So, I think, again, for me the reassuring part is there's, to my knowledge, and you didn't obviously, Monice, find it in the literature, reports of high frequency of eruptions with these workers. You know, obviously if they developed the eruptions then we have to decide what type. It could be the pesticides or whatever, but in this case they didn't have a high incidence of dermatitis, whether it be photo or allergic contact or photo-allergic. So that's reassuring, although it still doesn't address the issue of having a direct study showing that the grape leaf extract is not a phototoxin cutaneously.

How would you suggest we handle it, Ron? At this point should we say an insufficient for the leaf extract? Pull that out? Then we would obviously -- we couldn't go to a final, which is okay. We would pull it out and say insufficient because of photo testing on the leaf extract. We could say safe with everything else and insufficient for the grape leaf extract.

DR. SHANK: I would recommend all the ingredients except the leaf extract are safe. And then insufficient for the leaf extract needing

photosensitization data. And then we'll see if the other team responds with energy. We could then argue should we rely on clinical experience.

DR. EISENMANN: So this report would not go final then; it would have to go back?

DR. MARKS: That's correct.

DR. SHANK: That's correct, sorry.

MS. FLUME: And then Dr. Shank, so it would only be the leaf extract and not the other leaf ingredients?

DR. SHANK: My understanding is the other leaf ingredient -- the other grape ingredients are used at such low concentrations -- the ones that are colored are used at such low concentrations that it wouldn't be a problem. Is that correct?

MS. FLUME: Well, as of right now the leaf oil, leaf seeds, leaf/seeds/skin extract, leaf water, and leaf wax, they are not reported to be used, so we include the caveat that if they were used it is the expectation that they would be used in the categories and concentrations comparable to the others. So would they also therefore be insufficient?

DR. HILL: We'd expect that the oil and the wax would not have those colored components. I'm not sure about that leaf seed skin.

DR. SHANK: Right. It would be only for colored ingredients.

DR. MARKS: Which could be put in the discussion. And again, Ron, to repeat, the 3 percent was in --

That was a leave-on?

DR. SHANK: The 3 percent was in the leave-on. I don't -- Monice says it's in the perfume. What's the next highest concentration?

MS. FLUME: For the leaf extract, the next highest concentration is 0.04 percent in face and neck creams, lotions and powders; 0.02 in lipstick; and then 0.01 in other skin p reparations. So with the exception of the perfumes, everything else is very low.

DR. SHANK: Okay. And that's in our book here?

MS. FLUME: Panel Book page 111..

DR. SHANK: All of the page numbers -- in that section, all of the page numbers in my copy were not -- were cut off..

DR. MARKS: Actually, it's on the back page.

DR. SHANK: The back page?

DR. MARKS: It is actually -- meaning it's only -- if you go looking at the opposite pages, it actually is there. It's page 4 of 4. Instead of going forward the way we usually do, Ron, go backwards and you'll see it's on the back of the page.

DR. SHANK: Thank you. Okay, so its concentration is also very low.

DR. MARKS: Except for the perfume.

DR. SLAGA: So that can be put in the discussion.

DR. SHANK: That can be put in the discussion, and therefore, I withdraw my request for additional data. Thank you, Monice, for pointing that out. I missed it.

DR. MARKS: Why is that, Ron? Why would you feel more comfortable with a perfume?

DR. SHANK: Because I would assume you use just very, very little. Don't you?

DR. MARKS: So the coumarins in one perfume, which gives a berlock dermatitis, and

that's a phototoxic reaction, and so Shalimar was the name of the perfume. So it's not reassuring to me that it's in a perfume.

DR. SHANK: Oh, okay. I thought a perfume you just touch your skin with a little bit. You actually put it on a fair --

DR. BERGFELD: Aftershave?

DR. MARKS: Oh, yeah. You can --

DR. SHANK: Aftershave would be different, but perfume you put --

DR. MARKS: Directly on and --

DR. SHANK: Very much?

DR. MARKS: -- anyplace -- if it were phototoxic, any place you dabbed it on, whether it's little spots or streaks if it were true. So I wouldn't eliminate -- I would still continue the insufficient for phototoxic and photosensitive unless we find that the concentration in perfumes, that's not right. That it were in those very low concentrations that you have below there.

DR. SHANK: Okay, thank you --

DR. MARKS: 0.02.

DR. SHANK: -- for clarifying that. Thank you.

DR. MARKS: Page 111. So actually, I won't be the one making the motion tomorrow. I have a feeling I may not be seconding the motion. And then I will bring up the issue of continuing with a draft final. But the new draft final will say safe for all except for the grape leaf extract, and that's insufficient for phototoxic, photosensitive data. And we'll see where that discussion goes, whether or not there's also a strong feeling from the Belsito team that the clinical impression and experience would override the need for a phototoxic, photosensitive testing for the leaf extract.

Any other comments? Over to the Alkyl Esters. It's the Pink Book. So this was reopened in March to expand the ingredients and also to decide whether isopropyl linoleate is now safe. So Ron and Tom -- the Rons and Tom, are the ingredients okay? And they're from Panel Book page 3, 211, large number of ingredients.

Monice, what number is that? Two hundred and what?

MS. FLUME: Two hundred fifty four.

DR. MARKS: Two fifty tour. Tom?

MS. FLUME: And 60 of those have previously been reviewed.

DR. SHANK: I had a question on the ethylhexanoates. On page -- let's see, Panel Book 28, the European chemical substances information system lists ethylhexanoate as a reproductive risk. So the embryo would be a target. And I think we have information on cetearyl ethylhexanoate. That has been reviewed already and found to be safe. So in the discussion we could handle the question of the ethylhexanoates relying on the information we have on cetearyl ethylhexanoate. Or eliminate the ethylhexanoates because they're not no- brainers.

DR. MARKS: So you would just handle that in the discussion?

DR. SHANK: Well, either handle it in the discussion saying that we're not concerned about the ethylhexanoates because we have data on cetearyl ethylhexanoate or don't add the ethylhexanoates to this list of ingredients because they're not no-brainers. One or the other..

DR. BERGFELD: But the decision that we

made was it should be no-brainers on the add-ons.

DR. SHANK: That's my position. I would just take those out.

DR. MARKS: Ron Hill? So you would take them out, Ron, because you can read across. You didn't feel comfortable with reading across?

DR. SHANK: That's correct.

DR. HILL: Which one is it you're looking at? I mean, I know which one is in the text, but which ingredients of them are we talking about because basically the chain length mattered and absorption rates mattered. A general thing -- a general issue that I identified in going and looking and saying -- and this was the one where it stood out glaringly to me, thus and such ingredient has been previously reviewed and found to be safe, but then what we're really not capturing in statements like that is safe when we have a document is contingent on conditions of use and the ingredients that are reviewed in that particular document. And we're not always picking that up, which is why you sent us those three big thick supplement books so that we could look at all those old reports. And I didn't

remember -- I remember basically grilling people on the ethylhexanoate in particular and that we got data eventually to suggest that we were okay, but now --

DR. SHANK: The European --

DR. HILL: I thought we looked at that one before. Isn't that on the list? No, we didn't according to this.

MS. FLUME: So Dr. Shank, in the discussion, the draft wording that is there, want to alleviate the concern for the ethylhexanoate component, it would be the first full paragraph on CIR Panel Book page 35? It's report page 9.

DR. HILL: The trouble is there, and I noticed that statement but I didn't notice it necessarily, terephthalate is very different molecule than these extended esters. And so I'm not sure we know how the hydrolysis rate compares, how the systemic availability would compare in those two cases. Do we know if that was a chronic oral study or a single-dose oral study or -- the terephthalate?

MS. FLUME: I'm trying to find right now if I pulled that from the discussion on cetearyl

ethylhexanoate.

DR. HILL: Okay, well, we'll wait.

DR. SHANK: My feeling, that's a good paragraph but I didn't think it went far enough to cover no-brainers. And since there is a concern on some of the ethylhexanoates, I didn't feel comfortable just including all of them without any data.

DR. HILL: This is a case where the reported use concentrations are pretty high. Up to 55 percent body and hand creams, lotions, and powders.

DR. MARKS: So, Ron, specifically, do we have -- which tables should we look at that we can see the ingredients you would delete? Are they in one block or are they scattered throughout?

DR. SHANK: They are scattered throughout, so you just have to look at the list. Go down and see where it says ethylhexanoate.

DR. MARKS: Okay.

DR. BERGFELD: I think page 36, maybe.

DR. SHANK: Pardon me?

DR. BERGFELD: The page 36 CIR Panel is

the list.

DR. SHANK: 35 and 36.

DR. MARKS: 35-36. So like the first one that I see on page 35, Panel Book 35, is the C12-13 alkyl ethylhexanoate. So anything that has a hexanoate in the ingredient would be eliminated. Now, none of these, Monice, have been reviewed before? Because obviously we aren't going to eliminate ones that have been reviewed before.

DR. SHANK: Some of them have been reviewed before should be left in. It's just the add-ons that are ethylhexanoates I don't think should be added on because they're not no-brainers. But if they've already been reviewed, that's fine. Keep them in.

DR. MARKS: Okay. So obviously we want to at this point identify those. We won't go through all those now, I don't think Ron Shank, unless you want to. But eliminate the ethylhexanoates that are add-ons that haven't been previously reported, and that's because of your concern about was it reproductive?

DR. SHANK: Reproductive.

DR. MARKS: Reproductive. Okay..

MS. BRESLAWEC: Dr. Shank, what about the ones that start with ethylhexyl but have the group on the other side?

DR. SHANK: I'm sorry, which ones.

DR. EISENMANN: The ones that start with ethylhexyl.

DR. HILL: They would be the alcohol.

DR. MARKS: So you're talking about on page 36 there in the first column. There are a number that start with ethylhexyl, like ethylhexyl adipate, ethylhexyl C10 to C4, et cetera. Those. They're the ones you're questioning, Carol? Yes. Ron, what do you feel about those?

DR. HILL: I thought we had data on that alcohol but perhaps not.

DR. MARKS: Again, I think the question is can we read across? We obviously aren't going to eliminate ones that were assessed to be safe previously. It will depend on you, Monice, when we get this new list and the next rendition of this report.

MS. FLUME: As far as those starting

ethylhexyl, there are quite a few that have been reviewed. The cocoate, isononanonate, maristate, palmitate, pelargonate, and stearate have all been reviewed. So far the only one I'm finding that ends with ethylhexanoate that has been reviewed is the cetearyl.

DR. HILL: And even in those ones you just mentioned, the commonality of long chain, large fatty acids, shortest would be, what, myristoyl in that list I think that you just read?

MS. FLUME: If you say so I'll agree with that.

DR. BERGFELD: I saw in the list on page 36 the isodecyl was reviewed and then, but not reviewed was the octyldodecyl. Is that the one you mentioned? Correction, I see that has a star.

DR. MARKS: Any other comments about the ingredient list? Am I correct that we decided isopropyl lineolate is now safe. The conclusion will be safe with formulated to be non- irritating with these ingredients. But Tom, page -- the genotox okay? I had page 67 highlighted. Let me see what was on page 67. But you were fine with the genotox?

DR. SLAGA: Mm-hmm.

DR. MARKS: Okay, good. Yeah, that was the isopropyl lineolate from previous insufficient. Okay.

Any other comments? So I think will this continue procedurally to be a draft tentative amended report of safe to be -- with the tentative conclusion safe to be non-irritating or can we issue a tentative amended report just without these ingredients?

MS. FLUME: We should be able to move on and issue a tentative amended report.

DR. MARKS: Okay. With a conclusion safe to be non- irritating. And deleting those ethylhexanoate add-ons because we don't have clear reproductive toxicity on those. Any other comments?

MS. FLUME: Then before we move on further can I ask, as far as the discussion goes, were there any other changes that you would like to see to the discussion or was that okay?

DR. SHANK: It's okay.

MS. BRESLAWEC: I think the reason you're removing these is not because they don't

have data but because they're not a no-brainer, correct?

DR. SHANK: That's correct.

MS. BRESLAWEC: Thank you.

DR. MARKS: Any other comments? So tomorrow I will move that a tentative amended report with a conclusion of safe as long as formulated to be non-irritating for these alkyl esters and the add-ons which will be eliminated are the ethylhexanoates because they are not no-brainers and we would need reproductive toxicity. If there is discussion, Ron Shank, I'll ask you to weigh in on that. Thanks.

Okay, yes, Ron Hill.

DR. HILL: This is just an after -- a tag on. I remember one of the groups that I had flagged last time and looked at was the -- anything that was an undecylenic acid ester based on some toxicology of that. Did that concern anybody else? If not, I'm going to let that drop for the moment. We know that has biological activity because it's used as an anti-fungal. Nobody else picked up on that, all right. Okay, I'm going to let it go then.

Monice, I thought that the inhalation portion of that wasn't as good as in your other ones. So maybe you could have a look at that again.

MS. FLUME: Okay.

DR. MARKS: Okay. Let's move on to the a-amino Acids. My goal is to get done all the ingredients by lunch. At any rate, the a-amino acids, as you recall, in June the panel issued a tentative safety assessment with a safe conclusion. And again, it's the a-amino acids. We did get some more data. It looked okay.

So I assume tomorrow I will be seconding a motion to issue a final safety assessment of the a-amino acids with a safe conclusion. Is that -- comments?

DR. HILL: I'm sure I should have responded after the post-meeting notes came out last time, but basically, if the DLs are safe then the Ds are safe. DL is just a 50/50 mixture of the two, so I'm not sure I made myself clear in the last meeting but if DL is safe, then D is safe. There's no reason to believe otherwise.

DR. SLAGA: On page 18 of the Panel Book, it lists a number of tables that are not in the

book related to irritation and sensitization which we're counting on.

MS. BURNETT: I believe they were supposed to be sent in the e-mail. They were cut off in the production of the Panel Book.

DR. HILL: Wasn't that the one we got by FedEx afterwards where we got the replacement copy?

MS. BURNETT: Yeah, you were either mailed or e- mailed.

DR. HILL: Yeah, we got FedEx, a replacement.

DR. MARKS: Here they are, Tom.

SPEAKER: Sorry about that..

DR. SLAGA: In this particular version of it -- I have the other.

DR. MARKS: Okay. There was -- I have -- so let's go back. Ron Hill, we haven't resolved, because obviously that's going to be important since the ingredients that we're making, issuing a final safety assessment are the a-amino acids. So if you want to go back and include the D and DL, we need to halt the progress of this and go back and have a different conclusion obviously

if we're going to consider those safe.

DR. HILL: Upon extensive reflect, I didn't see any reason toxicologically to remove those d-amino acids based on the likely exposure levels. And it seems absurd, which is probably not a good enough reason to delay the progress of this, but it seems absurd to just exclude D if we're allowing DL because, again, 50 percent of DL is D. It's not like it's a different molecule. It's a 50/50 mixture of D and L. So if DL is okay, then D is okay. And it sounds chemically absurd. I mean, I'm thinking Dan will pick up on this. So I don't know what that does to the progress. I don't see --

DR. MARKS: I don't think it's important. I think getting the end result, rather than just moving it forward. So you're -- so you wouldn't even have the alpha in front of the --

DR. HILL: No, no. The alpha should be there because we wanted to make sure we were pairing out any beta amino acids or any other amino acids. But it's just stereochemistry. You've got L, which are abundant. We have minor quantities of D in our bodies, primarily because

we get them in diet but there are a few other occasions where we have D in our biochemistry, but typically not in proteins.

So I was thinking hypothetically, well, if a lot of D was smeared on somebody's skin, yeah, maybe. But it just wouldn't be synthesized into something that would likely create a hapten. And I just, upon extensive reflection, thought one, there's no reason to exclude it toxicologically that I could really dream up; and two, if DL is okay, then D is okay. So we either need to have just L-amino acids, which is going to make some people unhappy because they're using DL, and only -- and we've discussed in the restricted cases where D could potentially be a problem if the levels got high enough. I think that's all been handled in the discussion, so it's just to pair out d-amino acids exclusively doesn't make any good sense. It looks technically moronic, I guess, is the best way to put it. That's part of my job, is to catch these sorts of things. I want to make sure the report doesn't go out that way I guess is the best way to put it.

DR. MARKS: So really it's not changing

the conclusion; it's changing the discussion, that last paragraph?

MS. BURNETT: Just strike the last sentence. Okay. It's just an editorial change.

DR. MARKS: Yes. Is that acceptable?

DR. HILL: Yeah, for me it is.

DR. MARKS: Page 19.

DR. HILL: And I went back through --

DR. MARKS: Because of the lack of data specifically supports the safety of disomers that (inaudible) could not address a-amino acids or their disomers. You would just strike that last sentence and then that would take care of it?

DR. HILL: For me that would..

DR. MARKS: Yeah, okay. It's editorial.

DR. HILL: Because I couldn't come up with any good reason why we would really need to see any additional toxicology. For me that seemed an unreasonable demand.

DR. MARKS: Okay. So that's editorial. It doesn't change the conclusion.

There were other -- and I don't know where I placed the letter, but on page 15, and then again on the conclusion page 51, there was

reference to the monosodium glutamate syndrome complex and there was concern from the MSG group that we shouldn't be referring to this symptom complex. So comments from the panel members?

Christina, that had to be on one of our -- was that in this document, page 51?

MS. BURNETT: The letter from the --

DR. MARKS: Yes.

MS. BURNETT: -- the committee is in Panel Book page 51.

DR. MARKS: Yes, there it is. So it's the International Glutamate Technical Committee. If you look on page 51. And it's in reference to the paragraph on Panel Book page 15, whether or not that paragraph should be removed. It's under the Introduction and it's the fourth paragraph, starting out with "Monosodium glutamate has been reported associated with human condition known as MSG symptom complex.

MS. BURNETT: I will note that his comments were to the language as it was in the original SLR. He is not commenting on what's written currently. I think the committee would like just any mention of MSG allergy to be

stricken because they don't want any association.

DR. HILL: Well, glutamate is glutamate is glutamate. I mean the reason that you don't worry about MSG syndrome or whatever you want to call it is because the levels that you could get from any conceivable cosmetic exposure based on the fact that it's glutamate are irrelevant with respect to that. You have to have enough concentration in order for that to occur. So, I mean, but glutamate is glutamate is glutamate and MSG is glutamate. I mean, that's --

DR. MARKS: So in handling the concern with the International Glutamate Technical Committee, would you have just what you said, Ron Hill? I mean, there are basically three ways we can handle this. Leave it as is and make no changes in the report. Second would be to leave it as is but also have a clarifying sentence that the level in cosmetics we are not concerned this syndrome would be induced. Obviously, the International Glutamate Technical Committee really is concerned that this syndrome really exists is how I interpreted their letter.

DR. HILL: The syndrome does exist. And

as I say, it's been heavily researched and the science behind it is known. They say remove any arbitrary references. I don't know if they mean remove any references, because I would disagree with that and decline to do that, but I think it could be moved to the discussion out of the introduction and make mention of the fact that the levels required are a lot higher than you could get from any conceivable cosmetic exposure and that's that.

MS. BURNETT: I don't know if I should mention that the original reference (inaudible) was Dr. Klaassen's book.

MS. BRESLAWEC: We kind of like the report as it is in reference to the MSG. We like the report the way it is.

MS. BURNETT: The discussion does say that, you know, we're recognizing that in a diet there is no (inaudible) but through cosmetic use it's significant exposure. So I think we've already handled it.

DR. HILL: But, yeah, in the same token, on the exposure thing, when we were talking about editorial in the discussion section, it's report

page 6. Since it's loose from the panel, I don't have a panel book page number. It says, "Perhaps most notably the ammo acids in this assessment are found in foods and the daily exposure for food use, blah blah blah, would be -- I can't say blah blah -- would result in a much larger systemic dose than resulting from use in cosmetic products." That's true for L-amino acids only. So that sentence is going to have to be modified.

MS. BURNETT: I'm sorry, you've lost me.

DR. HILL: Okay. Let me -- I know, because I went sequacious.

You have a sense in the discussion, which is true of L-amino acids but it is not true of DL-amino acids, and it is certainly not true of d-amino acids. And if you look in the discussion -- one, two, three, four, five, six, seven, eight -- eight or nine lines down it starts -- it says, "Perhaps most notably..."

DR. BERGFELD: On page 18.

DR. HILL: Well, like I say, I have the loose copy so it's report page 6. But yes, it is Panel Book page 18 if it hasn't changed. It says, "Perhaps most notably the amino acids in this

assessment are found in foods and the daily exposure from food use would result in a much larger systemic dose than that resulting from use in cosmetic products." That's true of L-amino acids. It is not true of DL-amino acids, and it is certainly not true of d-amino acids. So that sentence just needs to be written to somehow capture of L- amino acids this is true. It has to say L.

MS. BURNETT: I'm going to come over.

DR. HILL: You're not finding it yet?

DR. MARKS: It's in the middle of that paragraph.

DR. HILL: I still consider this to be entirely editorial, but it's because where we started in this report, where we didn't get the L versus DL versus D.

DR. MARKS: The sentence exists in both discussions, whether you're on Panel Page book 18 in the Blue Book or on the loose leaf you're on page 6.

MS. BURNETT: I think it's under the inhalation.

DR. MARKS: Under discussion. And it's

the second paragraph.

MS. BURNETT: Right. Discussing the inhalation.

DR. MARKS: Yeah, it's --

DR. HILL: No.

DR. MARKS: It's perhaps most notably --

DR. HILL: Oh, okay. It is in the inhalation discussion. I see. Okay, I agree with you but it's still -- that's the point -- is that it is true of L-amino acids. That statement is true.

MS. BURNETT: Okay.

DR. HILL: It is not true of DL and D because, in general, in foods you wouldn't get exposed to DL most of the time for D unless it's been intentionally added by a processed food.

DR. MARKS: Is that sentence important to include in the discussion? Would this be -- rather than trying to clarify it, just eliminate it? Does it add?

DR. HILL: I think if you just took that sentence out, life is good. That's my opinion..

DR. MARKS: Okay. Ron Shank? Fine. So eliminate that sentence.

And then where Christina did you say in the discussion -- so we aren't going to change the report with reference to the MSG symptom complex at all. That was my sense that we would not change it at all. You said the discussion that was addressed?

MS. BURNETT: Yes. The following paragraph from where we just were.

DR. MARKS: Oh, yes. Sure. Okay. Good. Does the panel like that the issue of the syndrome is introduced in the introduction and then actually explained in the discussion? To me I don't have a problem with it being separated. Okay.

Any other comments? So tomorrow I will second a motion to issue a final safety assessment of the a-amino acids, that they are safe and that we have two editorial comments to leave two sentences in the discussion. The one on page 18 and the one on page 19. Ron Hill, do you think it's important -- Christina has got them from today. Do you think it's important that the other team hear which sentences we feel should be deleted? I think -- I think it would be helpful,

so I will probably call on you, Ron. You can use this book, it'll be easier, rather than the loose leaf one. We'll be using these books so it'll be Panel Book page 18. And Panel Book page 19. And we'll delete that sentence that starts with "perhaps," on page 18. And the last sentence of the discussion on page 19.

Alan, were you here when Ron made the point for that last sentence on page 19 that this is Ron Hill, that if DL is okay, then D is okay? And that last sentence relates to those stereoisomers..

Okay. Any other comments? Now, we're onto the PEGylated oils. That's in the Pink Panel Book. In March, we reopened the safety assessment of these oils to expand the report to other ingredients. And we're at the point now that we could issue a tentative amended safety assessment that these PEGylated oils are safe as long as formulated to be nonirritating. And the list is on Panel Book page 30 and 31. Any comments, Tom, Ron, and Ron?

DR. SLAGA: I have none.

DR. SHANK: I think the conclusion is

okay. I think we need to add something to the discussion. In the previous report we put a 50 percent limitation for sensitization on some of the ingredients. And we're dropping that now and we need to discuss why we no longer need that limit. And I have a cryptic note here that on the fourth paragraph of the discussion, is this enough or should we expand it? And then there are some editorial things.

DR. MARKS: Yes. Thanks, Ron. My notes are that the use concentration are less than 50 percent. So as long as we say "use concentrations," that it should be in the discussion why we don't have that limit now. And it's reassuring that the use concentrations now are less than that limit used before.

DR. SHANK: That's good.

DR. MARKS: Any other comments?

DR. HILL: Yeah --

DR. BERGFELD: No, go ahead.

DR. MARKS: Yeah, what I saw, Ron, just to elaborate even more, the highest use concentration looks like 22 percent. Most of them there's a 0.11, less than 10 percent. Ten percent

and then 22 for the PEG-40 hydrogenated castor oil.

Okay.

DR. HILL: Yeah, so, this is really --

DR. MARKS: So we'll capture that in the discussion. Sorry.

Christina?

MS. BURNETT: Here the concern is leave-ons because there is a 97 percent (inaudible).

DR. MARKS: Pardon?

MS. BURNETT: There is a 97 percent concentration rinse-off. So I assume that the concern is only leave-ons.

DR. MARKS: Right. So we'll capture that in the discussion.

Were you going to say something, Ron?

DR. HILL: Yes. And this is probably, ultimately, and doesn't affect the conclusion and it's ultimately in the category of editorial but nontrivial editorial changes, is even though there are cases where we have a fatty acid or a mixture of fatty acids that are esterified with PEGs in general. We don't end up with a fatty

acid -- If you look at what's going on what the chemistry here in general. You don't end up with a fatty acid, and then the PEG group at the end and then a free hydroxyl group because this trans- esterification going on here such that in most cases it appears that you've got a fatty acid at one end, PEG in the middle, and another fatty acid on the other end. The only time where you would, I think, ever see that is in the PEG-2 or maybe -- what's the next smallest one? PEG-5? We see PEG- 2s and PEG-5s. So I think I made enough comments to be sure that we captured that.

And this might be a question for the toxicologists. On Panel Book 7, near the bottom, I was just curious how one might explain the results in that paragraph that continues onto the next top of the page. In other words, there was a result without metabolic activation and then with metabolic activation it disappeared. That seemed in this case strange.

DR. MARKS: Again, which page are you on?

DR. HILL: I'm on Panel Book, page 27. It's the last paragraph on page 27, Panel Book 27 that continues onto the top of the next page. This

isn't going to affect the conclusions in any way either. It's just an added result. And the reason I raised it is because since we are adding in PEG-2 ingredients, we will have in those cases some free castor oil. There's not enough PEG to go around basically. But of course, in this case, since it was PEG-60 that was studied, I'm not sure -- I just wondered if anybody could explain this result to me. Without metabolic activation we affect proliferation; with metabolic activation that affect disappears.

DR. SLAGA: That happens with a number of compounds.

DR. ANDERSEN: It isn't the norm..

DR. SLAGA: It isn't the norm but it does happen.

DR. HILL: Yeah, I mean, maybe the fatty acids are getting -- I just wouldn't expect any metabolism of this PEG- ingredient. That's why I was -- I mean, maybe the studied is flawed and the whole thing ought to go out or something like that because it doesn't -- I don't know. It doesn't affect my conclusions at all.

DR. MARKS: Okay.

DR. BERGFELD: Could I make a comment? A couple comments on this. And the previous one. Our conclusions are beginning to vary. I just picked it up on this. This conclusion, which appears in Panel Book 30, it concludes that the PEG oil ingredients listed below are safe when formulated to be nonirritating. We had agreed are safe in the present practice of use and concentration described in the safety assessment and formulated to be nonirritating. We had begun to delete the portion are safe in the present practice as mentioned or descripted in the safety assessment. That needs to be added.

DR. ANDERSEN: Let's add that back.

DR. BERGFELD: Yeah. And it disappeared also in the alkyl esters and maybe in others.

And then the next comment I have to make appears in the table on page 33. And the title of the table. I'm not sure, and I didn't take the time to go back to see when we are capturing the results of previously reviewed ingredients, what we title those. But certainly not this previous CIR safety assessment related to proposed expansion ingredients. That would not be the

title. But these are summaries -- summaries of previous reviewed CIR cosmetic ingredients.

DR. ANDERSEN: I think that's a question of what stage are we at. That title was particularly important so that the panel understood exactly what the status was. When we take the next step, the back end of that title would disappear.

DR. BERGFELD: So what are these going to be titled so that it's consistent? Because we have these for other ingredients as well.

DR. ANDERSEN: It's CIR findings on previous safety assessments.

DR. BERGFELD: Okay.

DR. HILL: I had an additional set of general comments here. If we look at the discussion for a second, at the end of the first paragraph of the discussion it says, "Overall single-dose and repeated-dose toxicity, reproductive developmental toxicity, genotoxicity, carcinogenicity, dermal neuro-ocular irritation and sensitization and photosensitization data were available. That's true only for the components, not for the

molecules themselves. And when you go back and look at selected discussions, for example, under carcinogenicity, it says carcinogenicity data were available supporting the safety of. And then that list is practically not pertinent. I mean, the PEGs -- alkyl PEGs and ethers, none of these are alkyl PEG ethers and none of these are PEGs. So other than pertinence to impurities, it makes it look like we have carcinogenicity data when, in fact, we do not. So this is, again, not affecting my conclusion but it's just a truth in advertising thing. And so all those cases, except sensitization where impurities could come into play, I suggested moving those out and putting them in the discussion and making sure we capture it such that what we're really talking about is clear because if we're looking at the toxicology for these ethers and the PEGs, that's practically irrelevant to what we're really reviewing here.

DR. MARKS: Tom, good point. So Ron Hill again, where is the sentence you were -- or sentence you were talking about in carcinogenicity?

DR. HILL: That particular sentence I

read was at the beginning of the discussion. And it just needs to be clear that this is only for the -- we should only include data for the PEGylated compounds and not the "components," because the fact that they're components is almost irrelevant except where we're talking about impurities or maybe where the PEG-2 and PEG-5, where we could have a few residuals. But again, basically impurities.

DR. MARKS: So where is that in your Panel Book? Is this page 30?

DR. HILL: Well, I'm looking at Panel Book page 30. It's the second -- in this case it's the second sentence of the discussion.

DR. MARKS: Second sentence.

DR. HILL: What I wrote here is this list must only include data for PEGylated compounds, not the "components," because that isn't part of the read across. It's supporting but it's not part of the read across.

And then so if you go back to the beginning of some of these other sections that includes toxicokinetics, that includes toxicological studies under acute, that includes

the first sentence under genotoxicity, it includes the first sentence under repro and developmental toxicity, and it's the first sentence under carcinogenicity. All of those sentences are talking about, again, "components" and not the actual things that we're reviewing in the report. And to me, that clouds things in a way that shouldn't be.

DR. MARKS: Okay. So we will note that, Ron, in your Panel Book. Christina, you can pick that up from Dr. Hill's Panel Book..

Ron. Ron Shank and Tom, is that a good point and clarifies?

DR. HILL: It doesn't change my conclusion.

DR. MARKS: Right.

DR. HILL: The conclusion in any way. Just truth in advertising here.

DR. MARKS: Yes. Now, I hear you, Ron Hill. So under the discussion, should that -- since you're eliminating all that, it hasn't changed your conclusion. Is the discussion now robust enough? Because it sounds like that second sentence in the first

paragraph --

DR. HILL: All of that needs to be rolled into the discussion and captured in such a way that it's clear we're talking about these, by and large, unrelated compounds in terms of bio handling. Dan doesn't like that word but we all know what it means.

DR. MARKS: Ron, I'm going to ask you to speak to this point tomorrow.

DR. HILL: I'll try to make sure I can state it more clearly tomorrow.

DR. MARKS: Well, I think you did a good job at stating it now in terms of why, you know, you really want to be directed towards the ingredients and not other comments or components which aren't directly related to the ingredients.

DR. SLAGA: We could go ahead and say after are available, you know, with the components --

DR. HILL: Right. I mean, basically because with the possible exception of the very small PEG-2 or PEG-5 -- I apologize for interrupting -- and even with those, they're not going to be cleaved back to the components. So

only if they're there as impurities or in the case of the PEG-2 or the small molecular weight PEGs, we might have some unreacted material, then it becomes relevant. But that's the only cases. We have no reason to believe that these PEGylated esters are actually getting cleaved to the components. In fact, they won't be because in most cases we have ether link, which is anesters. So even if the esters cleave, we're not going to get back to a component

Easter -- Easter -- ether -- because that is not likely to happen in skin. Actually, it just isn't going to happen in skin.

DR. MARKS: So Ron Hill, in your case, even if we did it in the discussion and used that second sentence "were available for the components," that's really not relevant to the safety assessment of these ingredients.

DR. HILL: It's relevant if it gets written in the right way. If we want a really thoughtful construction of it, it's going to take some time. But it needs to be clear what we're actually talking about there so that --

DR. ANDERSEN: I think the distinction

that you made that may be most useful as we go forward is the use of component data in read across in this case just doesn't fit.

DR. HILL: Correct. That's what I'm trying to say.

DR. ANDERSEN: The absence of red flags in the component data is supportive.

DR. HILL: Yes.

DR. SLAGA: That's the thrust..

DR. MARKS: Okay. So Ron, I am going to ask you, Ron Hill, to comment tomorrow and to give editorial comments about the ingredient toxicity and clarifying what the toxicity of the components or lack thereof is supportive. Something to that effect.

So again, tomorrow I expect I will be seconding a motion to issue a tentative amended safety assessment of the PEGylated oils that they are safe in the present practice and use so we have the right conclusion or a more --

DR. BERGFELD: Standardized.

DR. MARKS: Yeah, standardized and more complete conclusion when formulated to be nonirritating. And then the editorial comments

are that we don't have the 50 percent limit because the use on leave-ons is significantly less than that. We're not worried about the rinse-off at that 97 percent concentration.

And then Ron Hill, the editorial comments you have about the -- clarifying the components in the read across.

Okay. Any other comments? Okay. Fatty acid amidopropyl dimethylamines. And that's in the Pink Book. In June, the panel issued an insufficient data announcement asking for percutaneous absorption. For example, the shortest chain of fatty acid, lauramidopropyl, dimethylamine, and if absorbed, repro and developmental tox. And then sensitization irritation data on oleamidopropyl dimethylamine. We've received nothing to my knowledge. Let me see. What's this, Halyna? Just that we have a memo on August 16th at the REACH Consortium for stearamidopropyl dimethylamine does not support a read across approach. So --

DR. EISENMANN: I saw that they're preparing new additional data on stearamidopropyl dimethylamine.

MS. BRESLAWEC: Which won't be ready until March -- or May 31, 2013. And I think that data would be relevant to this review and will be available next May.

DR. MARKS: And this is on the sensitization?

MS. BRESLAWEC: This includes a range of data, including the developmental and repro.

DR. MARKS: And do you think, Rons, that if we have development and repro on stearamidopropyl that that will be able to be a read across for the other ones?

DR. HILL: I think we still had the concern about the shortest chain ones in terms of their ability to penetrate to a greater extent than some of these larger ones. And my comment was given the complete lack of any biochemical effect data of any kind for these, what we should get from the REACH report would be really helpful. I think it might still limit the read across to some of the shortest chain ones where we don't have -- in the absence of dermal penetration data, which we understood would likely not be forthcoming because either very small amount of

use or no use.

MS. BRESLAWEC: Yeah, we are not -- the data on lauramidopropyl dimethylamine will not be forthcoming.

DR. EISENMANN: Not that we're aware of.

DR. HILL: That was my expectation.

DR. EISENMANN: I think most of the industry is acknowledging that it's a sensitizer, so they're not going to be developing more data..

DR. HILL: I'm wondering if that's also true of myristoyl, which is, I think C-14, isn't it? So.

DR. EISENMANN: I think they're basically looking at -16 and above because the stearamide is a mixture of -16 and - 18. So they're looking at that and above and not anything smaller.

DR. HILL: So then we need to go back to the amino acid compositions in my estimation and see what we might could read across. And they're saying they don't support read across if I understood correctly.

DR. EISENMANN: For below.

DR. BERGFELD: Is it possible that such

a statement could be sent to us, the status of their review and why they would not be looking at the lower PEGs so that we could use that as a document?

DR. EISENMANN: I did send statements.

DR. MARKS: So how would you like to proceed? Should we move --

MS. BRESLAWEC: It was an August 16th statement.

DR. BERGFELD: I had it somewhere. I guess I didn't put it in my book.

DR. HILL: I think that came in Wave 2, didn't it?

DR. BERGFELD: You could table it until you have the other information that's been promised but also without the understanding that you will relate to the statement of sensitization and state that it would not be considered safe under this PEG-18. Is that what it would be? 16/18?

DR. EISENMANN: Well, you have to remember that these are -- it would be nice to have a conclusion that they're safe at the contaminant levels of (inaudible). That's probably the level

we'd like.

DR. BERGFELD: So you could use that in your discussion.

MS. BRESLAWEC: Yeah, but we feel it would be appropriate to table this discussion until the REACH data are available.

DR. MARKS: Rons, Tom, is that -- that was not one of the potential conclusions I had for this table. But --

DR. HILL: I would say that would certainly be my preference just, like I say, based on the absence of any biochemical effects data of any of these. If we get at least indirect assessment of that through this information, that would be, for me, extremely helpful because I haven't been comfortable with these amidoamines since way back when we were looking at cocamide propylbetamine.

DR. MARKS: So with those, as you recall, sensitization was the most concerning.

DR. HILL: Everybody but me..

DR. MARKS: Okay. And it was red flagged. We were actually, as a team, were going to move forward with it safe. We didn't have the repro

and the development issues as I recall. But --

DR. HILL: I'm thinking that was true for everybody but me in the last meeting, and I don't recall whether I abstained from the vote, which might have been what I did in the full-day meeting.

DR. MARKS: No, I think it was actually Dan who raised the issue of getting those -- if absorbed, getting that data again for the shortest chain fatty acid.

DR. HILL: But I also wanted to see it. I was happy that he mentioned it and it wasn't me that was the problem child that day.

DR. MARKS: So table is what I hear. And I will be making the motion tomorrow, awaiting -- am I referring to his correctly, the REACH data?

MS. BRESLAWEC: Right, which is due end of May next year.

DR. ANDERSEN: I think, Jim, a question that I would have is how are we going to get the REACH data? Is that something that the Council will be in a position to provide or are we going to have to get it ourselves?

DR. EISENMANN: I'll keep working with the company that belongs to the consortium. They've already provided some data in the report, so I will --

DR. ANDERSEN: Fingers crossed.

DR. EISENMANN: Right.

MS. BRESLAWEC: Keeping in mind that the REACH data that is generated by a consortium, and so the best we can often get for that is a summary. And since Carol is working directly with one of the companies that's providing the data, we may be able to do something better.

DR. EISENMANN: And they provided most of the data -- a lot of the data that's in the report already that's in the format of three summaries.

DR. MARKS: And again, did you say that it's just going to really be focused on the stearamidopropyl?

DR. EISENMANN: Correct. That's all this consortium --

DR. MARKS: That's all. So we get this next spring. Are we going to be able to move forward with a conclusion or are we still going

to have more data needs that this is not going to be -- maybe we'll be able to say more about stearamidopropyl dimethylamine, but my concern was the oleamidopropyl because we have the case reports and we don't have RIPT.

MS. BRESLAWEC: Well, those are sensitizers.

DR. MARKS: Yes. Well, but we can't determine a level at this point, I think, to go forward and say it's safe at this level. Unless we take the tact that we did with the cocamidopropyl betamines is it's safe when formulated to be nonsensitizing. And that is what we were going to do the last meeting when we were going to move forward with a safe conclusion as long as formulated to be nonsensitizing. So that doesn't allay our fears, Ron Hill.

DR. HILL: I think it does because when you drop it down to a level where that's not an issue, that essentially serves as a sentinel, I mean, that's how I resolve the issue in my mind when we looked at cocamidopropyl betaine, that if you got the levels down to where we didn't see a significant incidence of sensitization, then any

of the other biological concerns basically go away in my mind at least.

DR. MARKS: So you're okay with the repro and the developmental. Obviously, Ron Shank was before it was Dan who brought up the issue on the other team. Or the other team brought up the issue of the repro and developmental toxicity. So I'm going to backtrack a little bit and say are we going to table it awaiting the REACH data? Is that going to really change much of anything?

DR. HILL: I mean, I was very comfortable with the discussion section as it was written. I opened this report with a great deal of apprehension, but once I read the discussion as it's written I was very happy with it. What it doesn't provide is a loophole if there are data that supports a little higher concentrations, for example, that come out of the REACH studies. But I don't know, I guess you could reopen at that point, right? And amend the conclusion if we do that sort of thing, don't we?

DR. ANDERSEN: Yes.

DR. HILL: Are there negative impacts

in the meanwhile, I mean, given that timeframe? And you guys can answer that better than me..

DR. MARKS: Well, in that case we're back to a conclusion of insufficient. So we've had requests from --

DR. ANDERSEN: Insufficient for the shorter chain ones.

DR. SLAGA: Right. That's what the insufficient is for.

DR. ANDERSEN: Not for the entire group.

MS. BRESLAWEC: And we don't expect to be able to provide that data.

DR. EISENMANN: Right.

DR. BERGFELD: But I don't understand why you couldn't handle that in your discussion. They've already said it's a sensitizer. They've given you a document you can reference. So you could handle that in your discussion and even in your conclusion.

DR. EISENMANN: So would you change the conclusion for safe as used for the stearamidopropyl and then safe -- and larger and insufficient for amidopropyl?

DR. MARKS: So we need to be specific

as to exactly where are we going to make that cutoff? Insufficient for the shorter chain. So what chain length is that going to be? Obviously, the prototype we were going to use was the lauramidopropyl, but --

DR. HILL: Part of the significance of that was because we have some that are natural oil-based. So I don't remember from our fatty acid review which ones had the greatest -- I was trying to pull an example that would have the greatest percentage of shorter chain fatty acids and I can't -- my memory is simply not that good.

MS. BURNETT: If you want to look at page 97 in the Panel Book.

DR. HILL: You have that in there. All right.

MS. BURNETT: Fatty acid composition.

DR. HILL: Yeah, I knew that was here. I guess what I'm saying is I didn't look before I opened my mouth to speak just then. The point being that some of them will have smaller quantities of the shorter chain fatty acids, and then we have to decide. But then again, if the whole ingredient is there at 0.5 percent, let's

say, then the maximum amount of this one would be 0.02 percent or whatever that happens to be. So, 97 you say?

MS. BURNETT: 97.

DR. HILL: So if you look at Babassu, there are quite a few shorter chains in there. But most of the others, palm kernel, same deal. Most of the others it's C16 and up. And the larger quantities of the long-chain ones. However, that is where I was saying if you require formulated to be nonsensitizing, that means somebody has to do those studies, right? And then to me that's sentinel because if they keep it at levels below where we see sensitization, probably none of that other biology is going to be of any concern. Highly likely none of that other biology would be of any concern, so that was my mindset. These ones where there are larger amounts, considerably larger amounts of even C8 fatty acids, I don't know. That makes me less comfortable.

DR. MARKS: So with that in mind we could, again, the conclusion could be safe to be present use in concentration when formulated to be nonsensitizing. And then for the shorter chain

ones, which one are we going to pick out as being insufficient?

DR. HILL: Even, this is there were, you know, it would be awfully nice to have data but it's not going to, you know, even there I'm thinking if you formulate it to be nonsensitizing, the amounts that we'd be talking about I'd be curious to see what Dan would think on this, but anybody on the other panel, it's likely we're going to develop the kinds of concentrations one would need to see significant repro tox effects. I'm going on thin air at a level.

DR. MARKS: So I would still raise the concern about oleamidopropyl dimethylamine, although, again, when you do formulate it to be nonsensitizing, it's below my concern. You know, it's not going to be sensitizing. So that's where we were the last meeting. Our team felt that we could find these ingredients to be safe as long as formulated to be nonsensitizing. Ron Shank and Ron Hill, you were concerned about the repro and the developmental toxicity. So shall I move tomorrow that rather than table, that we move with a safe conclusion? And we can see how it runs

again tomorrow. See whether we have a run -- and then Ron Hill, you and Dan can have a discussion.

DR. HILL: And anybody else who wants to chime in, by the way.

DR. MARKS: Yeah. So we'll see whether the other team's changed. So I'm going to move tomorrow that it's safe, nonsensitizing. And then we'll see what occurs.

So it seems like our team then is not going to await the REACH data. We don't think that will change our conclusion, so we don't think it needs to be tabled. Pardon?

DR. SLAGA: It still would be insufficient.

DR. MARKS: Yeah. Okay. Safe to be nonsensitizing. So we would move that there would be a tentative report on the fatty acid amino propyl dimethylamines with a conclusion that it is safe as long as formulated to be nonsensitizing. Safe in the present practices and use and concentration if they were being used, et cetera.

Any other comments? Ron? The two Rons? This is a rerun for us. At least we're consistent.

Okay. We'll see what happens tomorrow.

It should make for an interesting discussion.

DR. SHANK: In the discussion I would like to change the word "trepidation." I don't think the panel really expressed any fear.

DR. HILL: I did.

DR. SHANK: Did fear, okay.

DR. HILL: I did.

DR. SHANK: Perhaps the CIR --

DR. HILL: But you can remove it. It seems silly.

DR. SHANK: Expressed concern..

DR. HILL: It seems silly to use that word.

DR. SHANK: I like the colorful language.

MS. BURNETT: I think that's going for another adjective or whatever.

DR. HILL: Something other than concern?

MS. BURNETT: They had been writing concern in several spots and I was just --

DR. SHANK: Yeah, just wanted to spice it up?

MS. BURNETT: Yeah.

DR. HILL: I liked it but at the same token I agree that it probably needs to go.

DR. MARKS: Ad obviously, the discussion will delete that last -- that paragraph about insufficient and the data needs.

Christina, thank you.

DR. BERGFELD: Do you want to add there that if present that the PEG-18 and under could be sensitizing? I mean, you already have there that the North America Contact Dermatitis Group test panels added one of these ingredients.

DR. MARKS: Yeah, that was oleamidopropyl dimethylamine. And I want -- my initial request was to see an RIPT because as I recall it was sensitizing in a -- let me see -- allergic contact dermatitis had been reported at levels of 0.03 percent and the use concentration in cosmetics is up to 1 percent. But, if we're formulating it to be nonsensitizing then it'll be inherent on the industry to have it a low enough concentration that that's not going to be an issue. Presumably, it's going to be something significantly less than 0.3 percent, so that use concentration will be lower probably,

unless they have data that suggests that 1 percent in that particular formulation is nonsensitizing.

Rachel, did you have -- no? Okay. Comments. We know you'll have some comments about our next ingredient so I'm looking forward to that discussion.

Any other comments about this? I will issue -- I will move that we issue a tentative report with a conclusion safe as long as formulated to be nonsensitizing. The discussion, Christina, will obviously include the comments about oleamidopropyl dimethylamine.
So, now we're in -- is it lunchtime yet?

DR. BERGFELD: Nope, you've got a half hour..

DR. MARKS: Oh, good, a half an hour. So -- well, that's because we didn't have the presentations this morning. So, do you think we'll get done Triclosan and the parabens before lunch? That's what we're up to now.

So, what we've gotten are additional studies, papers with these two ingredients, and the obvious question is, does this trigger a

reopening? So, that's in the Buff Book under "new data" section.

So, let's do -- let's start out with Triclosan. So, there was a report of urinary levels of Triclosan associated with aeroallergen and food sensitization. That report also talks about parabens, but let's not muddle the two ingredients, let's do one at a time and be clearer since they're separate reports.

And then also there was this report of impaired muscle contractivity and we have some comments from industry and obviously we heard this morning about the issues with getting that paper where there was concern about RYR and calcium channel signaling impaired by the muscle contractivity, both in vivo and in vitro of non-human experimental tissue.

And so, Rons? Ron Shank? Ron Hill? And Tom? Any concerns with either one of these that would trigger enough to reopen Triclosan?

DR. SHANK: I don't think we need to reopen the Triclosan document. I think in the review that we'll have -- shows that the panel has considered these reports and will continue to

consider all the new reports that become available.

But the CIR panel report on Triclosan contains a lot of information on repeat oral exposures, which did not indicate any kind of allergenicity response, IG, immunotoxicity, muscle toxicity, and these are interesting reports, but not really pertinent to the use of this compound in cosmetics.

DR. SLAGA: I had a similar conclusion related to this, that it's really hard to relate this to cosmetics and, sure, the combined exposure can create some kind of a different thing, but related to cosmetics, I thought we had sufficient data in the past report.

DR. MARKS: Ron Hill?

DR. HILL: I basically agree. This is used in mouthwashes sometimes, is it not? Toothpaste? Yeah, but toothpaste, most of the time we're talking fluoride toothpaste, so we don't consider that, right? That's not a drug because --

DR. SHANK: Toothpaste.

DR. HILL: Toothpaste? Yeah, but

toothpaste, most of the time we're talking fluoride toothpaste, so we don't consider that, right? That's not a drug because --

MS. BRESLAWEC: That is a drug.

DR. HILL: But not mouthwash?

MS. BRESLAWEC: The relevant use here is deodorant.

DR. HILL: Is what? Is deodorant?

MS. BRESLAWEC: The largest use for Triclosan is deodorant.

DR. HILL: Yeah. But there is some use in mouth rinses?

MS. BRESLAWEC: Those are considered drugs as they are anti-gingivitis.

DR. HILL: They give a gingivitis indication and therefore fall out of our scope. Okay.

DR. MARKS: Rachel?

MS. WEINTRAUB: Yeah, so, I spent a lot of time looking through this material and I think one of the comments I think that Dr. Shank made was that, well, if you look at cosmetics use and the interaction of people with cosmetics, that's one thing, but if -- but the problem is that no

one's looking at total exposure. And each sort of -- there are different entities, not necessarily one entirely parallel to ours, but I think that's a huge problem here.

I mean, I think this study shows, especially what I found concerning, was sex differences and aeroallergen sensitization. So, what is this explanation? Could there be some link to cosmetics? Some link to the use in deodorant?

I found this data to be of concern and thought that this should be reopened to consider this and see -- and for us to review the impact of this specifically on cosmetics as used in deodorant.

DR. MARKS: Halyna.

MS. BRESLAWEC: If I remember correctly, when CIR last considered the Triclosan report, at the end of the report, Dr. Katz, who was representing FDA at that point, asked the panel to consider the dosage that came out of cosmetic use together with other uses and that the panel determination on Triclosan safety was to have reflected that. That's my recollection. I would

like, you know, to check the record on that because I do think that that was something that was a very, very thorough review that the panel did last time.

DR. MARKS: Okay, but --

MS. BRESLAWEC: We have, again, please note for the record the comments that we have provided on the individual studies. There are, we believe, some very serious issues with the study in terms of the relevance to human use and particularly cosmetic use, but, again, my main point here is I think the panel looked at that the last time it did its very thorough review of Triclosan, and I would like the record to be checked to see if that recollection is correct.

DR. MARKS: So, what I recall the prototype of do you consider just cosmetic use or do you consider all uses was with the phthalates in nail polish, and so there was concern of phthalate exposure from many different sources and we limited our consideration, again, to cosmetics because I think once we open up to all exposures it becomes a very difficult to handle, but I would like -- perhaps, Alan, obviously, you

comment, but also the two Rons and Tom. I would be more in favor, as Dr. Shank indicated, we're looking at this as a cosmetic use, not in the total use of the universe.

But Alan, do you want to comment?

DR. ANDERSON: Yeah, I think Halyna's recollection is exactly correct, that for Triclosan at the end of the discussion, the panel was focusing on the use in cosmetics and the question was posited whether all of the exposures, and there were a great of information in the safety assessment on Triclosan in a wide range of product types, and the panels conclusion was, well, none of them, even if you added them all up, reached a threshold of toxicologic concern. And the way you phrased it was available study data, wide variety of studies, then the end points are listed. "Triclosan may be used safely in a wide variety of products in the present practices of use and concentration even if all product types were to contain Triclosan were used concurrently on a daily basis."

So, that was intended, and the discussion record will show that it was beyond

just the use in cosmetics.

DR. MARKS: Okay. So, Rachel, that has been addressed before.

DR. SHANK: We have chronic oral exposures with Triclosan and very good skin penetration data, which shows that it is poorly absorbed. Much of it remains in the epidermis and little enters the circulation as Triclosan. Therefore these new studies are very interesting, but are not relevant to cosmetic use.

MS. BRESLAWEC: Many of them are IP studies.

DR. MARKS: Repeat that, you mean these studies are interperitoneal?

MS. BRESLAWEC: The two studies here are interperitoneal, yeah, so you have that issue too.

DR. MARKS: So that, again --

MS. WEINTRAUB: So, why would that not be relevant to cosmetic use? Could you just explain scientifically?

DR. SHANK: In cosmetic use, there is very little transfer from the surface of the skin into the circulation, but in these studies, there

was direct injection into the peritoneal cavity, so there was a bonus effect, rapid absorption across the serosa of the intestine, so the blood levels would go very, very high. Never would that be reached by cosmetic use. There would be a slow diffusion at best..

And then some of the other studies were actually adding the Triclosan to media, these were (inaudible) fat amidyls or something like that, where these animals live in a solution of this. Interesting scientific studies, but not relevant -- the results are not relevant to cosmetic use because the amount entering the blood at any one time would be very small.

So, the concentration would never reach anything like these experimental studies that we've just received.

DR. MARKS: Any other -- Rachel, does that help answer the concerns you had?

MS. WEINTRAUB: Yeah.

DR. MARKS: And I thank you, Halyna, for expanding that the panel had in the past addressed for all exposure to it. I had not recalled that.

Now, how should this -- so, this will

go in -- the minutes is not reopened? Or will this go in as a re-review in the Journal -- itself -- of Toxicology, not reopened and the reasons why, under a discussion section?

DR. ANDERSON: We still have to talk about parabens, but saying parabens brings to mind the last time we did this, which was in December of last year for parabens. The European Commission had considered the Danish proposal for parabens that they not be used in baby products, and the panel looked at the available information and simply reconfirmed that the margins of safety that it found for the use of parabens were appropriate and no change in the CIR conclusion was needed.

I think that is appropriate here, that further data have been evaluated and no change in the conclusion is appropriate.

Now, if you thought that these data were sufficiently significant, you could have said, I'd like you to reopen this, but if you don't think they cross that threshold, and my reading is you don't, then you would say so in the post meeting announcement. All this would be captured in the

minutes as well, so the record would be established.

Now, where CIR would also be obligated to send a response back to Dr. Scranton to Women's Voices for the Earth, that explains what we did as well, because they are on record as encouraging us to look at these new data and see what their impact is, so we owe her a response and we would do that.

So, I think there will be no lack of public display of where we came down on this..

DR. MARKS: Okay, so this would be handled differently than a formal re-review. It's looking at the data, deciding that we would not reopen it and no change in conclusion. That would be captured in the minutes and in the letter that you will send. Okay.

Any other comments? I mean --

DR. BERGFELD: May I ask a question? Have we ever done these in the Journal where we've said, not reviewed and updated with literature and not changed our conclusion? I thought we had.

DR. MARKS: That's a formal --

DR. ANDERSON: We've done it when --

DR. BERGFELD: For the re-reviews, but this is not --

DR. ANDERSON: I'm trying to figure out a way to describe it succinctly. The first time we looked at parabens a second time was after all of the estrogenic effect data had been published in the late '90s. So, we had reviewed them in the early '90s. Those data weren't even on the radar screen.

Then they appeared and there was sufficient data that warranted an open discussion of those data. So, we reopened it in order to provide that. Not that we -- and the panel clearly said, we're not going to change the conclusion, but these data are sufficiently important to provide an assessment of it.

Subsequent to that, last December, you looked at the EU situation and the Danish proposal and said, this doesn't reach a threshold of having -- in fact, there were no new data, it was simply a reassessment of the existing data, and you said, no need to reopen this.

DR. MARKS: Right.

DR. ANDERSON: So, there is a threshold

phenomenon here that we're calibrating and I'm -- I don't know that that's final, and I hate to say it's, you know, we know it when we see it, but it's a question that each time new data are available, what are the significance of those new data, has to be part of the discussion, and if the significance is such that everybody should see a full discussion of that, you should reopen it. I mean, you really should.

But I think the explanation, as Dr. Shank has provided it, that vis-à-vis use in cosmetics, these data are not particularly informative means you cannot reopen it.

DR. HILL: Well, I'm assuming in the -- I'm not assuming anything. In making the response to the Women's Voices group, grant you BSF has an extremely vested interest, but I thought that the letter that Dr. Finken -- I assume it's Dr. Finken -- supplied, it's a sort of a very thoughtful analysis of the Savage papers, it is a very thoughtful analysis, and one of the things they point out near the end was the correlation is between urinary concentrations and allergic sensitization, the IgE stuff and

basically that people who are hypersensitive in the first place are advised to practice much stricter hygiene, therefore using much more of this and somewhat more likely to -- so, it's a cause and effect confusion that hasn't been sorted out.

I'm not an immunologist, so that -- once we got much deeper than that I had to stop, but having seen the paper and then this, that was my reaction, it captured my gut reactions pretty well.

DR. MARKS: Ron Shank, when -- in this one paper, and this is just for my own edification, when you talked about Triclosan not being absorbed and not having a systemic effect, is the level of urinary concentration presumably what they're finding in the urine is actually being excreted, perhaps, not being washed off into the urine? Are the levels so low that we aren't -- because there's something -- obviously, either, there's only two explanations -- two or three -- finding it in urine. One, that the assay wasn't correct, two, it was washed off the skin in the urine, three, it was contaminated, or four,

it was absorbed and now we're seeing it in the urine. So, just to clarify that if --

DR. BERGFELD: Found in foods?

DR. MARKS: In foods?

DR. BERGFELD: It might be ingested.

DR. MARKS: Ingested. So, and then it was also -- no, that's parabens. So, again, just in case that would come up, somebody would say, well, how is it in the urine if it's not absorbed? It's because other sources?

DR. SLAGA: Yep.

DR. MARKS: Okay, that's fine. I just wanted to confirm that.

Okay, so we --

DR. BERGFELD: I'd like to propose, when you are giving a statement on this, that we considered on these important, worrisome, ingredients, especially those that the FDA has asked us to review, that we not just have it in the minutes, but we have something else -- develop something else that says what we have done and why, so they're a quick reference for anyone that wants to see on these (inaudible), we've been asked to re-review and we decided not to, we can come up

with a discussion paragraph and what the references were that we used, and have that be called something and retained.

I would suspect, maybe even on the website, that that would be a good place.

DR. MARKS: I would say, Wilma, we do do that for the hair dye because we update the epidemiologic study, but there are so many hair dye ingredients that that's periodically seen in a report. I don't know how we do it, as you suggested, other than saying, this is a formal re-review and it will go out as a re-review with a conclusion not to reopen and no change in the conclusion and have that paragraph -- that would go in the public literature, so to speak.

But Alan, do you what to -- your proposal was to capture it in the minutes and be very clear and if somebody wanted to go back, I guess we could ask -- where is -- whether or not that would be searchable. Are the minutes searchable?

DR. ANDERSON: Almost certainly not. I mean, I suppose a web search could uncover that information. But we're certainly not making it

easy for anyone to find. It's -- while we were clear in December what our conclusion was about the Danish view of life regarding parabens, we didn't go out of our way to make that readily available or hallmarked or at all visible. We didn't try to bury it, but we didn't highlight it.

What we're talking about here is potentially a circumstance where it's important enough to highlight and we don't have a good mechanism for that. Just as you were talking, Wilma, I was thinking about what the Academy does and there's got to be that intermediate thing that gets issued that isn't a publication but is commentary, is something --

DR. BERGFELD: Update.

MS. BRESLAWEC: Press release.

DR. ANDERSON: Well, press release is certainly targeted at visibility.

DR. SHANK: How about a letter to the editor?

DR. ANDERSON: Also appropriate. Interesting, Ron, thank you. Since it concerns a published study, I don't know if PNAS takes letters to the editor, but certainly the -- what

the heck is it -- the Academy of Allergy, Asthma, and Immunology I'll bet you takes letters to the editor. That's not a bad idea.

DR. BERGFELD: How about all of the above? I really think that the CIR has been looking for ways to promote itself and to have an impact on many different disciplines with all these safety results because they're a little bit boring when you get to safety if they're all safe, but one that's controversial is certainly a hit in hook, and so I would think highlighting that you actually tackled a difficult subject and had an opinion on it would be most important.

DR. MARKS: Couldn't it be a letter where we publish our reports already? Would the editor accept a letter to the editor? I like that, Ron Hill, in the Journal -- or was it Ron Shank, yeah -- n the Journal of Toxicology?

DR. ANDERSON: It certainly can't hurt to ask. My only concern in that regard is, were I the Journal of Allergy, Asthma and Immunology, I'm not sure I'd like you writing a letter to some other journal commenting on something that appeared in my journal.

DR. SLAGA: Yeah, it would have to be --

DR. ANDERSON: We need to --

DR. MARKS: I guess there though --

DR. ANDERSON: -- scope that out, but --

DR. MARKS: Then we'd need two letters because we're addressing both the allergy issue and also the muscle issue, so now we have two different -- so, that would either generate two different articles or letters or we'd just combine it in one. And then what you could do, perhaps, if the Journal didn't like it is obviously once the letter is formulated you could send it to the respective editors in the other journals.

DR. ANDERSON: Well, the other logic would be a letter to the editor of the International Journal of Toxicology that says, "CIR previously published a safety assessment of Triclosan. Since that was published, two new reports have appeared and here's our analysis of those two new reports." That then packages it in the venue of where we publish. I think that is worth exploring.

DR. BERGFELD: And it's a reference.

It's a documented reference.

DR. ANDERSON: Yeah.

DR. MARKS: Which is searchable.

DR. BERGFELD: Yeah.

DR. ANDERSON: Yeah.

DR. MARKS: Good. So --

DR. ANDERSON: Now, that would require a write up, which we would bring back to you, essentially what the letter to the editor would look like, and we come back to you in December, assuming we can get it done, and have you review that.

DR. MARKS: And then I don't know if our discussion included for the allergy, Alan, you had made note in your memo to me that the results were not linked to IgE serum levels. To your point, Rachel, that you made, it's problematic that it's sex differentiated, why did it occur in men but not in women, so that's more problematic in the study is that an issue with this epidemiologic study, and in the last comment you made, Alan, was that this was a cross-sectional study, which is not readily applicable to this issue either.

Okay, so not reopened for Triclosan and

no change in the conclusion, and you explore the idea of getting this searchable via a letter to the editor. So, there won't be a --

DR. ANDERSON: And press release.

DR. MARKS: Oh, yeah. That's --

DR. BERGFELD: And the website.

DR. ANDERSON: And the website. So, you know, again, we may have lost some contact with some of the special features of the website and we're working to improve that, but an example of something we did once before was when the panel re-reviewed paraphenylenediamine as a hair dye and said, there's no real new data, it's continues to be safe. However, we really don't like the idea of putting this in tattoo ink or in henna, in particular, and that's a very dangerous practice and is considered unsafe.

That went up on the website as a special alert. Now, that was on the hazard side, but this would be on the flip side that this is to be highlighted. Again, right now our mechanism for doing that probably isn't as good as we would like, but that's impetus to fix it.

DR. MARKS: Okay, we're going to delay

the discussion of parabens until after lunch. We're going to break for lunch now and we'll re-adjourn at 1:05..

(Recess)

DR. MARKS: Okay. Rachel's here. Good. Let's start.

So, we finished Triclosan and now we're on to the parabens, and, again, we were sent this second -- part two of this one article is the association urinary level of parabens with aeroallergen and food sensitization, and so the same question -- let me see, were there any other articles that concerned about parabens? Oh, we also have parabens -- Tom, I'll ask you to comment about parabens found in human breast epithelial cells and in parabens concentrations of breast tissue at serial locations across the breast from maxilla to sternum.

MS. BRESLAWEC: Excuse me. Dr. Marks, did we have any studies presented on that in there? Okay, sorry.

DR. MARKS: So, where did I get these from?

MS. BRESLAWEC: I don't know.

DR. HILL: Wave 2.

DR. MARKS: Since they're printed out, they have to be Wave 2. So, the one is by Darby in the Journal of Applied Toxicology, June 2012. That's the one of human -- did you see these, Tom, by any chance? Oh, you didn't? Okay. Well then I'll give you a minute as we discuss the sensitivity, but I'll give you a minute to look at these two.

MS. WEINTRAUB: There's a number of them.

DR. MARKS: Yes. Well, they were the two I printed out.

MS. WEINTRAUB: In Wave 2 there were a number of different abstracts.

DR. MARKS: Thank you. So, the two Rons, were you concerned about the potential link between urinary levels of parabens and food sensitivity or aero sensitivity? It's the same study, same issues that we discuss with Triclosan, so I assume they're similarly applicable. Is that correct? Not enough to reopen?

DR. SHANK: As far as I'm concerned, that's correct. The argument that we use for

Triclosan also applies to the parabens.

DR. MARKS: Good, and Lillian, you're sitting in for the director, is that correct?

MS. GILL: Yes.

DR. SLAGA: I totally agree with Ron, related to that article, that I have no problems --

DR. MARKS: Okay. Should we delay the other discussions, Tom, until you've had a while, or Ron -- did you see these abstracts and the articles?

DR. SHANK: I did.

DR. MARKS: Okay, good. Did that raise any concerns in your mind, again, with reopening?

DR. SHANK: No, again, these are interesting observations, but there are no data relating causally parabens to breast cancer. So, how one extrapolates from finding parabens in breast tissue to parabens causing the carcinogenicity is too -- right now it's just too large a gap. And, again, I would say the panel should continue to review these articles and studies as they become available, but right now I don't see a need to reopen the paraben document

to consider any kind of a change in the conclusion.

DR. SLAGA: Looking at the abstracts -- I haven't read the whole paper yet, but I agree, it's not -- you can't relate it to cosmetics. There's no causative relationship here. You know, they can be coming from other sources just like we had with the Triclosan, but I don't think this is needed to open it because we really don't have any data related to cosmetics.

DR. SHANK: I think you'd find parabens in a lot of fatty tissues.

DR. SLAGA: Yup, and in your sweat glands you'd find parabens, in BHT, BHA all of those type of things accumulate.

DR. MARKS: And Tom, then, in the original document there was no evidence of parabens having a carcinogenic effect or mutagenic or whatever -- genotoxic -- that whether they're in the tissue or not, you're not really concerned that that could be related as this one was in breast cancer?

DR. SLAGA: Especially at the levels

that were used. I think, you know, there were a few that had mixed mutagenicity type of activity, but it wasn't consistent and the concentrations were -- that are used are much below that.

DR. MARKS: Rachel, any other comments? And anyone else have comments?

MS. WEINTRAUB: I mean, I think at a minimum what needs to be documented is that the panel looked at these, considered them, and concluded, based on the information, that it was applicable or not. You know, and I think that's what's minimally important here.

You know, I think, issues of causation -- and there was some other letters -- I don't think it was actually on parabens, I think it was on Retinol A, but there is some interesting information about causation, how to establish causation, I guess, and I think it gets into sort of deep views about how to view this type of information within scientific analysis.

But at a minimum, I think it's very important that the panel establish that it did review these studies and the reasons why it was found persuasive or not in the context of

cosmetics.

DR. MARKS: So, I think this is -- Lillian, were you here the end of the morning where we discussed how we would perhaps capture this? So, I talked to Kevin and he felt that our minutes would not be searchable for these ingredients, so what we landed on this morning was that there would be a letter to the editor, so it would be in a peer reviewed journal, which would be quite searchable, that there would be a press release, and then it would be readily available on our website.

MS. GILL: Yes.

DR. MARKS: So, I think, Rachel, that's how we would address and it would have a -- again, we wouldn't reopen, there's no change in conclusions for parabens, but we would have a robust discussion for both of these concerns, in this case, one the allergic concern, the other one the potential cancer concern.

Any other comments about parabens? If not, then tomorrow I will make a motion to not reopen either one of those, if there need be a motion, and of course, that would indicate

there's no change in conclusion and then capture the CIR's review of these two ingredients, the Triclosan and the parabens, and the nuances of why we didn't reopen and why we still feel they're safe.

Next is the Polyether Lanolins. And the conclusion is on page 20. There are a number of ingredients there.

Any -- so, the panel can -- reinforces the safe conclusion. Any editorial comments for Lillian? Rachel?

MS. WEINTRAUB: Editorial comment, CIR Panel Book page 18, there is a font size change in the third paragraph, the last sentence.

MS. BECKER: I'm sorry, could you say that again, please? I'm sorry.

MS. WEINTRAUB: Sure. CIR Panel Book page 18 or page 9 of the report itself, the third paragraph from the top, the very last sentence, there's a font size change where it gets even smaller.

DR. MARKS: Any other comment? Yes?

MS. BRESLAWEC: This report is a re-review of -- it's a reopen, re-review. To the

best of our understanding, there's absolutely no new data covered in this report, that's been presented in this report. Everything in the report is from previously published reports.

Our concern is that the amount of information that's summarized and in the way that it is summarized suggests that there is new data in here that have not previously been reviewed, reported on, or published. In fact, I mean, the studies that are sited in this report go back to 1945. There are some studies that have citations of 2012, which in fact were not submitted this year.

So, what we would like to see, just for purposes of transparency in terms of panel review is just a recognition that there is no new data that were reviewed in this report. We have absolutely no issue with the conclusions, but we are concerned that the report as presented suggests that a whole bunch of new data were presented and reviewed and based on that, this assessment was made when, in fact, that is not the case.

In previous -- in some other re-reviews

that have similar situations, but they have some new data, there's a format that CIR has used that clearly identifies what has previously been published and reported on and what hasn't, and this report doesn't adhere to that format, and so it's not clear that there's no new data here.

DR. SHANK: Didn't we reopen this just to add other ingredients?

MS. BRESLAWEC: Again, we have no problems with reopening it and adding new ingredients, but what's in here is essentially a reprinting of two previous reports that have already been published and there's no indication in this report that this information -- that you're making the decision based on two previous reports. The suggestion is that you're re-reviewing -- or you're reviewing data that's not been previously submitted, which is not the case.

DR. BERGFELD: So, are you suggesting in the discussion and maybe in the introduction there be a couple of sentences to put that together?

MS. BRESLAWEC: That would help. Also,

I think the way other reports have been done, it's very clear that this information was obtained -- here's a brief summary of information that was in a previous report. This reads like a denovo report.

I mean, we're fine with two paragraphs saying, there's information here and information here that supports the addition of this -- these new ingredients. The suggestion is, just looking at the report, that there's a bunch of new information and the panel considered none of this as new information.

MS. BECKER: Yes, there was only one new piece of data added to it and up until this version, it said new data so that the panel knew that that was new data and not to be lumped in with the rest, but it was actually something new to consider.

And at the end of the introduction is says, most of the data below are summaries of the above safety assessments which lists the -- where the rest of the data came from in this report. It reads like old -- like brand new data because the panel requested that the original citations be put in the text and not, this is from the alkyl

report, so it reads like that.

So, that's why we have what we have.

MS. BRESLAWEC: Again, my understanding is that the IGT won't republish this because it's already published verbatim, what's in here, in two other (inaudible), but that's for you all to deal with.

This is just -- you know, our concern is -- continues to be the credibility of CIR and CIR reports, and if it's a regurgitation of what's previously been done, what's the purpose for that? The data in the two previous reports support adding new ingredients.

DR. HILL: Yeah, and we have the same problem here, I notice in this report, with the one we talked about before lunch, which is here you have a section and now we have alkyl PEG ethers. Why? Here we have a section on carcinogenicity and now we have alkyl PEG ethers. Why? We're not reviewing alkyl PEG ethers other than the fact that we have PEG ethers of those lanolin ingredients, so that's --

DR. EISENMANN: Question. Is the PEG-3 methyl ether data really relevant to these

lanolin ingredients? I thought -- I mean, in general, the report might be relevant that you've reviewed the whole group and said they're safe, but the specific ingredients like PEG-3 methyl ether or even maybe PPG-2, dipropylene glycol, are those really relevant to these ingredients?

DR. HILL: Right, and so, I mean, if it's not structurally within the class, then it's supportive data in the sense that we've reviewed other PEG ethers, that should be in the discussion. It doesn't belong smeared out through the report when it's not compounds of that class in my estimation.

It's supportive data that you can mention and the discussion is here, or unless it pertains to impurities that might be there, which -- so, I mean, the fact that we reviewed propylene glycols is useless in terms of reviewing PEG lanolins unless they happen to be there as low level impurities, which, in most cases, they won't be.

Because the only other reason you'd be concerned about them is -- and we've probably overplayed the component thing is -- if,

biologically you know those are going to be generated by route that's at least reasonably likely or documented, then it doesn't relate.

DR. MARKS: Okay. So, there are two issues. First we'll go back to Halyna's issue of a largely regurgitation other than one reference, if I heard you correctly, Lillian, that is new, and since we reopened it to add no-brainer add- ons, I think that's still our primary purpose. The question is, how does that now then get, well, to be a final report in the CIR website that will be searchable? And I guess I would leave it to Lillian, you, to figure out how to get it in the Journal if they'll accept it.

I think that's more an issue of -- how would you want to compose it, Halyna? You would want one sentence or two right in the beginning saying that this has largely been published before and the data we're using is published not new other than the one study? Is that how you would approach it?

MS. BRESLAWEC: You know what, I don't have any particular suggestions. I do, but I think it's inappropriate. I -- you know, my

concern is --

DR. HILL: Credibility matters.

MS. BRESLAWEC: I think credibility matters and, you know, it just takes a lot of effort to produce a document like that.

DR. MARKS: Oh, yeah.

MS. BRESLAWEC: And the question is, is it warranted? And I think if you're saying you've got two reports that support the addition of these no-brainers, then why do you have to regenerate this sort of thing? And I think I'd like to stop there.

DR. MARKS: Yeah, I think we have to have a full- fledged report if we change the conclusion, that's my sense, so the conclusion is changed.

DR. SLAGA: With add-ons.

MS. BRESLAWEC: You do have two other re-reviews that you've looked at.

DR. MARKS: Yeah, the conclusion has changed because of the add-ons.

MS. BRESLAWEC: Right, and you do have two other re- reviews that you're looking at right now. I think that the report -- one of them is pegylated oils where there are some new data that

have been added and in those cases, the existing reports that formulate the basis for it are summarized briefly. That seems a reasonable format and it better reflects what the basis for adding new ingredients is.

DR. MARKS: So, is the panel okay with -- again, to -- with the idea of maintaining credibility right up front saying this is largely a document in which the data is from the preexisting conclusion?

DR. BERGFELD: With the addition of it's an expanded --

DR. MARKS: Right.

DR. BERGFELD: -- ingredient.

DR. SHANK: We've had several re-review summaries, none in this -- for this meeting. Aren't those published? I thought those were published.

DR. MARKS: The --

DR. SHANK: Whether we reopened or not, we always had a summary for what we did, why we reopened it or why we did not, so can't you just have a re-review summary saying that we have -- we looked at the lanolins and added these because of

read across so it's a one-page thing.

Aren't those published, the re-review summaries?

MS. GILL: Yeah. My understanding is they are.

DR. MARKS: Oh, yes, they're published. The question is, has the conclusion changed?

MS. BRESLAWEC: Yes, because things have been --

DR. MARKS: No, the summary. Usually the summaries are like two paragraphs and this is why -- have we changed the conclusion and done it as a re-review? Or we did a full- fledged new document?

MS. BRESLAWEC: There have been re-reviews where additional ingredients were added that were published that were much, much, much more concise.

DR. MARKS: Okay.

MS. BRESLAWEC: Where the review of the original data which the original report is not reviewed and summarized in such detail essentially the reference is the previous report rather than all of the individual citations.

DR. BERGFELD: So, you're really asking to go to the format that we've established for this rather than to have this voluminous -- well, not that voluminous but voluminous document?

MS. BRESLAWEC: Right, and again, there are two other re-reviews that you're looking at today, which utilize that format. The difference is that there are some new data in those reports and so they're a little bulkier because there's new stuff that was looked at. This is about as bulky, but there's nothing that was looked at that was new.

DR. MARKS: So, Ron, Ron, and Tom, do you like the idea that we make this a re-review summary, make it much more abbreviated?

DR. BERGFELD: She's not saying that.

DR. MARKS: Well, but that's one thing we could potentially do.

MS. BECKER: I don't know if we can. Because we're adding ingredients, I think we have to actually publish a report and not -- re-review summaries are just for things that -- okay, nothing's changed, here you go.

DR. MARKS: That's what I said

previously, but I thought Halyna said that we had done re-review summaries with that --

MS. BRESLAWEC: No, we published reports that have been very concise.

DR. MARKS: Oh.

MS. BECKER: Well, basically what this started out with was just the summaries of the reports that we were referring to in the report, and then I got questions of, well, what was the concentration? How long was that chronic study (inaudible)? So, the summary became not good enough for people reading it and giving me comments. I've added all that information, you know, including the panel's request for going back and digging through some horrendous filing systems to get the original references. It took me an entire week spread out on my dining room table, by the way.

MS. BRESLAWEC: And I think, Lillian, that's our objective is to eliminate something like that when it's already been reviewed, it's already been thoroughly reviewed by the panel and a conclusion has been made.

MS. GILL: But I think what she's

suggesting is that we tried that approach and we were asked for more information. I think if it were summarized like we've done some of the others where we indicate that these are previous studies we've looked at, we've opened them, and we present it to the panel as do you have any concern for the newer ones we've added, that's what you're after.

MS. BRESLAWEC: The way the other two were done --

DR. MARKS: The other two meaning? Which two?

MS. BRESLAWEC: There are two other -- one of them is -- I'm sorry, one of them is pegylated oils, alkyl esters is the other one.

DR. MARKS: Okay, well, how do you want to proceed? Despite Lillian's investment, a week, which was important so that whoever the panel members were that asked you for more detail, we've gotten that detail. Do we want to keep it in this report or do we want to make it a much more abbreviated report?

And then the second part of that is, do we want to get rid of those sections that you mentioned, Ron Hill, that aren't directly

pertinent? So, let's first start with the -- how do you want this final -- this amended final report to look like with the polyether lanolin ingredients? Do you want it much reduced in size and just reference the previous ones?

DR. HILL: And one thing before we comment on that question, I'll take a short rabbit trail, I wasn't suggesting to totally dump the information that I was -- it's supportive, it just can be concisely put in one spot in the discussion without --

DR. MARKS: Right.

DR. HILL: -- again, seems like a truth in advertising thing. The other thing is, we do need to include the direct lanolin review as part of this as well because now we're down to PEG-2 and PPG-2, because when you get small amounts like that, I'm not sure about the purification procedures, but in general you're going to have some free lanolin in that case, I would think the purification would make it practically impossible to remove free lanolin, but that safety has been reviewed, so we need to be sure that gets captured whereas before we didn't have

anything that small, so odds of any free lanolin would be just -- but not with those 2s in there.

DR. MARKS: So, Ron? How would you like to proceed, Rons? Do you want to keep this much more robust report, which is repetitive? Or to shrink it down to, perhaps, a page or so?

DR. SHANK: I think just having the summary is adequate and the panel expresses its apologies to Lillian for messing with her report to begin with. It was fine. And we asked you to do more, and now we're saying thank you, take it out. It's very embarrassing.

But I think just the summary, since it's been all published, and just refer to the other report is fine.

DR. HILL: My guess is, though, that the formatting of the tables and all of that is quite different than what was in these previous reports. We've gone to a very different -- we're looking at, what, 1997 and -- what are the --

MS. BECKER: Which tables?

DR. HILL: All the tables in your new report, formatting has changed from one of the ones that we're originally referencing -- '99,

'97, is there one that's newer?

DR. MARKS: So, you're suggesting, if I hear you right, Ron --

DR. HILL: The report could get a lot shorter, but I'm not necessarily sure that you want to shorten the tables --

DR. MARKS: But keep the tables.

DR. HILL: -- at all because I think this is laid out in a way that probably wasn't there in the original reports, it would be greatly valuable. And this is just something I'm suggesting.

DR. MARKS: No, I think that's an excellent suggestion because the tables summarize a lot and take a minimum amount of space.

So, essentially we would reduce the report, have an introduction, obviously, I presume an abstract, or maybe the introduction would be the abstract, and then a summary and a discussion, the conclusion, and then the tables. Is that correct? And perhaps the summary and the discussion is going to be combined because, again, there's not a lot of -- we don't need a lot of

redundancy.

DR. HILL: Yes. I agree.

DR. MARKS: Okay. And then the tables. So, let me make sure I've captured the gist of this -- thanks, Halyna, for bringing that up. So -- oh, Lillian?

MS. BECKER: Just on the tables, there's only two that carry over from previous reports, and that's Table Three and Table Five..

DR. HILL: Didn't I say keep all the tables?

DR. MARKS: Yes.

DR. HILL: Although Table One could be cut down if it's an exact duplication of what was in the older report.

MS. BECKER: Table One is a whole new creation, Table Two is a whole new creation, Table Four is a whole new creation.

DR. HILL: Right.

MS. BECKER: So, just Three and Five.

DR. MARKS: So, Three and Five.

DR. HILL: I'm thinking Three and Five ought to stay. Does anybody disagree?

MS. BECKER: And Five is an adaption.

It's not the original table.

DR. MARKS: Okay. So, tomorrow I am going to move that we issue an amended final report on the polyether lanolin ingredients used in cosmetics with a conclusion that they are safe in the present practice of use in concentration, and in deference to all of Lillian's hard work, I'm going to recommend significant editorial changes of the document so essentially there will be an introduction, a discussion summary, and then the tables, so that the overall size of the report will be much smaller and will reflect that the data that we used for this safety assessment was virtually the same data as used previously.

DR. SLAGA: One of the ideas we had originally is to put all the data together when we had add-ons so it would be easier for someone to do the comparisons.

DR. HILL: Well, and that's why --

DR. SLAGA: It would be difficult.

DR. HILL: Well, that's why I was suggesting, at least keep the tables because a lot of it's captured there in the tables.

DR. MARKS: So, Ron, Ron, Tom, am I

capturing the spirit of what the team wants to do? Shall I ask Lillian to step out?

DR. SLAGA: If you have add-ons -- shouldn't you still have the abstract?

DR. MARKS: Well, say an abstract, right, that will depend on the Journal.

DR. SLAGA: And a discussion in it too?

DR. MARKS: It depends on how they put this in the Journal. They may not want an abstract if it's so sure, like the re-review summaries don't have abstracts, I don't think. Do they or do they?

MS. BECKER: Yeah, I think the abstract is required.

DR. MARKS: Okay. So, abstract, obviously an intro, discussion summary and then the tables. Does that sound okay? Tom?

DR. SLAGA: Yeah, if a table has changed somewhat, if it's not exactly like the other table or --

DR. MARKS: Yeah, there's one table that's --

DR. SLAGA: -- in some case it could refer to a table and you put the reference where

you got it. That's not a copyright -- and they no longer have permission to do that. If it's important for this document.

DR. MARKS: From what Lillian said, there's only one table, which is exactly the same as previously, and that's a small Table Number Three.

Okay.

MS. BECKER: And it's our report, so --

DR. MARKS: Yes. Okay. Any other comments? The Borosilicates is our next ingredient, the Borosilicate Glasses. This is Blue Book. And a draft final safety assessment was issued, that it was safe in cosmetics, and now we're at the point of issuing a final safety assessment with that conclusion. Any comments?

And that's what I will move tomorrow. Okay, since this isn't amended we don't have the issue of taking data from previous reports, do we? So, any editorial comments? So, as difficult as the last one is, Lillian, this one is easier.

Okay, we'll move on. So, I will move that we issue the final report with a safe conclusion.

Next is the Panax Ginseng-derived ingredients, and this is actually root derived. And, again, a draft final report was issued previously. We're now at the point of issuing a final report with a conclusion of safe. Discussion? Rons and Tom? Agree with the conclusion?

DR. SLAGA: I agree with the conclusion.

DR. SHANK: The conclusion is fine. I have an edit for the discussion. On page 11 of the report, 28 of the Panel Book, let's see, the fourth paragraph near the very end, it says that the total amount of pulegone in the product should not exceed 0.03 percent, et cetera. Rather than giving it as a concentration, I would suggest that we say that the cosmetic product -- pardon me, the panel limited the amount of pulegone in these ingredients or in combination with other ingredients in the cosmetic product to yield an exposure of no more than 20 mg of pulegone per/kg body weight. This is an exposure rather than a concentration because our concern is how much pulegone one is exposed to, not the concentration.

So, the concentration depends on how much you apply, a little bit or a lot of it, and it's better to do it as an exposure, how many mg/kg body weight. So, it depends if you apply a half a gram or 10 grams. Just a suggestion.

DR. HILL: I like it, but are we breaking new ground, I'm wondering, in making such a -- I mean, I like it.

DR. SHANK: I don't think so, but --

MS. BRESLAWEC: I don't have any problem with it. Could you explain how you calculated the exposure number?

DR. SHANK: Oh, dear. A very good question. Somewhere I found the panel did the calculation and had the limit on pulegone as 20 mg/kg body weight in some report, which I found --

MS. BECKER: Probably in the Peppermint Report.

DR. SHANK: Thank you. Maybe that's where it was. I'll have --

DR. HILL: High probability that's the case.

DR. SHANK: I found it once, I can find it again. But somewhere we said that --

MS. BRESLAWEC: Again, just for the record.

DR. SHANK: Yeah, thank you.

MS. BRESLAWEC: Again, no problem at all with the conceptual --

DR. SHANK: That's all right..

DR. MARKS: Yeah, that was going to be my comment, is this consistent with --

DR. SHANK: Where did I get that 20 milligrams? From a previous report, and I'll have to just go back and try to find where I found it.

DR. MARKS: Go ahead, Lillian..

MS. GILL: On page eight of the Panel Book in the previous transcript, it's discussed there as 20 milligrams.

DR. SHANK: Thank you very much.

DR. HILL: She beat me to the punch.

DR. SHANK: You saved me.

DR. MARKS: So, if we --

DR. EISENMANN: Dr. Marks, one comment. I'm a little concerned about you setting a level like that pulegone without -- you haven't really gone back and looked at the new data on pulegone, because there is a new NTP bioassay on there. I'm

not sure -- I mean, you haven't written it up, it hasn't been written up in here. I mean, you're just relying on that peppermint --

DR. HILL: We had all those papers last time. Did we not have that one? I mean, we had a very thick -- I'm pretty sure that's what it was -- we got along with our report last time.

We had a pile -- I mean, I think it was about that deep, on pulegone. And I'm pretty sure that was in there.

DR. EISENMANN: I don't remember seeing that.

DR. HILL: Yeah, we had -- I left that all at home in my closet on the bedroom floor, but that's where it is, and it's about that high. We had a lot.

DR. EISENMANN: I don't remember it being referenced in here, the NTP bioassay. It's relatively new.

DR. HILL: I don't remember if specifically that one was included in all of that what we got, I remember it.

DR. MARKS: Lillian, did -- what is presently in the report that pulegone in a product

should not exceed 0.03 percent in rinse-off, 0.002 percent for leave-on products, is that straight out of the peppermint oil?

MS. BECKER: Yes, it's straight out of peppermint.

DR. MARKS: And that was in -- that probably was not in the conclusion, that was in the discussion?

MS. BECKER: That was -- I think that was in the conclusion and you decided it was not necessary here last meeting. Yes, it was in the conclusion.

DR. MARKS: It was in the conclusion. So, now we're taking a little different tactic with the conclusion that we used to -- because if we don't go with the concentration, the products, leave-on and rinse-off, now, Ron, you're saying that it's the pulegone exposure is the more important?

MS. BECKER: Actually, there was a lot of discussion last time on how to remove it from the conclusion and put it into the discussion in this wording.

DR. MARKS: I would be hesitant to

contradict the previous conclusion. Otherwise, we need to reopen it.

DR. BERGFELD: Well, why do you have to have that sentence at all, though? If you just stop at the sentence above it, where it says the panel is confident a toxic concentration of pulegone could not be reached in cosmetics, period, and delete that next qualifier.

MS. BECKER: The additional concern was multiple cosmetics that have pulegone being used at the same time, that's why that was added.

DR. BERGFELD: You have the next sentence, though, after that that deals with that. So, it qualifies it, so maybe you don't need the actual restriction.

DR. HILL: We definitely had this NTP document. I'm looking at it now and I'm recognizing. It's technical report 536 from last November.

MS. BRESLAWEC: What's the title?

DR. HILL: I'm about to tell you. It is "Toxicology and Carcinogenesis Studies of Pulegone" gives a CS number F344/N rats and B6C3F1 mice. I'm recognizing the first page of the

actual report. I don't know how many -- 212 pages, that -- I remember having that.

MS. BRESLAWEC: Thank you very much, Dr. Hill. If we could make sure that's cited in this report, then that's --

DR. HILL: I think we got it either the day of the meeting or it was in Wave 2, I'm pretty sure it was in Wave 2.

MS. BECKER: Yes, Wave 2.

DR. MARKS: So, Ron Shank, how would you, going back, looking at that paragraph on pulegone, either that, or Tom, we're concerned about this, how would you -- I know you had suggested an edit and how to reword it in relationship to exposures. Are you still -- after the discussion are you still comfortable with rewording that last sentence as you had suggested?

DR. SHANK: I just felt that giving a limit to pulegone in terms of concentration in products was not very useful and a total exposure would be more useful.

And I came up with the 20 mg/kg body weight. Given the concentrations, you don't know what the exposure is unless you know the amount

of product that is being used. So, it's just more useful to give an exposure rather than a concentration. If nobody wants to use an exposure number, then leave it with the concentrations.

DR. SLAGA: I think the concentrations would be fine, that's how we related it in a number of other products in the past.

DR. HILL: But I also remember --

DR. SLAGA: I agree, exposure is better, but this relates more like we have done other ingredients.

DR. HILL: Could we not put both, or, I don't know, I guess that would be cumbersome. But I remember, we discussed the use of multiple cosmetic ingredients, and that's where the context came up of the total exposure is that we were concerned that people might very likely be using multiple products where they were getting it from more than one source, and that was, as I recall, the issue, or maybe it was multiple ingredients in one particular -- it was probably multiple ingredients in one particular cosmetic that we were discussing, but I guess that's covered if you keep with the concentrations.

You could ask the question in terms of what would give a better margin of safety, that would be --

DR. MARKS: I guess the other question, Ron, is how comfortable do you have with this 20 mg/kilo per day? That's just the transcript and this is a quote from Dr. Belsito. I don't know the reference to it, so, is that really a true -- it talks about a greater (inaudible) was reported and then we talk about the 20 mg/kg per day, no effect (inaudible).

So, Tom, you're happy with the way it's --

DR. SLAGA: Percentages are fine.

DR. MARKS: Percentages are fine. Ron? Is that okay, then?

DR. SHANK: Okay.

DR. MARKS: Yeah. Ron Hill? Okay. So, no change, so that we won't have an editorial comment to that, but it was good to discuss it. Lillian -- or not, Lillian, I'm sorry, Rachel.

MS. WEINTRAUB: Right.

DR. MARKS: I was looking at you and thinking of Lillian over here.

MS. WEINTRAUB: I just wanted to point this out. I may know what the panel view is, but in the summary, when I was re-reading it, there seemed to be a particularly stark statement, and this is on CIR Panel Book Page 27, and the statement is basically a list of different data that was not discovered.

So, my question is to the panel to make sure that the fact that there were these data gaps was adequately explained in the discussion. It is, sort if, the main point. I just want to make sure that you think the data gaps were explained sufficiently.

DR. MARKS: So, are you talking about under the summary Panel Book Page 27, it would be an equivalent of the fourth paragraph --

MS. WEINTRAUB: Yes.

DR. MARKS: -- there were no dermal percutaneous or inhalation toxicokinetic data discovered.

MS. WEINTRAUB: Yes. Yes, and the discussion does begin with, although there are data gaps, I just wanted to make sure that stark sentence was adequately explained. And if not,

it should be.

DR. MARKS: Exactly. So, I'm sure when we first discussed it last time in terms of without having dermal or percutaneous or inhalation data, we felt that these ingredients were safe if they were absorbed from a systemic point of view. Is that correct?

MS. BECKER: And you do have a large amount of oral data.

DR. MARKS: Yes, that --

DR. HILL: Well, I'm looking at your table way back at the beginning of the book. You're showing repeated dose toxicity for Panax Ginseng root extract, dermal and on the same thing, you're showing repro-tox, geno-tox, carcinogenicity and photo-tox. That's all in the root extract.

And then you drop down to hydrolyzed ginseng saponins, and you've got repro-tox, geno-toxicity, and phototoxicity. And then there were irritation studies.

It seemed like there was one more -- and we also had geno-tox on root powder and root extract. And, yeah, so I think, if I remember

right, the major thrust of the discussion was, given that there's more than one Panax species, have we captured enough of that variety to read across the entirety? And so I'm not sure how that connects with what we've got written in the summary here.

MS. BECKER: Well, that just refers to toxicokinetic data, not toxicity data.

DR. HILL: Right.

DR. MARKS: So, I think the issue Rachel raises is does the panel feel comfortable with that stark sentence, and does it need to be addressed or do we have -- in the discussion, or should that sentence be -- well, you can't alter the sentence if we don't have the data.

MS. BRESLAWEC: Get rid of the sentence.

DR. MARKS: Pardon? Get rid of the sentence?

MS. BRESLAWEC: Yeah.

DR. MARKS: Yeah?

MS. BECKER: But you do have the oral data in that area.

DR. SLAGA: You do have dermal.

DR. MARKS: Dermal?

DR. SLAGA: Yeah, it's here.

DR. HILL: Toxicokinetics? Okay.

DR. MARKS: So, you would just eliminate that sentence, Rons? Tom?

DR. SHANK: Well, we don't have inhalation, but we have dermal percutaneous to say there were no inhalation toxicokinetic data.

DR. SLAGA: Although there are data gaps, I mean, (inaudible). Because we are looking at the similarity of the plant sources, constituents, function, concentration, to come up with the extrapolation.

DR. MARKS: Correct, but going back in the summary, the point Rachel makes is that is a rather stark sentence. Do you like that sentence the way it is written at this point, or do you want to just, as you suggested, Ron Shank, to modify it there were no inhalation toxicokinetic, but then if we say that, then we need either the inhalation boilerplate in the discussion or we need to say there's no inhalation exposure, which I don't think is the case.

So, you're saying, Ron Shank, we do have dermal?

DR. SHANK: Yes.

DR. MARKS: And we have percutaneous. So, it's really only the inhalation.

DR. HILL: Where?

MS. BECKER: In the toxicokinetic section.

DR. HILL: Irritation and sensitization, I'm still not seeing the toxicokinetics data.

DR. SHANK: No, not toxicokinetic, dermal data via animal and human.

DR. HILL: Right, it's just that we don't have the toxicokinetic data and that's what the sentence says. We don't, in fact. And actually obtaining that would be very challenging because we have a large number of ingredients you'd have to --

MS. BRESLAWEC: Perhaps if the sentence summarized the data that were there on toxicokinetics rather than what wasn't, that might take care of the issue.

DR. HILL: Well, we don't have any.

MS. BECKER: Which would be the next sentence.

MS. BRESLAWEC: Which is the next

sentence, yes. So, if you delete that and then just summarize the oral --

DR. HILL: You're right. All right, so the idea is remove that sentence, correct?

DR. MARKS: That's possible. But, again, you don't want to remove it if what Rachel is -- has raised is, okay, can we move on to a safe conclusion with that sentence being intact unless we have it in the discussion or --

DR. SHANK: Just modify that sentence to say there were no inhalation toxicokinetic data discovered.

DR. MARKS: Okay. And do we need --

DR. SHANK: Because we do have dermal --

DR. MARKS: Right. Okay. So then under the inhalation, do we need to have our typical boilerplate?

DR. SHANK: I'm looking for the uses.

DR. BERGFELD: The root had some..

MS. BECKER: You got the inhalation boilerplate in Wave 2.

DR. MARKS: Oh, we did get it in Wave 2?

MS. BECKER: Yes. It was one single

page.

DR. MARKS: Okay.

MS. BECKER: Yes.

DR. MARKS: Okay.

MS. BECKER: Because Ivan was astute enough to notice that it wasn't here, so I wrote it up for you.

DR. MARKS: Okay. Now that you say that I remember that I didn't put it in the front here. Okay. So, that's in Wave 2. That's taken care of. So, we'll have that one editorial change on page 27 where we say there were no inhalation toxicokinetic data discovered. Okay. And that's taken care of in the discussion.

DR. BERGFELD: Found it.

DR. MARKS: Yes.

(Laughter)

DR. MARKS: Okay. Any other comments? Thanks, Rachel, for noting that.

Do we need to mention that tomorrow?

DR. BERGFELD: Wave 2?

DR. MARKS: No, both of those -- the wave -- how this sentence is being edited, or is that an edit and should we bring it up during

the --

DR. BERGFELD: Discussion.

DR. MARKS: -- discussion tomorrow. Yes. Okay. Edit page 27. Okay. So, that's how we'll handle that then.

Rachel, we're going to delete the dermal and percutaneous and we'll limit that sentence to an even starker sentence, "No inhalation toxicokinetic data discovered", and then of course now that's been handled by the inhalation boilerplate in the discussion. Thanks, Lillian, for reminding us that that was Wave 2.

Okay, any other comments about ginseng? So, otherwise I assume that I will be seconding a motion with a conclusion that's a safe, and the only editorial comment will be about that sentence in the summary and I'm going to leave the pulegone concentrations the way they were in the discussion.

Okay. Next is the Diakyl Malates. And that's Blue Book. And we have a draft final report in front of us and tomorrow I assume I will be seconding a motion that these ingredients will be concluded to be safe.

Any comments? First of all, any concerns about the conclusion? I assume no.

DR. SLAGA: No.

DR. MARKS: And are there any editorial comments? And is this -- Lillian, you've got a string of these, don't you?

MS. BECKER: Yes.

DR. SHANK: I had an editorial comment on the discussion. I don't know if it's worth taking panel time, it was just the relationship between maleic acid and malic acid. I'd reword it to make it a little clearer.

DR. MARKS: Okay, well --

DR. HILL: If this would have been red ink I would have bled the first two pages, (inaudible), but it relates to those sorts of things. I mean, it's okay to say there's a succinic acid core, but then that should be the last mention of succinic acids and so I made notes of all of that, because --

DR. MARKS: So, I don't think we need to mention Ron's editorial comment for tomorrow in discussion. Do we need to mention yours, Ron?

DR. HILL: Mine? No.

DR. MARKS: Yes, Ron Hill.

DR. HILL: I don't think so..

DR. MARKS: No, okay. So, Lillian will take note of that and you can look at both Rons' editorial comments and include that in the final report.

DR. BERGFELD: I had a comment, and that is on the ocular. Malic acid is a pH adjustor and it's an irritant in the eye, as I recall. Malate is -- malic acid, so I just wondered if you should mention that in the discussion. We've handled those pH adjustors before.

MS. BRESLAWEC: Malic acid is not covered in this report. None of the ingredients covered in this report function as a pH adjustor.

DR. BERGFELD: Okay. So, in the beginning, I went back to look at this, in the abstract --

DR. HILL: It says so, and that should be deleted. Yes, that's wrong.

MS. BRESLAWEC: Right, there's an error. Right.

DR. HILL: That's wrong.

DR. BERGFELD: Okay.

DR. HILL: Didn't we have malic acid in there at some point -- I don't remember --

MS. BECKER: Yes, we started with malic acid.

DR. HILL: So, there's some carry-overs that should have gotten zapped.

DR. BERGFELD: Are you going to take out the malic acid that's under I then too? You have malic acid under dermal. But you kept some of the malic acid studies in here.

DR. HILL: I assume it's the idea that you could potentially by ester hydrolysis get back to malic acid, but --

DR. MARKS: Any other editorial comments?

MS. WEINTRAUB: Just a question. So, what's the conclusion here? There's -- under the chemistry there's a whole heading of malic acid. It's the first bolded paragraph.

MS. BECKER: The last paragraph of the introduction, because they may metabolize in the alcohols and penetrate the skin. That's why the information was provided to the panel.

DR. HILL: For me, this went more to the

purities issue, how pure do we think that the initial ingredient malic acid is that's used to make the esters, and then, yes, I mean, any possible formation of it after the fact. But for me this mainly related to the purity of the esters as prepared, that they don't contain fumerates, that they don't contain maleates, and also what goes on with the chirality there.

DR. MARKS: So, getting back to Rachel's point, would you keep malic acid under the chemistry even though that's not part of this -- that's not one of the ingredients being concluded upon?

DR. HILL: Maybe you don't want the header malic acid, but I'm thinking all the information that's there needs to definitely stay. It certainly was important for me in reflecting on the rest of what was in here.

DR. MARKS: Certainly a lot of the toxicologic datas are related to malic acid. I mean, you could start that by saying, although malic acid is not one of the ingredients in this report, it provides important background information, something to that effect, which

again would be editorial.

MS. WEINTRAUB: That's exactly what I was thinking would be an accurate, clear way to explain why it's here and show why it was important for it to be used and relied upon.

DR. MARKS: And that could be either under the chemistry and structure or it perhaps could be right in the introduction because a lot of the toxicologic data is from malic acid. There's sections in each one of these, almost, that are -- that malic acid is --

MS. BECKER: I'm looking at the second paragraph after the list of ingredients in the introduction. Just make that the first sentence of that paragraph.

MS. WEINTRAUB: Also, in that --

DR. MARKS: Yes, I see what you're saying.

MS. WEINTRAUB: -- I guess second sentence that beings 2001, it brings up what Dr. Bergfeld had raised before about the use as pH adjustors.

DR. HILL: Right. I think that -- actually, that sentence -- those two

sentences ought to go out, except that we do have to have at least somewhere in there point out that we -- I don't know. I didn't strike them, I kept them in.

Yeah, moving that might not hurt.

DR. BERGFELD: If you look at Panel Book 26, you have ocular irritation list under Table Four, the last entry, severe ocular irritant to hair styler and hair shampoo. I was trying to figure out what study that was going back to the eye -- ocular testing.

DR. MARKS: Yeah, that specifically relates to malic acid, that's what I didn't -- it is a bit confusing, I think, that we're saying that the data on malic acid and sodium malate are safe as a pH adjustor, then they say -- then we say it's insufficient for other functions, and now we're using malic acid a lot in this report and these ingredients have other functions, if my reasoning is correct.

Yeah, these ingredients function mostly as skin conditioning agents and pH adjustors, although the data we had of these agents are they're safe.

MS. BRESLAWEC: Dr. Marks, no pH adjustors.

DR. MARKS: Pardon?

MS. BRESLAWEC: None of the ingredients in this report are used as pH adjustors.

DR. MARKS: Correct. That's why I was saying we're referring that malic acid is safe. We have malic acid in this report repeatedly and kind of referencing back, and these agents are skin conditioning agents, not pH adjustors. So, I don't know if that's confusing or not. We didn't bring that up before.

MS. BECKER: The original thinking was having to do with the breakdown of these ingredients in the skin and having to worry about malic acid and the alcohol, and that's why the extra information was put in there.

DR. MARKS: So, perhaps actually stating it that way, Lillian, in that second paragraph in the introduction, one more sentence might be worthwhile. What do you think, Rachel?

MS. WEINTRAUB: I think that's a good way to do it.

DR. MARKS: The data from the safety

assessment are summarized in the appropriate sections below. We included malic acid. Does that sound good, or not? You don't like that, Ron?

DR. SHANK: It's fine the way it is. It's historic. We've reviewed malic acid. It's certainly pertinent to this review. I like it the way it is.

MS. WEINTRAUB: But do we need a clarifying sentence stating that we are not reviewing malic acid in this report, none of these ingredients are used as pH adjustors?

DR. SHANK: No, it's clearly stated, doing the malates, they're bulleted and we have already reviewed the acid. We have to say under what conditions we reviewed it. We reviewed it as a pH adjustor, but that's not an issue here.

DR. MARKS: Correct.

DR. BERGFELD: I think you need to take the other Table Four then, the irritation to ocular studies that are in there.

DR. SHANK: But that's all the information on malic acid.

DR. MARKS: Correct.

DR. BERGFELD: Then it should say malic

acid.

DR. SHANK: It does at the top.

DR. MARKS: It does at the top.

DR. BERGFELD: Oh, I'm sorry. I missed that.

DR. MARKS: Okay, so, Ron Shank, you like it just the way it is. Tom, you like it? Ron, do you like it just the way it is? And although we've explored this idea trying to clarify a little bit more, actually, I agree with you. I mean, it says right in the abstract they're skin conditioning agents, they aren't pH adjustors, that paragraph puts in context why malic acid is in here.

So, I'm happy with the report as it stands and let's see what happens tomorrow.

DR. HILL: So, that part I have to find out if we're concluding, then, we still have this unresolved issue of sensitization for dioctyldodecyl, for which I guess we did not get any new data.

So, my -- I remember the last time I was the only one who said lacking data. I have a question about this one and since it's not -- no

current uses are reported, the conclusion with insufficient for that one wouldn't seem out of the -- doesn't seem unreasonable, but I think I was the only one who came to that conclusion. So, we'll probably make that same statement tomorrow because no new data was received.

DR. MARKS: Fine. Any other comments? So, when we have the discussion, Ron, you can mention that. Any other -- so, again, I will second a motion that a final report for dialkyl malates be issued with a safe conclusion.

DR. HILL: There are two general issues, while we're on this report, that would be a good place to deal with and they're quick. One of them was, I had mentioned earlier, we were talking about the possible use of material safety data sheets. This was one where essentially all of the physico- chemical properties listed in Table Two are calculated, and this bothers me because calculated is calculated. They're only as good as the programs that are used to calculate it.

So, we're giving information that really is not -- I mean, it's clearly indicated as calculated, but I'm wondering if the

information isn't available, if no where else, from material safety data sheets, from the people who are making this stuff to sell, because it just bothered me to see a table that consisted entirely of calculated data, and I guess that's useful, except with knowing the limitations of calculated data, bothersome.

DR. SHANK: That's the information that's out there.

DR. HILL: Well, I know, but then the question is, do we even give it or do we leave it out, because, I mean, we're over relying on whichever resources, whichever calculation programs were used to generate these, which I'm guessing I know where they probably are, and, you know, these are probably good numbers, but it just bothers me to give a table. It almost conveys a false impression.

So, I was just tossing that out there. The other one is, and this is not the only --

DR. MARKS: Well, no. Let's resolve that, Ron, because I think to me it's transparent when you have the word calculated there.

DR. HILL: It is.

DR. MARKS: It really highlights that.

DR. HILL: Just the question is, why do we even put it in there when it's -- I mean, yes, those routines are getting more and more reliable, and, yes, these numbers may be very good, but there were two questions I had. One is, isn't there experimental data out there even if it's a material safety data sheets, because the companies that sell this stuff -- now, if these ingredients aren't in use and there are no reported uses, that data won't be out there, but I think -- and all of these are.

DR. MARKS: So, Ron Shank, did you have a problem with that table? I think, including the physical and chemical properties are important. I wouldn't want to leave --

DR. HILL: They're calculated and so as somebody who does computational chemistry as part of their living, there's always a -- you know, until you validate that information with experimental data, you're not that comfortable. And so -- and so if we had -- even if we have calculated information from multiple -- I mean, you can get -- there are at least five or six

programs that will make these calculations and listed all of them, then that would be at least a little more.

But somehow we're suggesting that this value from this program is more reliable, that's why we've chosen to include it, or I don't know. Just, philosophically it bugs me and I'm just tossing that out there as a chemist to say I find this uncomfortable, if nothing more.

And did we at least try to go and find the experimental numbers from material safety data sheets, because if we didn't, we should.

The other general issue -- I would like to just leave that hanging and you can think about that --

DR. MARKS: No, I'd like to hear Ron Shank's answer and then Lillian's --

DR. HILL: Okay, that's fine..

DR. MARKS: -- rather than switch into a different subject. So, let's try and make a conclusion to this.

And Tom, you comment.

DR. SHANK: Well, the calculated values, in my opinion, are better than no --

DR. SLAGA: That's right.

DR. SHANK: -- no information whatsoever. The numbers may not be exact, but they're probably reasonable estimates, so I would think it's better to leave it in than to delete that information.

DR. SLAGA: Yeah, they at least give you some idea that you're pretty close, and I think we should leave it in or otherwise it would look like there's no physical chemical properties that we have available.

DR. MARKS: Lillian, did you have any other comments about MSDS?

MS. BECKER: Only that if there was actual experimental data reported somewhere I would have included it, yes.

DR. MARKS: Okay, so we're going to leave Table Two in, so noted, certainly it will be in the minutes, and it's quite transparent that it's calculated, and the goal here is not to be perfect, but to be as good as we can.

And your second comment, Ron Hill?

DR. HILL: Yeah, okay, well, let me just end that discussion by saying that then if I were

reviewing this paper as a peer reviewer, I would ask at least the question why did you choose that calculation routine and not somebody else's in some other program. So, in general, it would be nice if there was at least one experimental data point somewhere in all of this.

Okay, the other question, and this is just general philosophy, but I've seen it in a lot of -- and so I'm wondering if there's a better way to stat it is, we say -- let me just give an example of cosmetic use, which is Panel Book Page 18, Report Page 2, was reported to be used at a maximum of 0.001 percent to 82 percent, so we say, and at a maximum, and then we give multiple concentrations, and I know why that is, but it just looks funny every time I encounter it, and I'm wondering if -- that's really fully editorial.

Just tossing that out there for staff members to think about more than anything else.

And then in parentheses, (up to.2 percent to 82 percent), you know, it's because you have multiple kinds of products.

DR. MARKS: Yeah, so I think it could

be --

DR. HILL: It looks funny.

DR. MARKS: So, a maximum concentration in different product uses from -- perhaps, I don't know.

DR. HILL: Something.

DR. MARKS: Okay. If you want to wordsmith that, Ron Hill, I hear you.

DR. HILL: I didn't know what to do with it. I sat -- I mean, because like I say, there were at least five or six reports where I encountered this formatting and it bugged me every time, but I didn't quite know how to fix it succinctly.

DR. BERGFELD: I like it.

DR. HILL: It's just at a maximum concentration, and then you give a range, and you don't know why, you know, and a casual reader who's just coming to these reports for the first time would look at that and, I think, seriously scratch their head, so then you have to go back -- you know, when you eventually go back to the table and you know what's going on, you understand why there is a range there, but even

if it just said --

DR. BERGFELD: Well, you can say range rather than maximum if that's what's bothering you.

DR. HILL: Well, maybe at a maximum concentration in multiple product types or something like that so you at least understand why there's more than one number --

DR. MARKS: There you go.

DR. HILL: -- when you're saying at a maximum.

DR. MARKS: You work, that's good.

MS. GILL: Ron, that statement is in most of the reports that talk about it, so we'll have to make that uniform change across the board.

DR. HILL: It seemed like if we were using this uniformed format before now, I would have noticed it, and this is the first time -- it's just jumping out at me, so I'm sure it's uniform, but I don't remember seeing it like that in all of the reports previously. If that's true, I just -- it's just suddenly hit me as funny now.

MS. BECKER: And it is a recent switch because our previous understanding was that when

they gave us the numbers, that was the range, but not the range of the maximum possible concentrations. So, we did reword that, but that was over a year ago, wasn't it?

DR. HILL: Well, sorry that I just noticed it.

DR. MARKS: Okay, so another editorial comment, perhaps, to change it to reflect its maximum concentration in different uses.

DR. HILL: You can veto me. I'm just trying to explain why it struck me as odd.

DR. MARKS: Okay. I think we're onto the last, are we not? And then we have to go to the priorities.

So, the last ingredient, the Dimethicone Crosspolymers. It's a Blue Book. And we're again seeing a draft report with the Dimethicone Crosspolymers with a conclusion of safe. And it's time now to issue a final report with that conclusion, and I, again, will assume I'll be seconding that conclusion -- that motion tomorrow.

The only note I had was Ron Hill's, is monomers okay, page 28. So, under the discussion

in page 28 I have, on the third paragraph, the ingredient's suppliers should take steps to ensure that there are no residual monomers or catalysts in the final products. Did that meet your concerns?

DR. HILL: Yes, although in practicality, to say no to the state of the art analytical limits of detection might be problematic for the manufacturers. I realized upon reflecting, I don't want to say what were demands, but concerns, is that unfortunately, in giving up monomer data you're also telling somebody else about your process, so those are typically closely guarded secrets and proprietary, so I sort of put a quandary out there and I knew it. I'm not sure I felt it the day I was making the statements, but -- so, the word no is going to be a problem in that, I think in practicality, you can never guaranty zero, and so then the question is, how do we deal this in the way that basically we're trying to convey we want these down to where they don't represent a toxicologic concern, which is monomer by monomer?

MS. BECKER: The other group asked me

to change it to minimize --

DR. HILL: Minimize? I guess right now I'm comfortable with that. I still believe most companies in the world don't want to sell something that they know is going to be harmful and that they will be conscientious.

DR. MARKS: Okay. Any other comments? So, yeah, I want to be sure to bring that out. Any other comments in terms of discussion or other editorial comments about this report?

If not, then other than changing no to minimal -- that's back to the Buff Book that has the minutes. Are there any comments about the priority list? And I have a September 10th memo also from Alan. Did the panel members see this memo? This was probably Wave 2 -- just a memo.

DR. EISENMANN: I just gave it out today.

DR. MARKS: Wave 3. Real time.

DR. HILL: Was it in that pile we got this morning? Because I don't see --

DR. MARKS: Yeah.

DR. HILL: I probably have it here and I'm sure I'll find it in a second. Thank you.

DR. SLAGA: It's probably in one of the --

DR. HILL: Well, I got two of another one that were the same, so I'm wondering if I got two of the same and didn't get this one. I'm not sure. I didn't see this earlier.

DR. MARKS: Bart, any comments from you?

DR. HELDRETH: Sure. I think a lot of this boils down to, in this memo, is to the way we've been doing the groupings. Yes, we're only looking at these groupings from a chemical perspective at this stage, but so far that has worked well for us because we don't stop at this stage and just look at chemical parameters, we go and do the research. The writers do the searching and find the tox data and present it for the panel to review and decide if the group really does belong together.

And the panel has not been shy to delete groups or separate groups into separate reports or two parts of a single report, and I think that has worked really well. And I don't think that trying to frontload the process of trying to find out what the tox data is before we even agree on

a priority list is getting a little bit ahead of ourselves.

DR. MARKS: I'm going to take a moment and leave the panel members read over the memo. So, if I understood what you said, Bart, correctly, you continue to search based on chemistry, but we will handle ingredients as they come and decide what to include and what not to include based on our individual knowledge, so to speak.

DR. HELDRETH: Right. In concept, I agree with the idea of pairing these groupings based on toxicological data, however, until we go out and do those searches --

DR. MARKS: Right.

DR. HELDRETH: -- and put the report together, we don't have those bases to put the report together. However, we do have chemical structure, source data, that we can start the grouping of the reports on and then leave it to your expertise, once you have all of the data in front of you, to decide whether that group exists logically or not.

DR. BERGFELD: I had a comment. I'd like to give a perspective of many years. When we first

began the priority listing, we did it on biological activity and we ceased to have that real problem because we've taken care of most of the very active ones. Now we're primarily focused on volume of use and I would approve this if this is -- and we've been moving to doing it in groups, and we have a heading of a general group, I would approve of proceeding as you've described.

DR. MARKS: Yeah, I think the exception to that would be is if an alert occurs, obviously, a new study or a new understanding of a biologic activity occurs, then obviously that could be moved up..

DR. HELDRETH: Absolutely.

DR. SLAGA: I agree. That's a logical way to do it.

DR. MARKS: Rons, do you -- do you have any comments? Were you able to get through the memo?

DR. HILL: Still working on it.

DR. SHANK: I'm not too sure what question is being put before us.

DR. HILL: Me neither.

DR. MARKS: I suspect as a final

approval for what's going to be on the priority list, and you have that on page 21, is that correct, Bart, in the --

DR. HELDRETH: That's correct, all you need to do is approve or make changes to this priority list, but as of today, it should go final.

DR. SHANK: I have no problems with the current priority list.

DR. MARKS: Halyna?

MS. BRESLAWEC: We have no problem with the way that the groupings are being done and the way the priorities are being selected. I think the council is long -- well, over the couple -- past couple of years, has been a proponent of doing it by, you know, the number of uses as a primary and looking at it chemically, and I don't think that was the point we were making. We were simply saying that in grouping -- in grouping the groups, we would like to see a little more consistency in how ingredients that have already been reviewed are dealt with in the grouping. Sometimes they're in the grouping, sometimes they're not.

It could be a question of, you know, just timing and being able to put the groups together in time for the panel to look at it.

Secondly, we would like to reiterate our concern that the grouping "phytosterols" is too broad. Recognizing that phytosterols is an INCI name, but it's very difficult to evaluate a group that's entitled "phytosterols".

Second, we would recommend that Pentaerythrityl rosinate be removed from the ingredients for re-review since it was insufficient data and I think typically CIR does not re-review ingredients that are insufficient data.

DR. MARKS: Unless we get new data.

MS. BRESLAWEC: Unless you get new data or --

DR. MARKS: So, that was the Pentaerythrityl tetra? Is that the one you were talking about should be removed?

MS. BRESLAWEC: Pentaerythrityl rosinate. Yes, under ingredients for re-review.

DR. MARKS: Oh, yes. Okay. Well, certainly that makes sense. If we don't have new

data, then there should be no reason to re-review it. I would think we re-review safe, that's a little bit different, even when we don't have much data, but an insufficient, it would be hard to imagine we would want to re-review it if we don't have data to change the conclusion.

So, you would suggest deleting Pentaerythrityl rosinate from the re-review. Okay. I assume the panel members agree with that reasoning since we have no new data. And then the phytosterols is an interesting -- I agree. So, Bart, we're back to you. This isn't -- with phytosterols, so this is any plant sterol? What's the chemistry going to look like in that one.

DR. HELDRETH: It's going to be a lot of steroid based molecules. But the issue here is phytosterol as the ingredient is actually the one that came up on the priority list and as Halyna pointed out, it's somewhat ambiguous group, the phytosterols. If we're already looking at that ambiguous group, I don't know why we wouldn't want to look at the specific components that are also ingredients at the same time.

DR. BERGFELD: Sort of like amino acids.

DR. HELDRETH: Yes.

DR. MARKS: So, can we give any guidance on this in terms of -- do we want to see something to begin with and see if we can chop away and, you know, maybe perhaps narrow it down? Or maybe perhaps narrow it down? Or how does the -- how does the team want to proceed?

DR. SLAGA: I'd rather see all of them and see what we can do. Maybe we can group them.

DR. HILL: Well, and there is a significance to this, which is, we are seeing an increased volume of botanicals. I think that's only going to go up. And then when there are however many phytosterols in there, I mean, at least have -- I don't know, it could be a nightmare.

DR. BERGFELD: Some of the re-reviews will be the botanicals because we have had a lot of them for a lot of years and we're going to have to revisit this issue with them.

DR. MARKS: So, I think the sense of the team is that let's leave phytosterols in there and see what shakes out when you give us the first rendition of that. Does that sound reasonable?

Is that what you're saying, Ron, Ron, and Tom?

DR. HILL: Yep.

DR. MARKS: Yep. So, we note that this is going to be difficult, but at the same time, we're not shying away from difficulty.

Any other comments about the priority list? So, otherwise, then, the priority list on page 21, the only ingredient that would be deleted from these two boxes, so to speak, is the Pentaerythrityl rosinate. And that would be it.

Yes, you were going to say --

MS. BRESLAWEC: I'm reminded there's one more comment, and that is the minerals, where we think it's inappropriate to group a variety of minerals together in the same grouping.

DR. EISENMANN: It's the sulfate group.

MS. BRESLAWEC: The sulfate group, right.

DR. EISENMANN: I mean, you took out -- you didn't want to do different valence states of ten, and I was a little concerned that do you really want to do -- what is it, zinc and --

MS. BRESLAWEC: Zinc and --

DR. EISENMANN: -- I don't remember what

all -- what other metals are proposed.

DR. SLAGA: Where are we?

DR. EISENMANN: Sulfate, barium sulfate, calcium sulfate, copper sulfate, ferric sulfite, ferrous sulfite, magnesium -- I don't know, do you really want all those minerals and metals in the same report?

DR. HILL: So, all we have is magnesium sulfate.

DR. EISENMANN: No, it goes on -- it's on another page, I think.

DR. HILL: Oh, okay, yes.

DR. EISENMANN: I think it's on the back of another --

DR. HILL: Yes, yes.

DR. MARKS: This is from Alan's memo on the second page, inorganic sulfates, is that what you're referring to?

DR. HILL: Yeah, page 17.

DR. EISENMANN: That's the group, another group of concern.

DR. HILL: Page 17 of the memo?

MS. BRESLAWEC: Actually, if you look under the tab "new data", it's on the back of the

cover memo for Triclosan and parabens. That's where the list of the sulfates continues.

DR. HELDRETH: Yes, some things got misprinted and put in the wrong place. So, while I agree that some of the transmission metal sulfates might be a little bit different, or maybe they're a lot different, I think if you have all of the data before you, you can make that decision to make that, per se, a separate group than Group 1A and Group 2A sulfates and ammonium sulfate.

But if you have the data in front of you, why make the decision?

DR. HILL: I agree with them because toxicology here is going to be driven by the metal and not by the sulfate to counter (inaudible). Period.

DR. SHANK: I would think there would be a lot of data, if you combine all of these sulfates, you're going to get a lot of toxicological data, and --

MS. BRESLAWEC: (Inaudible) that toxicological data going to be -- is the group appropriate? You'll have a lot of toxicological data on each of the ingredients, perhaps.

DR. SHANK: Correct.

MS. BRESLAWEC: But is the grouping appropriate, that's the question.

DR. SHANK: Not likely.

MS. BRESLAWEC: I think that's the question that is one you need to be asking at this phase.

DR. HILL: And I vote no because toxicology will be driven by the cation, the metal, not the sulfate.

DR. HELDRETH: So, would you suggest each one would be separate?

DR. HILL: Yeah, I mean, if you made a category like iron sulfs, that would make good sense to me.

DR. HELDRETH: Because we've already done ammonium sulfate, sodium sulfate, and potassium sulfate and together.

DR. HILL: Yes, but grouping sodium, potassium, makes sense. Grouping iron and magnesium does not.

DR. SHANK: And copper.

DR. HILL: Yeah, and copper. It just doesn't --

DR. MARKS: So, what you would suggest, rather than having sulfate -- the sulfates a priority list, you would do the metals substitute, and under that there are 393 uses as of 2012, so now you get into what are the specific metals under that.

DR. HELDRETH: So, you're suggesting other salts of magnesium for a group?

DR. HILL: As an example, yes. That's the way I would look at it.

DR. MARKS: I see that it appears that Ron Shank agrees with that, all we're going to do is magnesium sulfate and other salts.

DR. SLAGA: I agree too.

DR. MARKS: So, we're going to expand it that way not in terms of expanding magnesium to the other metals.

DR. HILL: However, I should probably comment at that point, that you're going to keep it to inorganic magnesium salts, right?

DR. HELDRETH: We can.

DR. HILL: That would be my recommendation, because as soon as you get to organic ions, then that probably will drive the

toxicology.

DR. MARKS: And then, Carol, you had a comment. I was just --

DR. EISENMANN: It's more of a general comment about trying to get the data from companies. Already, they don't want to provide it until they see the SLR, so if you're going -- but then if you're going to change at the time of the first review what ingredients are in the report that's going to make it even harder for me to get data. That's why, you know, when you put out -- if this list is going out on the website and it's going to sit there all year, that this is how -- that's why the sooner you can decide what ingredients are in a report, the easier it is for me to try to get information from companies.

DR. HILL: We had this same discussion two meetings ago and I said almost word-for-word exactly that, and then we decided there was really no straight resolution for that. But I --

DR. EISENMANN: I mean, it's --

DR. HILL: And my feeling is if -- then if it's our review timeframe that's artificial, we're pushing this forward faster than you can get

the information, maybe that's the problem and that we need to fix that.

DR. EISENMANN: Right, or you could have longer pause after the SLRs because --

DR. HILL: That's all I'm --

DR. EISENMANN: -- frequently these companies are international and the data might be in Japanese or Italian or some other language, and it takes -- not only I've got to find what company, they have to find the data and they have to translate it, so --

DR. HILL: But that probably goes back to the rules of the CIR operation, right, I mean, if it's 90 days, 90 days, and I mean, if it's the rules that are wrong, because it's posing that kind of a headache, that was what I was saying two meetings ago, is that maybe we need to revisit that. And if it's written in the Code of Federal Register, obviously we need some action, but if it's our own rules, maybe we need to amend them so that they actually work.

MS. GILL: Unless we take another look at the process and started earlier where there is an opportunity to have this material out sooner

and Carol could have this much specificity when she asks companies for it..

DR. HILL: Well, you know, you had the pre-report process, but then as a panel we were -- and I'm taking responsibility here right now -- we were making very active changes to that and if we have a category that has 300 ingredients and we cut it down to 50, then she's done a lot of work trying to get the information for that other 250 ingredients that we didn't need right then.

And so, basically how to solve that problem, and I'm not sure there is a problem, and it may be that once the final -- once the panel finally acts and arrives at a list of ingredients, we make sure there's a longer delay from that point -- I mean, these big groupings is still relatively new, I think. I know there were some in the past, but the fact that we've been doing this more and more regularly, if there's a need for a longer delay at that particular point, if we need to amend the CIR -- what's the word I'm looking for -- procedures to allow for that so we can actually get the information we need before

we proceed, what's the down side other than the fact that we do have to look at the procedures and perhaps amend them?

DR. MARKS: Okay, I think the issue there is obviously how quickly we can proceed forward. We certainly have the timelines at this point and may have to just delay until we get the information.

So, I don't think we are going to be able to solve that issue with the phytosterols because we said we wanted to look at that first and then make a decision. For the magnesium sulfate, then, do we want to change that as what we want to see are the inorganic magnesium salts? And then that would be more helpful? And we've decided now we aren't going to move into other metals, but we're going to stick with just the magnesium at this case then we can expand it from sulfate to other salts.

Does that sound good? Okay. Any other comments about the priority list?

DR. SHANK: I have one.

DR. MARKS: Pardon?

DR. SHANK: I have one coming from a

citrus producing state.

COURT REPORTER: Microphone, sir.

DR. SHANK: It's not that important.

(Laughter)

DR. SHANK: I very much appreciate the chemical structure for camellias and for rosemary, but I have to point out on page 31 of the Panel Book, for lemons we have pictures of limes and oranges, there's not a lemon in the picture.

(Laughter)

DR. SHANK: Thank you.

DR. SLAGA: They have to be from California.

DR. MARKS: Either that or they're genetically altered lemons.

MS. BRESLAWEC: And they're all from Florida.

DR. MARKS: Yeah, they're from Florida. They're East Coast lemons. Thank you for some humor at the end of this, Ron, that makes -- are there any other -- is there anything else that we need to cover before tomorrow morning? If not, today's meeting is adjourned.

(Whereupon, at 2:53 p.m. 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.

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