121th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

BREAKOUT SESSION

Washington, D.C.

Monday, December 12, 2011

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Voting Members:

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PARTICIPANTS (CONT'D):
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Senior Scientific Analyst

Other Attendees:

JOHN BAILEY, Ph.D.

CAROL EISENMANN, The Council

LINDA LORETZ

DIEGO RUA, FDA

JULIE SKARE, Procter & Gamble

DAVID STEINBERG, Steinberg & Associates

JANE VERGNES, ISP

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P R O C E E D I N G S

(10:02 a.m.)

DR. MARKS: Let's go ahead and begin our reviews. Methyldibromo glutaronitrile is presented as a re-review. In 1996, the Panel reviewed this preservative and concluded it was safe as used for rinse-off products and safe at less than 0.025 percent in leave-on products. Uses have increased and probably the biggest question I had was why the EU in 2006 banned this for both rinse-off and leave-on products. We've got a large volume of information but there's also more data out there. So I think it's -- should we reopen this to look at all the new data particularly in light of the ban by the European Union? Or do we not reopen? I felt we should reopen it..

DR. SHANK: Well, I did too and we have the problem, too, that we're below the 0.025 percent for the leave-on. And we would have to reopen it, wouldn't we because they're changing the conclusion even though that was -- I mean, that's from going to the patient?

DR. MARKS: Right.

DR. SHANK: So do we use those?

DR. MARKS: When I looked at the HRIPTs from the original products they set the concentration at 0.025. So I agree, Tom, with that concentration.

So reopen -- Christina, did you get a sense from the -- I don't know if you did review the European Union report, whether this was based on sensitivity and I suspect that's it because there's been a mini-epidemic or epidemic of sensitivity to this preservative in Europe and that may have driven the banning of it.

MS. BURNETT: It was sensitivity but I think it was more that they couldn't -- the way I interpret it maybe I just didn't read the right report because there were several iterations of what they did that they couldn't prove that it was not causing sensitization in the rinse-off products. I don't think they felt there was enough. But that was just my interpretation. Like I said, there were several rounds of the reports that they went through and the very last one is very bare bones saying we're banning it. So, and they've taken -- they took it off the list

so it doesn't even show up. When you do a search on the directive you can't find the ingredient at all.

MS. EISENMANN: In Europe they have a positive list of preservatives and it's no longer on the positive list of preservatives. So that's -- and then the adaptation to the directive that used (inaudible) so they removed it from the positive list.

MS. BURNETT: It was hard --

MS. EISENMANN: It's not listed as being banned because it's no longer on the positive list.

MS. BURNETT: Yeah. It was hard to find unless I knew exactly where to go look for the actual report. You couldn't type it. There's a database and when you type in the name it won't show up at all.

MS. EISENMANN: Because it's not on their inventory anymore because it's not --

DR. HILL: Yeah, because that was my key unanswered question, too, is why did they ban it?

DR. SLAGA: The only real new --

DR. HILL: Sensitization?

DR. SLAGA: Besides sensitization is that we have an NTP study in males and rats and mice. And in both cases there's really no concern about cancer but there's a dose- dependent increase in inflammation and hyperplasia. And I didn't know they were trying to take that into consideration in both rats and mice.

DR. HILL: I don't know but in the concentrations of use, the best I could see there's still no problem and people need good preservatives.

DR. SLAGA: These were much higher doses.

DR. HILL: Yeah. I did the calculations to put them in percent based on concentrations of use. And it looked to me like we're still comfortable. And if you change the conclusion to formulate it to be not sensitizing I would think that --

DR. SLAGA: It could very well play out to be the same situation as glutaral where we open it, look at the data, and then decide to close it because of the concentrations are okay.

DR. HILL: But if we change the

formulation to be nonsensitizing, that's a change to the conclusion. Right? Substandard. So that would, you know.

DR. SLAGA: Yeah.

MS. BURNETT: We just want to make sure that you guys had the opportunity to look at everything because it was really difficult to get everything in. And I still am getting stuff trickling in from the published literature that they had to go out and find.

DR. MARKS: And then Christina, you're going to put that -- since there are so many sensitizing studies, put that in a tabular form?

MS. BURNETT: Yeah.

DR. MARKS: Which will be easy to scan.

MS. BURNETT: It'll be an expansion of the two that are already in there.

DR. MARKS: Right.

MS. BURNETT: If you like the way they were presented.

DR. MARKS: Um-hum.

DR. HILL: Yeah, for me that's really helpful.

MS. BURNETT: It's easier to write it

that way, too.

DR. SHANK: So the decision was to reopen?

DR. MARKS: Reopen. With the purpose of looking at all the new data, particularly the irritation and sensitization studies.

Okay. And then it sounds like we may not be able to find out exactly the reason why it was banned.

DR. SLAGA: Wouldn't they have that on their website?

DR. MARKS: We'll see if we can find it.

MS. BURNETT: I can --

DR. MARKS: That would be helpful.

MS. BURNETT: -- see if I can print out a copy of the report.

DR. MARKS: Okay. Do you know it off the top of your head? I assumed it was sensitization.

MS. BURNETT: Yeah. Basically, the history of -- do I need to re-find the mike?

SPEAKER: Yeah. Please come up to the table and introduce yourself.

MR. STEINBERG: David Steinberg. The

history of the product, this was a molecule that Merck had developed for a pharmaceutical was an active ingredient drug which never got anywhere in lab testing. And in the late '70s they did a study of all of these patented molecules they had synthesized to see if they had any value. Why keep the patents? And they came across that it could be a very interesting preservative. They submitted this to, I believe it was one company who took one look at it, ran a preliminary test and it was a severe sensitizer. And it was dead until around '85-'86 when the methylchloroisothiazolinone came under attack in Europe for using it at around 30 parts per million -- ppm -- in leave-on products which was causing sensitization. One company looked at the methyldibromo glutaralaldehyde and -- nitrile, excuse me, and they recrystallized it. And by recrystallizing the material and dissolving it into phenoxyethanol, the sensitization decreased significantly and it was promoted as a rinse-off preservative and got very popular in Germany in the late '80s-early '90s. People looked at it for leave-on products. The biggest use was wipes,

which were always a problem preserving. Then as popularity increased so did sensitization. And I can say right now since the EU banned it, I don't think anyone is using it anywhere in the United States either. That it's been formulated out. I get almost zero requests for information on it as a preservative, both leave-on and rinse-off. On leave-on, it's difficult to work with because of the solubility problems and you have to be at very low levels or else you will get sensitization. It is a sensitizer. I think everyone has pretty much concluded that.

I sort of look at this the way you looked at glutaraldehyde last time. No one uses it so conclusions are whatever but it doesn't change the fact that people are not going to use glutaraldehyde as a preservative in cosmetics. They're not going to use this either.

DR. MARKS: Interesting, because we have an increased use of more than doubling. Not huge numbers, 35 to 90. So it would appear at least from the data we have there is increased use.

MR. STEINBERG: The numbers -- I get the

same numbers that you get but I also get the Canadian numbers and Canada's uses have decreased. And Canada is mandatory reporting where FDA is voluntary.

DR. MARKS: Okay. And then the only other comment I would have, Christina, on page 11, where you refer to the North American Contact Dermatitis Group sensitization going up dramatically, that's actually a secondary reference.

MS. BURNETT: Okay.

DR. MARKS: So we need to -- obviously you will -- when you get it you'll get the primary and it's a -- when you patch test with this material it's an irritant so depending on how you interpret a weak reaction you could call it either an irritant reaction or an allergic reaction and that can confound how you interpret the data.

MR. STEINBERG: Just the other thing, Christina, do you need any of the documents from Europe or even the North American study, I'm keeping them because I track well to preserve this.

MS. BURNETT: Okay.

MR. STEINBERG: So with a little time I can get you all those features.

MS. BURNETT: Okay. Thank you.

DR. MARKS: Thank you, David. So we will -- tomorrow I'll move that we reopen methyldibromo glutaronitrile and look at all the new data and go from there.

Okay. The next is a re-review of polyvinyl acetate. It's in the same Buff Book. And in 1996, the CIR panel published a final safety assessment that concluded this was safe in the present practice of use. Uses have gone up. Concentration actually has gone up also with 47 percent being reported in mascaras. And we should decide whether or not we want to reopen or not. I didn't feel we need to reopen it certainly from a skin point of view because the original report has an HRIPT showing that 50 percent is okay and thus this new concentration that we see its uses within that.

DR. SHANK: And I agree.

DR. MARKS: Any other not reopen? Okay. And we can just, if we need to, Christina, in a little bit of the discussion and re-review you can

deal with the issue of it being used at a higher concentration in the original report but that's still safe.

MS. BURNETT: Okay.

DR. HILL: I did have one question. I might as well note it now. It was -- it wasn't clear. My note says what form is it in mascara? Panel Book page 59, yeah. Polyvinyl acetate is used in cosmetic products and reviewed in this report as the emulsion form rather than the solid form. What about mascara? I mean, can we find -- I don't think we need to know today or tomorrow but --

MS. BURNETT: I have no idea.

MS. EISENMANN: I presume the emulsion form because if mascara is the primary use --

DR. HILL: Yeah.

MS. EISENMANN: Forty-three out of the 50 uses were. So I presume that was the case.

DR. HILL: Okay.

MS. EISENMANN: In the original reports. I assume whatever the original report says is how it is.

DR. HILL: Sounds logical.

DR. MARKS: Anything else? Ron?

DR. HILL: Yeah, I was just -- I have some note here about impurities and I'm trying to interpret my own cryptic, even though I have notes this time as opposed to just written things in the book, yeah, I think it was mainly they listed impurity as dihydroxyacetic acid as preservative which I think is maybe glyoxal. So let's see. There seemed to be some -- we're not going to reopen this. Is that what our motion is?

DR. MARKS: Correct.

DR. HILL: Okay. Yeah, so never mind.

DR. MARKS: Okay. The next is in Blue Book. The anisoles. And we had a draft final report on 2-amino-4- hydroxy ethylaminoanisole and its sulfate salt. We're at the stage now that report was -- the draft report was issued after our last September 2011 panel meeting. The conclusion is on Panel Book page 25 that these two ingredients are safe for use in hair dye formulations, for the free dye to used, expectation, et cetera.

MS. EISENMANN: One thing on the et cetera.

DR. MARKS: Okay.

MS. EISENMANN: We changed the language at the last meeting and I need to re-change it at this one.

SPEAKER: Okay.

MS. EISENMANN: May be formed. At least may be formed.

MS. BURNETT: For some reason I thought I had them --

DR. MARKS: Exactly how was that Carol? Were?

DR. SHANK: Well, we have a boilerplate, do we not?

DR. MARKS: Yes.

MS. EISENMANN: I think you changed it to be "may be formed" last time because industry does not intentionally make products in which nicentro compounds are formed.

MS. BURNETT: May be formed.

DR. MARKS: Okay. That's an editorial comment.

DR. SHANK: Should we say safe for use in oxidated hair dye formulations? Because that is its use.

DR. MARKS: Yeah, that gets down to also another issue is do we add some editorial hair dye chemistry to this report now that we heard Julie's report this morning which was --

SPEAKER: Great.

DR. MARKS: -- very erudite and comprehensive. Thank you, Julie.

I'm not sure how we would -- I should say Christina, I don't know how you would boilerplate that so to speak to take all that and condense it into a couple -- to a paragraph but I think there would be no reason to delay issuing a final report and the question is how important is it or do we just develop a chemistry boilerplate in the future?

So let's go back to I think the conclusion you were talking about, whether or not we should use "for use in oxidated hair dye formulations."

DR. SHANK: Oxidated hair dye formulations.

DR. MARKS: Is that accurate? It seems to me -- I can't imagine --

DR. SHANK: Well, we state it in the

introduction.

DR. MARKS: Yes, it states --

MS. SKARE: This is Julie Skare. Yes, that's accurate. It is an oxidated hair dye used only in oxidated hair dye end products.

DR. MARKS: Ron, that's fine. If you want to add that.

DR. SHANK: It's fine with me..

MS. BURNETT: Oxidative?

DR. MARKS: Yeah. And again, I see that as an editorial comment rather than oxidative. And then getting back, Carol, was that the last sentence where you said the experts caution that these ingredients should not be used? How did you want that changed?

DR. SHANK: Well, we have a boilerplate now.

DR. MARKS: And how does that read?

MS. EISENMANN: You changed it last -- at the last meeting to "maybe" instead of "are."

DR. MARKS: So where is that? Where is the --

MS. EISENMANN: In the last -- instead

of "are formed," "may be formed."

DR. MARKS: Oh, yeah. Okay. I agree with that. May be formed. Okay, again, just an editorial comment in the conclusion. Did everybody get that then? We would add oxidative before hair dye formulations in the first sentence and in the last sentence the second to the last word "are" will be changed to maybe.

MS. BURNETT: Yes.

DR. MARKS: Okay.

DR. SLAGA: Also, we usually have to (inaudible) in the beginning before the introduction and the little summaries --

MS. BURNETT: I think, if I understand correctly, we've done away with the section summaries again.

DR. SLAGA: The rest of them have them.

DR. MARKS: Yeah, I like the section summaries.

DR. SLAGA: I do, too.

MS. BURNETT: We had conflicting discussion internally as to their usefulness. What -- their original purpose was for the journal.

DR. MARKS: Right.

MS. BURNETT: And then the last couple of reports that have gone to the journal, they've been kicked back saying why do you have these summaries? (Laughter) And so I was told to remove them but it's possible that we're still batting around whether they should be there or not. So.

MS. BECKER: As I understand the current standing, they are there for the Panel and then when we make the final report that all gets extracted --

MS. BURNETT: Yes.

MS. BECKER: Because it's in the final status.

DR. MARKS: Including the abstract?

DR. HILL: It's in the final summary.

MS. BURNETT: No, the abstract -- that appears to have been my fault for not including it on this ground.

MS. BECKER: But the italicized summary is at the beginning of the section so this is strictly for your convenience and for us to develop the summary at the end and then we take those out when we send it to the journal.

DR. SLAGA: Okay. So they'll be up to the last before the Blue Book?

MS. BURNETT: It can be, yes.

DR. SLAGA: Right.

MS. BURNETT: Depending -- we decided that they were report-specific. If the sections were shot it became kind of redundant to sit there and summarize summaries. So that's why some of them don't have them, some of them do, and then I was told we're not using them at all so I was like, well, why am I writing them?

DR. SLAGA: Well --

MS. BURNETT: I can still -- we can still make sure that for your sake, especially if it's a really long section we can still incorporate the section summaries.

DR. MARKS: So what do the Panel -- what do you guys feel? I like the summary but I'd like it here.

DR. SLAGA: Well, if it stays in up to the last before the Blue Book, that would be nice, then take them out.

DR. SHANK: It's more work for the staff. You just have to spend more time doing that. And

I don't like the idea that it suggests that we, the Panel, might just read the summary and then go on to the next section. We should read the whole thing. So I would say take them out.

MS. BURNETT: Okay.

DR. SHANK: Don't waste your time with that.

DR. SLAGA: Well, we originally put it in because of a reviewer. Right?

DR. MARKS: Right. The Journal. So Ron, do you feel the same way? You don't care if this -- you don't feel -- so Ron Shank clearly feels that the summary should be left out because it may give the impression we aren't reading everything under that.

DR. HILL: Yes. And if I feel inclined to cheat I can go to the summary at the end because it's there anyway. I'm just saying. (Laughter) But yes, I agree with Ron Shank.

DR. MARKS: Okay.

DR. HILL: Really, 100 percent.

DR. MARKS: So the Panel endorses the idea of not creating more work for you as the writers.

MS. BURNETT: Okay.

DR. MARKS: Not putting the summaries in unless The Journal changes their editorial back again.

MS. BURNETT: And I apologize for not having an abstract on this one or the sodium because that completely slipped my mind in the process.

DR. MARKS: Okay. We'll just, again, I look at that as editorial changes the abstract and a couple word changes we made in the conclusion. I'll move that we issue a final report with the conclusion as stated back here that they are safe as used in oxidative hair dye formulations.

Getting back to the hair dye chemistry, I think that's something maybe for the future would be worthwhile. Maybe -- Julie, what do you think? Do you think it should be part of the hair dye epidemiology boilerplate? Should we start out with a bit of chemistry and then do the epidemiology? Or should it be two separate sort of things?

MS. SKARE: Well, it would make more

sense to me that it would be a separate boilerplate because it's not really directly linked to the epidemiology. You don't know that you study what you're actually studying.

I would think that a relatively short statement that would justify the conclusion that I gave in my presentation about your ingredient reviews and focus on the precursors and couplers, the actual ingredient, rather than the reaction product. And that statement could appear somewhere in the safety assessment. You could either have a boilerplate statement on the website or you could simply cite the SECS's opinion in support of that statement. It's kind of up to you which way you want to go.

DR. HILL: Have you or are you going to publish what you presented today? Publish in the literature?

MS. SKARE: At this point in time there is no active plan to publish that. We had wanted to wait until after the SECS issued their opinion, which actually did come up last year. The data are owned by this joint consortium so it's not up to me to decide.

DR. HILL: We'd be giving away a lot of freely useful information, I guess.

MS. SKARE: Well, it's not that we're averse to giving away information. It's very important information. I can't (inaudible) at this point that it's going to be get published soon or what the time schedule would be right now.

DR. HILL: But there was one key piece of take-home information that's applicable here and that is that they did -- I guess what would amount to chronic, which is repeated dose dermal toxicology studies in animals and they applied the sulfate in tap water. To me that's artificial condition because we're talking really in the formulation where they did some of the dermal penetration work in the formulation that conditions of use would be pH 10, where as if you give sulfate and tap water you're probably at pH 5. So actually it's a disulfate. It might even be lower than that. So it's -- it doesn't, for me, affect this particular safety assessment because there's plenty of oral tox data and enough margin of error and so forth and so on but there could be occasions. And I'll just keep like a

broken record repeating myself that sometimes oral tox for rodents is way off because their first pass metabolism is so different than humans for some particular ingredient that you could get a very false impression. So there are times where --

MS. SKARE: That can be true..

DR. HILL: Right. So there will be times where --

MS. SKARE: I'll tell you that all the data that you're going to see for future hair dyes that you're going to be reviewing has been done because of the EU submissions we've had to make.

DR. HILL: Yeah.

MS. SKARE: And they require us to do oral sulfonic studies.

DR. HILL: Sure.

MS. SKARE: So I understand your point you're making.

DR. HILL: But I'm just saying that, you know, maybe I would think there's somebody over there that realizes that sometimes the oral study is invalid compared to what you get dermally. So if you had something, I mean, this is a case where

it's 30-minute exposure and you see most of it doesn't stay on the scalp, most of it doesn't and you get a pretty low scalp exposure even multiplied by the whole surface area, but there are occasions where that could be way off. Just a difference of first pass metabolism between rodents and humans. Of course, if you give very high doses then you're swapping out all of that. But dermal can show something different.

DR. MARKS: So my sense is that we would develop that for the future and move forward and issue a final report on this and not hold back for adding any hair dye chemistry. Cite boilerplate in the discussion. Does that sound good?

MS. BURNETT: (inaudible) and discussion.

DR. MARKS: Yeah.

MS. BURNETT: Okay.

DR. MARKS: But in the future that would be helpful both on the website and then for future reports. And we'll see what the Belsito team wants to do. If they would prefer to see something then what I suspect again it would be editorial and perhaps sent out to us electronically to sign

off.

MS. BURNETT: Okay.

DR. HILL: Yeah, because it would just have to say something like the toxicology appropriately focuses on the ingredient, not reaction products.

DR. MARKS: Well, I think it's --

DR. HILL: Which is why --

DR. SLAGA: That's almost my statement to put into the discussion.

DR. MARKS: Well, would you like to put that in?

MS. SKARE: Actually, because you have -- in this particular report you have a figure showing the formation of that reaction time.

DR. MARKS: Right.

MS. SKARE: That was because there was one publication that cites it. So if that's in this report, because you've got that one --

DR. HILL: And I raised the question in the minutes for that matter.

MS. SKARE: That would be kind of nice to have that boilerplate developed.

MS. BURNETT: I'm sure we could -- I'll probably just go over and talk to Bart and see if we can knock something out real quick maybe.

DR. MARKS: Between now and tomorrow?

MS. BURNETT: Possibly. It depends.

DR. MARKS: Great.

MS. BURNETT: He's battling pneumonia.

DR. MARKS: What?

MS. BURNETT: He's been really sick so it depends on how well he feels. So we'll see.

DR. MARKS: Okay. (inaudible) does not need to hold this up. Maybe Julie can help you tomorrow write up a couple sentences. Actually, your conclusion slide is basically it.

MS. BURNETT: I can also see maybe Ivan can help, too.

DR. MARKS: Yeah.

MS. BURNETT: We'll see if we can knock something out real quick.

DR. MARKS: Great.

MS. EISENMANN: In the discussion section, the first paragraph, the focus is on the reface. It would be nice if that, which is not used, it would be nice if the focus would be

changed to the sulfate which is used.

DR. HILL: But, all right, where are you?

MS. EISENMANN: The discussion. The gaps in available -- you focus on the gaps rather than what actually is there and on the ingredient, I mean, on the date or the sulfate salt, that's the ingredient that's used.

MS. SKARE: Yeah, I think that's a good point. I mean, I think you would want your discussion to start with the focus on the ingredient that's used, which is the sulfate salt and it covers both.

DR. MARKS: So is that just -- so are you just --

MS. SKARE: It's the basis of use.

DR. MARKS: So are you just suggesting flipping sentences and start with "the available data on the salt are sufficient?"

DR. HILL: Well, okay, I raised this gap the last time and it was just what I said again today, is that if you put sulfate on the skin and do the chronic dermal tox that way you're getting the wrong answer because under the conditions of

use what you've got is the freebase, period. I mean, at pH-10 there won't be any sulfate. It's totally dissociated. So what you've got is exposure to the freebase, whatever exposure there might be. So that's not irrelevant and I did raise that concern and it wouldn't be bad to keep that in there.

Whether gaps is the right word to cast that or whether you can tie this into what you're proposing to write, which I think is probably what needs to be done, the point is that that chronic dermal tox state is called into question by the fact that they did the study with the sulfate in water. So you're getting a very false answer. But we've got lots of oral tox, and in this case I think that makes up for anything that might come from that.

MS. SKARE: So really your point has to do with the data that are supporting the use of the sulfate salt and whether that chronic dermal study, which was done in an inappropriate vehicle, supports the safety of the sulfate salt.

DR. HILL: Well, as I say, once you -- once you put the sulfate salt in the

formulation and use it in conditions where it's pH-10, it's no longer the sulfate salt. That's kind of almost irrelevant.

MS. SKARE: Understand. Yeah.

DR. HILL: So I think -- I wasn't saying that there were gaps in the safety data for the sulfate salt. I'm not. It's just there needs to be recognition of what actually goes on once you put something into solution.

DR. MARKS: And that's what it says here. You were just saying how you ordered it.

MS. EISENMANN: Well, and also in the second paragraph it says that both are used as hair dyes. Well, that's not exactly true. It's really the one that is compensably used as hair dyes.

DR. HILL: It's the sulfate that people put in the formulation, right? I mean --

MS. EISENMANN: Right. Right. So it just seems that it could be -- it's not worded -- I don't know exactly how I would word it but, you know, I think I would start that you recognize that it's the sulfate salt that is used and these are the data on the sulfate salt. And then you

could also discuss that there are gaps in --

DR. MARKS: So the first sentence would -- under the discussion is "we recognize that sulfate salt is the ingredient being used."

DR. HILL: Right. And then all you need is this discussion you're talking about putting together to indicate what goes on in the conditions of use. And it's fine. And I just -- and I put into the minutes that the issue with the dermal tox doesn't raise any questions in my mind but the overall picture again because we've got all this oral tox data that shows it's fine.

DR. MARKS: I mean, the conclusion is very clear. So I don't think there should be confusion as to what's used and what isn't.

DR. HILL: So if that sentence bugs you, I don't mind it coming out. I just -- as long as we're capturing --

DR. MARKS: Okay.

DR. HILL: -- that it is free base that will be the exposure at the conditions of use on the scalp.

DR. MARKS: So if anybody wants to make

an editorial change in the discussion, Ron, do you want to give that to Christina and mention it tomorrow? If not, we'll leave it. Or Carol, if you have a better suggestion, let's, again, tomorrow, bring that up. Do you want me to bring -- Wilma always goes around and asks for editorial comments, so if there are any editorial comments I'll allow you to bring those.

DR. HILL: Like I say, if we get the new language right then I'm good.

DR. MARKS: Okay. Let me see here. So I will move that we issue a final report as I said earlier. Okay.

Well, our next ingredient, again Blue Book, is sodium lauri -- with an I -- iminodipropionate. And in September, the use of concentration was not available but we decided to go ahead and issue a tentative report anyway. And what we have before us is a draft final amended report. And we have the use concentration. And I think we can issue this final report with a conclusion of safe. Is that correct?

DR. SHANK: Mm-hmm.

DR. SLAGA: Mm-hmm.

DR. MARKS: And so on page 26 is the conclusion. Again, with the boilerplate, some of these ingredients are not being used. Any comments? Any editorial comments that we should make?

DR. HILL: I don't think we put to bed but maybe somebody can -- somebody else thought about this other than me, I don't think we put to bed the issue of the 5 percent possible impurity of the laurimino and the insufficient data on that which is the question we raised I thought at the September meeting. So we got -- we tabled it on no concentration of use data and determined that there wasn't any direct use of the free acid or the disodium salt at the moment.

DR. MARKS: No, we actually didn't table it.

DR. HILL: No, we went with an insufficient.

DR. MARKS: Right.

DR. HILL: I didn't mean table.

DR. MARKS: That way we could move ahead.

DR. HILL: That way we could move ahead.

But the issue that was raised was that the raw material of the imino could have as much as 5 percent of the amino and we didn't have data on the amino. That would have been one of the merits of keeping it in there but the problem was we didn't have the data. And they were different so we took it out. But I don't think we ever put it to bed, did we?

MS. BURNETT: I recall someone stepped up to the mike at the last meeting and I know it doesn't reflect -- I changed something as a result of that meeting so it no longer says there's 5 percent amino -- of the amino in the product. But I can't remember who.

MS. EISENMANN: If I remember correctly, that's what one supplier said. The material that was actually tested did not have -- was from a different supplier and it didn't have that issue.

DR. HILL: Yeah, but that's actually a negative because if it had had the impurity then we would --

MS. EISENMANN: Right. I know. I know. I know. But again, the use half a percent in hair conditions.

DR. HILL: Right. And so I remember the concern was with a high concentration leave-on and I guess we determined that -- what did we determine? I wrote notes..

MS. EISENMANN: And the only current use I have is the 0.05 in hair conditioners.

DR. HILL: Okay. Because we had -- yeah, because see, we had the 1995 report of a leave-on product with 5 percent concentration, which means we would have had -- if we had 5 percent impurity we'd have, what, 5 times 0.05.

DR. MARKS: That's interesting because I have in my notes that we were going to move forward with a safe conclusion. And I don't have that as a concern in my notes, Ron.

DR. HILL: Yeah, that's because probably I got tired of being the burr under the saddle by that point. But I --

DR. SHANK: There are no reporting (inaudible).

DR. HILL: We did discuss it in the -- it is in the transcript of our group meeting. And we were waiting on that concentration of use to see if that 5 percent leave-on was still out there

on the market. I don't guess we got anything more so right now we're saying -- so if we say under concentration -- current concentrations of use, basically we're saying 0.05 percent. Is that correct?

DR. SHANK: In rinse-offs.

DR. HILL: In rinse-offs. Yeah. Anything else would fall outside that. Yeah, with that I'm very comfortable.

DR. MARKS: Okay. Good. Okay. So tomorrow I presume I'll be seconding a final amended report with a conclusion of safe.

DR. HILL: The only other thing I had was -- and this is just really editorial is that we have -- I think it's predicted -- do we still have the metabolism scheme in there as a figure?

MS. BURNETT: Mm-hmm.

DR. HILL: We need to be very clear that this is predicted information, anticipated information, but not experimental information..

MS. BURNETT: And this is scheme 1?

DR. HILL: Yes.

MS. BURNETT: On page 28?

DR. HILL: Yeah, changing the title

would reflect predicted or anticipated or expected.

MS. BURNETT: Instead of purported you want predicted?

DR. HILL: Yeah. Purported suggests somebody has data to support the information and as far as I could tell there was no experimental data.

MS. BURNETT: Okay.

DR. MARKS: Okay. Any other comments? Next is another Blue Book. Pentaerythrityl tetraesters. So we tabled this report in September because there was concern about 45 percent in toilet waters and 50 percent in perfumes and the possibility that these products were sprays and so while we found out that the two ingredients in the data show that they are not on spray products, so Ron, do you feel now the inhalation data is okay? The highest concentration being used in a spray product now is -- appears to be 21 percent.

DR. SHANK: Okay. Actually, we do have inhalation data, page 36 of the Panel Book, page 4 of the report. At the very top under oral and

inhalation it says there are no inhalation studies. But under -- if you go down to genotoxicity in vivo, that is an inhalation study. As I recall, I couldn't find -- I think that's not in the literature. That's some industrial report so I don't know if there is any information about respiratory effects but it is an inhalation study.

DR. HILL: Yeah, it's HPB unpublished.

MS. BECKER: Yes, they gave no information on the condition of being handles after just what was presented here.

DR. HILL: So it's really incorrect to say there are no inhalation studies?

DR. SHANK: Well, I guess that's not an inhalation study; it's an inhalation exposure.

DR. HILL: Mm-hmm.

DR. MARKS: Mm-hmm.

DR. SHANK: But under inhalation at the top of page of the report I would add another sentence referring to this inhalation exposure to just say that there was no comment made about respiratory effects. Then you can use the boilerplate that's being developed for this

discussion.

DR. MARKS: So Ron, you are okay with the conclusion that these ingredients are safe?

DR. SHANK: Yes.

DR. MARKS: And we'll just use the inhalation boilerplate to address the issue of lack of inhalation studies. And essentially then again the way that reads, "If this were to be inhaled," the boilerplate basically, the conclusion there is --

DR. SHANK: The conclusion remains as is.

DR. MARKS: Right. Right. But the boilerplate, how does that get around not having any inhalation studies then?

DR. SHANK: Well, that's in the boilerplate.

DR. MARKS: Okay.

DR. SHANK: But to do mutagenicity tests inhalation five days a week for two weeks would suggest that it's not a big problem for inhalation to me.

DR. MARKS: Right. Yeah.

DR. HILL: I do still have problems with

the toxicokinetics section. And it's also reflected in the discussion. So we still don't have any hard data that suggests that these tetraesters are biotransformed to tri, di, mono, and fatty acid. And in particular, well, I guess my point being that it may not happen at all. We don't have any information whether these things are substrate to esterases. And so speculating anything on the basis that we might -- you took out a lot of language but there's still stuff in there that says, well, gee, that must be what would happen. And it was my contention that actually if they're not good substrates for esterases, which I suspect might be the case based on their geometry, what we really get is metabolism going on at the other end in a very different type of biotransformation.

So lacking any evidence to suggest that esterases cleavage is the root, which we have the zero, I'm still not happy with the way this discussion reads. I mean, I changed it to "might" instead of "would." And then I re-read it and I said, well, no, because we don't have any information along those lines. And I honestly

think what probably happened, but I'm just making a guess, is that for these special -- these long chain ones the metabolism would happen at the other end. We'd get a mega oxidation, the branching for the branch ones, the usual roots, cycles of beta-oxidation. I'm not sure what would come out. It would have been nice to have some metabolism data on a couple representatives but we don't have any toxicology that suggests we have to have that.

So I think we're just getting in trouble here speculating because we didn't find any data at all on the triesters or the diesters or the monoesters. It raises some toxicological concern that might not even be a concern..

MS. BECKER: So your suggestion is to remove the second paragraph?

DR. HILL: Yeah, basically. Yes.

DR. MARKS: This is in the discussion.

DR. HILL: No, I mean the toxicokinetic section.

DR. MARKS: What page?

MS. BECKER: Three.

DR. HILL: And I'm even troubled with

the -- expected that these ingredients would penetrate the skin. I disagree. I agree that they might not reach the systemic circulation but they do likely penetrate the skin. The molecular weights are not that high in some of these. There are a few of them that are very high, a thousand, but you know, anything under 700 can get into the skin, log Ps range up to 4-5. That allows dermal penetration. So log P of 5, molecular weight at 500-600, sure. It's going to penetrate into the skin. Whether it gets into the system by penetrating through the skin, I don't know. So I don't like -- I'm not happy with what's written there either.

DR. SHANK: While we're on that, why do we say in that same paragraph -- it's a low POW?

DR. HILL: No, it should be high.

DR. SHANK: Should be high.

DR. HILL: That's a mistake. I didn't catch that last time.

DR. SHANK: Yeah, and it says the log P is greater than 5 but in Table 3 it says 16.7 as the log POW. So why not just say that?

DR. HILL: I'm just wondering if that

whole section --

MS. EISENMANN: Well, I also noted under repeated dose they did a study that they say the dermal bioavailability of the test article was 2 to 6 percent.

DR. HILL: Right. So that's bio --

MS. EISENMANN: So I thought maybe that should be brought up to the --

DR. HILL: Yes. I think that should be put in there.

MS. EISENMANN: Because, you know --

DR. HILL: That's the most valid data we actually have.

MS. EISENMANN: I mean, there's a little bit.

DR. HILL: There is. And of course, it's only for one --

MS. EISENMANN: Right. And it's for the smaller one.

DR. HILL: Right.

MS. EISENMANN: So, the larger one should be less presumably.

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

MS. EISENMANN: Not for sure but --

DR. MARKS: So, Ron Hill, your suggestion is, again, under the toxicokinetic section here on page 35 of the book, page 3 of the report, you would delete both of those?

DR. HILL: No, I think the first paragraph needs a little bit of work and it needs to have that information that Carol just mentioned put in. It's probably just one paragraph.

DR. MARKS: And so where is that information that Carol mentioned?

MS. BECKER: The bottom of page 3.

DR. MARKS: Pardon?

MS. BECKER: Bottom of the same page.

DR. MARKS: Bottom of page 3.

MS. BECKER: About the middle of the paragraph, third line down.

DR. SHANK: "The dermal bioavailability of the test article was."

DR. MARKS: Right.

DR. HILL: How they measured that I have no idea.

DR. MARKS: Okay. So that one sentence would go up into the toxicokinetics, the dermal

bioavailability of test article is 2 to 6 percent. Is that what you're saying? Yep. And then up here you mentioned both --

DR. SHANK: It should say "in rat."

DR. MARKS: In rat, okay. And then both Rons, you mentioned where in that first paragraph, for example, the gonate has a log P and you said it was like 16?

DR. HILL: 16.7.

MS. BECKER: Yeah, some are pretty high.

DR. MARKS: 16.7. So, yeah, that's considerably greater than 5. Yeah.

DR. SHANK: And where it says on the second line it says low POW, it should be high.

DR. MARKS: Should be high. Okay, good. Those are -- boy, that's major.

DR. HILL: Yeah, I didn't catch it last time but I caught it this time.

DR. MARKS: Okay. So we got that for the first paragraph. Would you then leave the first paragraph stand the way it is with those changes?

DR. SHANK: Yes.

DR. MARKS: And then on that second

paragraph, Ron Hill, you had significant issues about the monodie and triesters. You would like to eliminate that altogether?

DR. HILL: I would because we don't have any information to suggest that metabolism goes that way. And to suggest that we strongly believe that it does, at least it doesn't accurately reflect what I think should happen here. I think the metabolism probably is going to go on at the other end. Because if you look at the geometry you've got a carbon here very hysterically hindered with four big ester groups coming up there. I just can't imagine these being substrates for esterates. And we have some -- actually, I think there's some intestinal data. I thought, well, maybe intestinal esterase is (inaudible) bioavailability but when you look at whatever information is in here I think suggests that it's even lower in the intestines. So I'd just rather doubt these things get cleaved on the ester end. I think that probably -- then I had asked the question about impurities. We don't really have any information on that but it's just raising a red flag where we don't have any

tox data to suggest there is a worry.

DR. MARKS: So let's go back to that second paragraph, Ron Shank, Tom, do you think the speculation should be removed? Should these ingredients enter the body and da- da-da-da? Or would you leave that in?

DR. SLAGA: Well, we don't know one way or the other.

DR. MARKS: Right.

DR. SLAGA: And we know there are esterases but we don't, as Ron stated --

DR. MARKS: So you would delete --

DR. SLAGA: We really don't have any data?

DR. MARKS: So this is speculation and you would delete it then? This doesn't add anything to the report?

DR. SLAGA: It doesn't add anything.

DR. HILL: It doesn't add anything and it raises -- because if I were reading this critically then I would say, well, do we have any toxicology data on those tri, di, monoesters? We don't. You did that search. And I'm not sure that red flag needs to be raised because --

DR. MARKS: So we'll put -- I'm going to put on here delete, Ron. I'll mention hat tomorrow, Ron Hill.

DR. HILL: So then we've got the same problem with the second paragraph of the discussion section because it's basically working on that same conjecture. I think you have to leave in a mention that these fatty acids have been looked at and reviewed. But the way this needs to be stated is if cleavage to parent fatty acids occur, these fatty acids have been studied. I grant you I'm splitting hairs here because it potentially raises the same question but I think you do have to mention that. But speculating about the esterase metabolism again, I think that's probably over the edge from where I sit.

DR. MARKS: Okay. So what --

MS. BECKER: Do you have your suggestion and your --

DR. HILL: I just marked the -- flagged the paragraph. I didn't write -- I can do that.

DR. MARKS: So what paragraph? Is that on page 38 under the discussion?

DR. HILL: Page 38, second paragraph of

the discussion.

DR. MARKS: The safety assessment.

DR. HILL: I think you have to mention that the fatty acids have been reviewed.

DR. MARKS: Okay. So you're talking about the sentence where it begins, "These are the esterase."

DR. HILL: The esterase metabolites. Yeah, I think we don't have any data to suggest that it goes that way.

DR. MARKS: Okay. So I'm going to put a question here again, Ron Hill. And then tomorrow I'll just mention. I look at these as being editorial changes. To me it wouldn't deter from issuing a safe final report.

DR. HILL: I agree.

DR. MARKS: Does that sound good? So I'll move that we issue a safe final report for these ingredients as noted in the conclusion on page 38 of the Panel Book. And then the editorial comments will be: 1, conclude the inhalation boilerplate in the discussion; and, 2, on page 39, the toxicokinetic editorial changes in the first paragraph, low to high, and 16.7 instead of 5. To

lead the second, move up the sentence about the dermal bioavailability that's at the bottom in rats and then there will be some bit of a change in the discussion concerning the esterase metabolites. Does that sound goo?

DR. HILL: Yes, sir.

DR. MARKS: Okay. Good. And then we had a new use -- this didn't affect anything I don't think, the new use tables on these. Okay. I think that was a Wave 2. Were there any --

MS. BECKER: Yeah, that was finding out the --

DR. MARKS: And there were no significant changes?

MS. BECKER: (inaudible)

DR. MARKS: Okay. Good.

MS. BECKER: And that's reflected in the new table.

DR. MARKS: Yep. Super. Green Book, ginseng root. First report, this is the first time we've seen this. Let me see here. So we have some -- it appears we go on page 8. We see the list of ingredients begins with a Panax. Is that how you say that? Panax?

MS. BECKER: Panax.

DR. MARKS: Ginseng root extract and hydrolyzed. And then we move onto powder, water. And then we move onto some other species, japonicus.

MS. BECKER: Notoginseng.

DR. MARKS: Notoginseng. And then the q compound or the q species. Yeah, so obviously one of the things we've got to talk about is do we have concerns about including different species in this? And do we -- the root and then we have extracts. So is that different? The powders, the water? And so on. Let me see. And then what is this? Ingredients include. Yes. Which ingredients do we really want to include from this? And we could include all of them. This is a first report so we don't have to have this no-brainer, but obviously we need to have ingredients that if we're going to include them we can read-across with some confidence and say that they're all safe.

So with that sort of background -- and we also have chemical compositions on page 21. They aren't quite all the same. Tom and Ron, there

are several things. What are the needs? Obviously, we always begin with that when we see the first report, and then Tom will get into the issue of do we limit this one ingredient. Pulegone? How do you say that?

DR. SHANK: Pulegone.

DR. MARKS: Pulegone. Yeah, because we have a previous limit set in the peppermint assessment of 1 percent. And in my review I saw that pulegone on the PQ but not in the P ginseng under ingredients. So, at any rate, should we tackle this with one -- what ingredients that we should include here on page 8 and what needs? Rons and Tom?

DR. SLAGA: Well, there is a statement made in the beginning that really it could be the same, too. You don't know that for sure.

DR. MARKS: Yeah.

DR. SLAGA: That's the hard part. But the statement is made that it could be all the same.

MS. BECKER: Yeah, I mean, they're all on different continents.

DR. SLAGA: Yeah.

MS. BECKER: But Duke posits that nobody can really tell the difference once they've been extracted.

DR. MARKS: Other than the pulegone, at least if I read it correctly, isn't in all these species.

MS. BECKER: It just showed up in the quinquefolium.

DR. HILL: The peppermint?

DR. MARKS: No. It showed up in the Panax, the quinquefolium..

MS. BECKER: It's only in the essential oil of that. So technically, according to this list, it's not used for the oil.

MS. EISENMANN: So I will check if I have any suppliers of the extract (inaudible) pull over and went into their extracts. But I can't remember (inaudible). I don't remember that they were very responsive with the one or had many uses of this ingredient anyway, so.

DR. MARKS: Yeah. This gets down to how we --

MS. EISENMANN: So we could set a limit if you want. That would be fine, too.

DR. MARKS: Yeah. This is how we got into the biological -- not biologics, into the botanicals as we've been before as we've generally, as I recall, we take some lead ingredients and use those across as far as the safety assessment.

DR. SHANK: Okay. Do we have any information that the extracts that were tested for toxicity are the same that are used in cosmetics?

MS. EISENMANN: Well --

DR. SHANK: I found nothing to answer that question. And if we can't answer that question then --

MS. EISENMANN: Well, you did get some information on that red -- from one of the suppliers. They're making an extract of red and think that's a cosmetic ingredient. In that data that were provided there are some data in the back that are on the cosmetic ingredients. But no, the NTP bioassay is a, as I understand it, it's an alcoholic extract. These are his material to be used as a dietary supplement. But I suspect that the cosmetic ingredients contains less

(inaudible), I mean, the (inaudible) supplements.

DR. SHANK: Okay, so we don't know?

MS. EISENMANN: But, like I said, you know the material in the back. This is the information on the cosmetic ingredients.

DR. HILL: Well, yeah, I mean, I made a note because I need to mark the pages what you're talking about and I even wrote down pages 64, 82, 83, 84, 90, 92, 93, 109, 116. And my comment, I wrote it in German because something came up in German, do we have medicine here because they're talking about a lot of biological effects that would be consistent with? So the reports that jumped to my mind when I read through this were three. There were the vegetable oils in terms of the multiple component situation, except that they're all fatty acids. Kojic acid because we were dealing with the threshold above which we started to see drug-like effects, which again, if you went through the back of this book, actually, that's what they're sort of touting as a sales pitch. And then the third one was marigold. That's probably the most complex botanical I've

seen since I've been on the Panel for the short amount of time I've been on the Panel.

And then the fourth consideration I had was that at least all the reported concentrations for cosmetic use are very low so they should be well below the thresholds where we should see any of these effects that they're talking about in the back of the book. But there might be a distinguishment. And based on what ingredients would it be, if it's pulegone or would it be certain of the saponins, which are plant steriles? Because some of the effects back here probably are traceable to the plant steriles, not pulegone or some of the other triterpines. So it's complex. This is a complex one from where I sit.

DR. MARKS: Right. I saw the ginseng, to take up what you were saying, Ron, the ginseng root extract, the Panax ginseng root extract, the highest use concentration is 0.5.

DR. HILL: The low.

DR. MARKS: For probably, well, at least dermal contract. And then the other one, when you look, that has a fair number of uses, 149. And then the Quinn species, 0.002. So very low there.

And the notoginseng is 0.004.

So getting back, Ron, to your -- can we even proceed forward if we don't know if we're using the same -- if we're not using cosmetic extracts? That's a major --

DR. SHANK: That's a question I have. So I would have to suggest an insufficient data announcement. That would be one data need.

MS. EISENMANN: Well, I don't quite understand data needs. I just wanted you to clarify a little bit more for me so I understand --

DR. SHANK: The only real data we have is on this one Panax ginseng and root extract.

DR. MARKS: Right.

DR. SHANK: But I saw nothing that told me that this is the extract that is used in cosmetics. And the extracts have a lot of uses besides cosmetic use.

DR. MARKS: Other than the skin. Skin irritation and sensitization. I assume that is the cosmetic extract for the HRIPT on those, other than that.

DR. SHANK: Okay. If that extract is the one that's used in cosmetics, then that one

is probably safe as used.

DR. MARKS: Right.

DR. SHANK: But the others we don't have any information.

DR. HILL: And I think one of the biggest places where you can see that is -- I was looking for the table while you all were talking on Table 9. The compared -- they're comparing -- we're comparing two methods of extraction. This is on book page 32, report page 25. One is a hydroglycolic extract. I'm not quite clear how they did that. The other is an ultra hypothermia biotic extract which is probably super critical carbon dioxide. I'm not sure. And you can look at there's a huge difference in the saponin contents which is plant steriles.

And then again, if you go to the back of the book where you start looking at the effects on this, that, and the other, at least some of those are attributable to the plant steriles, the saponin, but for me the overall safety assessment hinges on the fact that in the cosmetic use tables the amounts are so small. It's like they're using it so either they can say it's in there if we've

got ginseng or for odor.

MS. EISENMANN: Now, on page 50 of the Panel Book, this is like a summary of various supplies. Rather than giving each an individual supplier their opposition data I summarized it. And here they give the -- the levels of ginseng. And this is the cosmetic -- this refers to the cosmetic ingredients, the various extraction methods.

DR. HILL: So consistent with what the tox data was generated with is --

MS. EISENMANN: Correct.

DR. HILL: Yeah.

DR. SHANK: So this is what was used for the --

MS. EISENMANN: No. But this is what the supplier are providing.

DR. SHANK: Okay. That I understand. What was used for the toxicity test?

MS. EISENMANN: The NTP said it was an alcoholic X-ray as I understand it, which is, I mean, it is included in this.

DR. HILL: So I guess what, you know, what we're asking is is if you look at the Table

4, the very long Table 4 that goes on for how many pages? It's got a comprehensive listing of all the ingredients known to be in this root. And then if you look at how much is there you can see a lot of them are at high concentration and the rest are approaching trace. How -- how reflective of all those components listed was the composition of the things that were used for the NTP study of what is typically delivered as pharmaceutical ingredients -- excuse me, cosmetic ingredients and put in people's formulations at 0.05 percent or less, I guess? Or whatever the highest concentration is.

MS. BECKER: It was 0.5.

DR. HILL: Point 5?

DR. SHANK: The ingredients would be extremely small.

DR. HILL: Right. I mean, most of those would be vanishing.

DR. SHANK: So even if it varied by 10 percent you wouldn't -- or 20 percent? Whether whatever growth or growing conditions it wouldn't change it that much.

SPEAKER: But again, the NTPs are all

oral, right? Oral tox, I think?

DR. SHANK: With this it was oral. Yeah, it wouldn't have been topical.

DR. MARKS: So, Ron Shank, do you still want to proceed with an insufficient data announcement and are the extracts used in this -- these spearmints other than the skin ones? Are they really the cosmetic ingredient extracts? Is that what you would like to note?

DR. SHANK: That's what I'd like to note. And if that's the case, then let's state it explicitly that the extracts tested were cosmetic period.

DR. MARKS: So insufficient.

DR. SHANK: And then you could probably extrapolate from the Panax to the others.

DR. MARKS: Okay. That was the next question I had, whether or not insufficient -- and so really the only need then at this point -- so the first insufficient data need are extracts, the cosmetic -- is that an accurate way, Carol, to put it? The extracts cosmetic grade?

MS. EISENMANN: Well, the entity setting?

DR. MARKS: Other than the --

DR. HILL: No, not the --

DR. SLAGA: All of it.

DR. MARKS: Is that a good way to put it, cosmetic grade or does that imply it's a cosmetic --

MS. EISENMANN: There's not a whole lot I can do about it because I don't have the studies.

DR. MARKS: Yeah.

DR. SLAGA: But if it is the same and we state it as (inaudible), then it's safe and we can extrapolate for the others.

DR. MARKS: Safe as used in cosmetics.

DR. SHANK: So do we have to go to an insufficient data announcement to get industry to state that --

MS. EISENMANN: Well, I still don't quite understand what I can do because most of the data in this report is not from industry. It's from published studies. And one of my comments is that she needs to put a little more information about what type of extract it was for some of the studies. That was one of my comments. Since most didn't come from -- I mean, there's a lot of

published data out there on ginseng because it's widely used orally.

DR. SLAGA: Widely.

MS. EISENMANN: Widely. So, I mean, exposure orally is going to be much greater than exposure to cosmetics.

DR. SHANK: True, but there's a difference between putting it directly on the skin.

MS. EISENMANN: Correct. Correct. So I could see why you would want more -- your dermal irritation and sensitization data. I could probably help you with that.

DR. HILL: And there is some rodent data here. And lots of case reports actually which to me was the most information.

DR. MARKS: Well I thought -- actually, I thought the skin was okay because there's HRIPT and I assume that if you're using an extract and doing an HRIPT that that was the cosmetic grade. It was, what, 10 percent? One percent resulted in no. And then they did a 10 percent aqueous. They did actually both species.

MS. BECKER: Yes. There was a cosmetic

grade.

DR. MARKS: Yeah.

DR. SHANK: Could we state that?

MS. EISENMANN: My suggestion is try to update some models of the (inaudible).

DR. MARKS: No, I just assumed it was.

MS. EISENMANN: That some of them report the saponin levels in the cosmetic ingredient. If you can find -- I don't know if any of the safety studies that are published report those levels, so you can compare the levels with what is in -- I mean, that would be the only --

MS. BECKER: Well, the two standardized mixtures or extracts that they're using for the saponins, those are proprietary so they don't tell us what's in it. They told us what's in it but not the combination but they're used to standardized the testing. So that's the best I got on that because I (inaudible) for a couple of days.

MS. EISENMANN: So was the total level of saponins (inaudible)?

MS. BECKER: No, I really just said they're standardized to these three or four

saponins. And it didn't say what the standard was, just that they're there.

Anything that the council gave us, I assume that is cosmetic grade so we do have some of those studies, like the HRIPT.

DR. MARKS: Yeah. That didn't. So Ron, I wasn't concerned about sensitization and irritation. Were you concerned more in terms of with reproductive and development or with carcinogenicity or anything other than --

DR. SLAGA: What are used the same for irritation as they did for irritation as they did for genotoxicity.

DR. SHANK: Okay. We can probably handle this if we just say that these extracts would cause maybe great (inaudible).

DR. MARKS: Okay.

DR. SHANK: It's not a big thing. You seem to feel very confident that these non-NTP studies were using cosmetic (inaudible), so safety. Otherwise --

MS. EISENMANN: Well, the ones that we provide. I don't know anything about the ones that you thought were the published data.

DR. SLAGA: The ones in the report. Especially under human.

MS. BECKER: You mean the sensitization?

DR. SLAGA: Page 14 in your Panel Book, 7 of the report. You have dermal, human, Panax ginseng root extract. All I'm asking is was that which was tested cosmetic grade, the same stuff that is used in cosmetics? If it is it would be helpful to state that. If we don't know then we have to ask.

MS. BECKER: If it's 77 I don't know.

DR. SLAGA: It's a problem we have with all of these botanicals. We have to make sure the -- what we're reading is comparable to cosmetic ingredients.

DR. MARKS: It's kind of interesting because when I viewed this I didn't have that question because I thought for what reason would they be doing the skin irritation and sensitization other than if it were a cosmetic endpoint. If it were an oral, would you care whether there's any skin? So I wouldn't even think that would be done if it were a concern about

say as a food ingredient.

DR. SLAGA: Well, the extract taken, the Panax ginseng root extract.

DR. MARKS: Right.

DR. SLAGA: Wouldn't that be the same type that they would use for oral versus -- I mean, for cosmetic grade? Or would it be a cheaper version? If the extract is extracted under a certain condition, what would be the difference for the oral versus the --

MS. EISENMANN: I suspect they might standardize the material. I would hope to standardize the material for oral.

MS. BECKER: Mm-hmm.

DR. SLAGA: I'm not convinced they would.

DR. HILL: So we have this G115 and CNT2000 that's proprietary composition. What toxicology studies do we have with those materials per se?

MS. BECKER: Okay. On page 5.

DR. HILL: Of the report.

MS. BECKER: Yes. The third study down under repeat dose on human.

DR. HILL: Therapy 115. I marked it, flagged it in big red ink. Orange ink. All right.

MS. BECKER: Okay.

DR. HILL: Ninety-day beagle. Yeah, this was one I didn't know because it just says no consistent dose response relationship. That doesn't tell me anything.

MS. BECKER: Okay. And over in toxicokinetics the first one over Panax ginseng root.

DR. HILL: Let's see. Where is that?

MS. BECKER: On page 4.

DR. HILL: I see it. All right. So here it is again G115.

DR. SHANK: Nothing on that other one, CNT2000.

MS. BECKER: I think it's in the tables.

DR. SHANK: Okay, in the summary of studies?

DR. MARKS: Ron, could that concern you have, Ron Shank, that the extracts were the same as used in cosmetics, would another attach potentially to address that would be in the discussion where we state that the expert panel

assumes or that these extracts --

DR. SHANK: I don't think we use the word assume in the discussion, do we?

DR. MARKS: Because otherwise we go back to your suggestion that this is an insufficient unless we answer that. Is that correct?

DR. SHANK: For me.

DR. MARKS: Yeah. And was it only the skin you were concerned about, Ron, in those irritation sensitization studies? Because that should be pretty easy to answer.

MS. EISENMANN: Well, and I could probably get more on the low levels.

DR. MARKS: Yeah.

MS. EISENMANN: Of products.

DR. SHANK: Primarily the skin.

DR. MARKS: Yeah, okay.

DR. SHANK: The material is not without biological activity..

DR. MARKS: Right.

DR. SHANK: Sufficient (inaudible). That's why it's used medicinally as a tonic, a sera (?).

DR. MARKS: So how would the Panel like

to proceed? Do you want to go out with an insufficient? That really pushes industry to try and answer the question. Tom? Ron Hill?

DR. HILL: I'm just -- I actually am -- because, you know, what is the nature of the insufficiency is that we don't know.

DR. MARKS: Right.

DR. HILL: You know, I guess where I'm at right now with these proprietary compositions is, you know, I appreciate the need for maintaining proprietary but if our assessment is based on we have toxicology data with this range of compositions based on which this percentage and this cosmetic product used at this amount were well below whatever we see, no problem. But if you don't know what the composition is, then you have to rely on direct safety studies with that particular proprietary composition, which to me -- so, you know, you say we don't put assume in the discussion but can't you have language like the assumptions made in the safety assessment are -- these won't exceed thus and such amounts or something? I mean, I know we're breaking new ground but I haven't seen anything that looks like

this before because at least with kojic acid we were looking at one ingredient. At least with vegetable oils we were looking at a bunch of fatty acids. And I don't remember what the situation was exactly because I didn't pull up the old marigold. And sort of in an FYI, this is Wave 2. I found it sitting over there. All of this, and it's printed two-sided, is pulegone. Somebody had enough concern to do a lot of research.

DR. SLAGA: There's not enough pulegone in this.

DR. HILL: No, I don't think there is but the ones that we don't know the composition, actually, we don't know. Right?

And again, my comfort level was that in the cosmetic formulations these are all reported to be very low concentrations. Within that the small amounts, ppms and low concentration, I mean, sort of we're down to vanishingly small for even the most potent of anything is what gave me comfort level, I think. And maybe we don't need any additional data. Maybe it's just we get this all laid out to where we can cut through all the complexity and see what we have.

But at least having some information, whether our tox studies, you know, if there was any standardization whatsoever, and I'm guessing if you look at that, maybe 95 percent of them will have some information. We know there's variation depending on how they extract it. So we can't do anything about that.

DR. MARKS: Okay. So let's get back. Do you want to proceed with insufficient and the first data we need, we want, are the extracts tested in this report, the same as used in cosmetics or representative of those used in cosmetics.

DR. HILL: Representative of..

DR. SLAGA: Yeah, because if they're instructed the same way it would be okay.

DR. SHANK: In one of the -- the only one that's significant, in my opinion, HRIPT test, 99 subjects. It was a cuticle serum. Abbott Cosmetics..

DR. MARKS: Yes.

MS. BECKER: Yes.

DR. SHANK: Cuticle serum?

MS. BECKER: Yes.

DR. SHANK: Okay.

DR. HILL: What is a cuticle serum?

DR. SHANK: I have no idea.

DR. MARKS: It's to soften your cuticles and make them more pliable. So you have a small bottle of a little serum and then you physically rub it onto the cuticle. Isn't that right, David?

MR. STEINBERG: It's a liquid.

DR. MARKS: Yeah.

DR. HILL: Yeah, I was just wondering what you used it for. What does it do?

MR. STEINBERG: That's --

DR. HILL: Thank you.

DR. MARKS: With that in mind do you still -- do we still want to ask that question and see what answers we get, Ron Shank, in terms of --

DR. SHANK: Well, you can get around all this if you use the Panax ginseng root extract every time that's mentioned. That's representative of all the others.

DR. MARKS: Right.

DR. SHANK: Not to state that explicitly.

DR. HILL: Okay. And so where's the use

table? I thought I made note of it but I'm not -- the concentration of use table.

DR. MARKS: That one was, I believe 25 percent. Yeah, it's page 33.

DR. HILL: Yeah, okay. So where I am.

DR. MARKS: Panax ginseng root extract, the highest concentration was a dermal contact.

DR. SHANK: And that's the highest use of concentration of all of them?

DR. MARKS: Yes, exactly.

MS. BECKER: 0.5.

DR. MARKS: Much higher than the ones that we had. We don't have the use concentration of the root itself but the extract you would expect..

DR. HILL: Well, that's where we go back to page 32, the page before, at the bottom of the page where the extraction method can make a whopping big difference on whatever's in there. So when somebody formulates it at.05 or.5 percent but they're using an ultra hypothermia biotic extract, there would be a lot more compound delivered to the skin than if they're using the standard alcoholic low temperature white ginseng

extract.

DR. MARKS: So even if those higher concentrations with the altered thermia -- ultra hypothermia, Ron Hill, are you concerned about that much higher concentration?

DR. HILL: I have to do the calculations.

DR. MARKS: Comments? Okay.

DR. HILL: Well, and this is just saponins, but I mean, maybe we can make conservative assumptions about pulegone for example.

MS. EISENMANN: But, you know, in this case, again, I go back to page 50. This is what supplier told me. With some of them we're making (inaudible). I mean, this is what I would assume is what's in the cosmetic ingredients point of the ginsenoside content, 0.2 to 0.3 percent.

DR. HILL: Okay.

MS. EISENMANN: Versus --

DR. HILL: And I agree with you. I'm just --

MS. EISENMANN: And the list -- and the list of -- I'll go back again. The list of

solvents, at least in this case, did not include CO2. So I'm not sure that that was a -- that was a cosmetic ingredient.

DR. HILL: Well, you wouldn't because if they do a supercritical extraction basically what happens is you do it under high pressure and it behaves something like diethyl ether. And then you're pulling out the components and then, of course, it's CO2. So as soon as you drop the pressure and bring it to temperature, all that CO2 is gone. You never had any --

MS. EISENMANN: I know. But I've got that report of some extracts that do include that type of extract. But this one, I did not get that report. So I will go back and check again with the suppliers if that's the one you're concerned about.

DR. HILL: Yeah, because I don't see anything else where the levels are anywhere near that high unless they were using root oil. That's the other thing. The levels are a lot higher in the root oil than they are in the root extract. And there's no reported -- in the use tables there's no reported use of them.

So when we make the statement -- I'm just thinking ahead to the discussion and the conclusion and making the statement in the current manner of use, is somebody in East Smithfield, Arkansas, you know, who starts a little company who wants to make a cosmetic ingredient and then they buy the root extract from China, are they going to appreciate all of these nuances that are going into what they're putting in their product? Are they going to realize that they're making something unsafe if, in fact, they did that based on everything that's in this report? Because I'm just thinking in the real world in practicality how this will be viewed, how it will be implemented. We don't have premarket approval. Well, good. All the assumptions are going to be made -- going to be captured in our discussion and conclusion in such a way that people know what they're doing here when they put this to use because --

DR. MARKS: Sure. Lillian is going to capture that in the discussion.

DR. HILL: Well. (Laughter) This is what we need to have happen, I guess, and how do

we do that? That's really what I'm just going to.

MS. BECKER: Yeah, I'm still waiting for help on that. So I'm going to still get back to how our team wants to proceed tomorrow. I get -- as the discussion becomes more and more robust I get the sense that the extracts tested in this report really probably represent or are the same as those used in cosmetics. I don't know if you feel comfortable enough with that, Ron, whether or not we should move forward with an insufficient until we have that confirmed? Or whether or not we -- what if we have it confirmed by morning?

DR. MARKS: Okay. If we don't have it confirmed by morning then we would move forward with insufficient.

MS. EISENMANN: It's not going to happen. Just move forward with the insufficient.

MS. BECKER: My feeling would be that the cosmetic grade would be a better grade. We do have some of that in there. So anything that is not cosmetic grade in here would be worse-case scenario or at least not a bettered -- not the worst but worse case and cosmetic grade. That's

justified.

DR. MARKS: Yeah, I hear you..

DR. HILL: Yeah, my overall sense was --

DR. MARKS: It's a good thing it's not bee as refined with whatever else is being tested.

MS. BECKER: Right.

DR. MARKS: If it were an oral product then the cosmetic grade would be more refined, so to speak.

MS. BECKER: Right. So if we have the better and not so --

DR. MARKS: I see Ron. Ron's questioning that.

MS. BECKER: It's justified.

DR. MARKS: Assumption. Yeah. So Ron Shank, do you want to still move forward insufficient with -- the question is are extracts tested in this report representative or the same as used in cosmetics. That's the -- and if we can get confirmation --

DR. SHANK: If that can be handled in the discussion then we can avoid the insufficient data announcement.

DR. MARKS: Handle it in a discussion.

That's what I --

DR. SHANK: -- assume they would like to see that.

DR. MARKS: Pardon?

DR. SHANK: I wouldn't like to use the word the Panel "assumes."

DR. MARKS: Yeah, okay. I know..

DR. SHANK: If that issue can be handled, that the testing was done on cosmetic grade extracts. And there's enough information on the Panax ginseng root extract to conclude that they're safe as used.

DR. MARKS: Yeah.

DR. SHANK: It's the highest concentration, use concentration, is that particular extract.

DR. SLAGA: And what I really wanted to do but I didn't take the time because I didn't have the time to do was, you know, how we have with the vegetable oils where we had all the ingredients down one side and we had this oil, this oil, this oil, and this oil. Of course, this extends to four pages so the print would get a lot smaller but I was thinking if you just had all the ones that show

up above, I don't know, 100 ppm or 500 ppm, you can count the cosmetic dilutions because they're using (inaudible) and compare, I don't know.

DR. HILL: It's having trouble with the read-across, I guess, in a nutshell with the data in the form it's in.

DR. MARKS: And then as far as the pulegone -- is that how you say that?

SPEAKERS: Mm-hmm.

DR. MARKS: Pulegone. We can handle that. We don't have to set a limit or anything on that because there's so little that's in the ingredient as it appears in the cosmetic. Is that right? That obviously would be handled in the discussion.

SPEAKER: Okay. I want to make sure, and it's true because I'm looking at Table 5. I'm not sure if it's quinquefolius. Quinquefolius?

DR. MARKS: Yeah.

DR. HILL: I'm not sure how you're supposed to say it. I think it's quinquefolius. Pulegone is there at, let's see, 260,500 ppm.

DR. SHANK: Is that right or is that 262? Is that a range?

DR. HILL: I'm looking at page 30. Panel Book page 3, it's got 260,500 ppm.

DR. MARKS: Is that correct, Lillian? It's the 260,000?

MS. BECKER: Yeah.

DR. HILL: So that's 260 parts per thousand?

MS. BECKER: Yes.

DR. HILL: Twenty-six parts per hundred. That's 26 percent, is it not? That's higher than any of the saponins by a factor of 10. More than 10. No, the biggest saponin, it's about a factor of 10. And I kind of assume that's why we got all this data on pulegone.

MS. BECKER: Right.

DR. SHANK: Then I take back that the concentration -- the amount of pulegone is trivial. I thought that was --

MS. EISENMANN: But the root oil, it comes out in the root oil. I don't know how well. That was one thing. I was going to go back and see if I could find any information. If I had, I don't remember if they're a supplier of the extract of the root --

DR. HILL: That extract.

MS. EISENMANN: -- of the root to see if they measure this at all.

DR. MARKS: Well, it would be fairly easy to handle as we did in peppermint. We determined that 1 percent was safe, so we could handle it by saying as long as the amount of pulegone is less than 1 percent.

DR. SHANK: If the use levels are the same.

DR. HILL: In the finished formulation.

DR. SHANK: Yeah.

DR. MARKS: I assume -- how was it in the peppermint, Lillian?

MS. BECKER: In the peppermint it is 1 percent in the ingredient, which means in the formulation it would be even less.

DR. HILL: All right. So we need to make that same calculation here..

DR. MARKS: Well, or just state it the same way. How was the conclusion? What -- you've had that in here, correct?

MS. BECKER: Yes, I did.

DR. MARKS: I thought you included it

in here.

MS. BECKER: The concentration of pulegone in these ingredients should not exceed 1 percent.

DR. HILL: And then we get to look and see how high the peppermint oil is used. Maybe it's at the same level as the ginseng. How high does peppermint oil go in a finished formulation?

MS. BECKER: I don't have a complete report but you printed one out you said? You were holding it up?

DR. HILL: I got it off the table here. That's where the peppermint is?

MS. BECKER: Yeah, it's got a full report there.

DR. HILL: Yeah, here it is. Concentration of use table and this is old style. Or I can hand it to you. You can probably find it faster. I don't see it.

MS. EISENMANN: It may have been during that period of time when (inaudible).

DR. HILL: I think so because -- eh, 2001? I'm not seeing it though.

MS. BECKER: Just look under title use.

DR. MARKS: Well, for now --

DR. HILL: Use. All right. Here we go. Concentrations of use are no longer reported to the FDA. However, data submitted --.02 percent in a medicated face mask; 0.1 percent in a facial cleanser; 0.2 percent in lipstick; 0.5 percent in toothpaste; and 0.9 percent in a fluoride toothpaste; 1.2 percent in a mouthwash; 0.2 percent in a lip balm; and 3 percent in a hair lotion. So basically ranging up to 3 percent of which --

MS. BECKER: Which is far more than what the --

DR. MARKS: Right.

MS. BECKER: -- ginseng (inaudible).

DR. HILL: So that would be -- okay, so 3 percent of peppermint oil, 1 percent pulegone. So --

DR. SHANK: The use level of that extract is.002 percent. Small.

DR. HILL: Small. So actually there could be more than 1 percent pulegone in ginseng then. It could go up to probably whatever it is. Twenty-six percent and still be okay because

they're only putting such a small amount.

DR. SHANK: That can't be right, 26 percent.

DR. HILL: It says 260,000 ppm. Am I miscalculating? You do it. 260,000 ppm is 260 parts per thousand and 26 percent.

DR. MARKS: That's what I had. I agree. It sounds like it's -- do you want to confirm that's really the truth, parts per million?

DR. SHANK: You did.

MS. BECKER: I went back and looked at the source. It's not a cite.

DR. MARKS: Well, at any rate, now, again, going back and calculating, Ron Shank, when you look at the one species that had pulegone in it, it's used at such a low concentration.

DR. HILL: That's the thing..

DR. MARKS: We can still in the discussion say pulegone is not a concern and it could be handled in the discussion and refer back to the peppermint.

DR. HILL: Because even if you -- even if you had -- right. Because even if you had an extract where you got all the pulegone into the

extract, you could still take the percent in the finished cosmetic and divide by four. That would be the percentage of the pulegone. Right?

DR. SHANK: Maybe that's why the use concentration is so low.

DR. MARKS: Interesting.

DR. HILL: Well, could be.

DR. MARKS: Okay. So tomorrow I'm actually going to be either seconding or not a motion from the Belsito team but I still have in question here whether or not we move forward with an insufficient. I think it will probably depend on how the Belsito team decides. I'm not sure they're going to ask about whether the extracts in the report are the same or representative of those used in cosmetics. And there it's insufficient. If we want to know that or can we handle it in the discussion? And I don't know that we've come up with wording to handle it in the discussion. Obviously, assumed was not a very -- so Lillian, if you can wordsmith something better, we assume. That's not good.

DR. HILL: And just to put it in perspective on the pulegone and peppermint, if we

had a 2 percent in lip balm, then that would be a.02 percent maximum pulegone level in a leave-on --.02 percent. So ginseng extract below that.

DR. MARKS: Okay. Which we are..

DR. SHANK: You can say the Panel considered that the Panax would extract, which was cosmetic grade. This cuticle serum was representative of the others.

DR. MARKS: There we go.

MS. BECKER: Okay.

DR. MARKS: The Panel considered. Here we go. Now we've got it. So now we can go to safe. And the discussions are that we considered the extracts to be the representative or the same as used in cosmetics. And two, the Panax ginseng root extract we could use as the representative and read- across the other root extracts. And lastly, in the discussion, that the pulegone levels were very low and not concerned.

Okay. So safe. Thank you. That was -- that was tough.

DR. HILL: Okay. Yeah, and it's interesting -- one more thing that's interesting

is that if you look at the use concentrations of Panax in capoleum versus Panax ginseng, they are a lot lower because I was thinking you had 0.5 percent and 20 percent of that was -- you would be at a higher level than what was in peppermint limits. But with the kinkafoleum, the highest concentration reported is.002 percent.

DR. MARKS: Next we're, again, this is the first time we've seen this report. It's entitled the dialkyl hydroxysuccinates. And on page 10 we need to decide again do we all think that these acids and salts and esters belong together in the same report? And what are our needs?

And then we have a Wave 2, which were skin toxicity and that looked all fine, actually. So it's ingredients to Ron, Ron, Tom, do you like the ones, the acids, salts, and esters -- all the ones listed here?

DR. SHANK: I would take out all the malic acid data and just conclude the summary from the 2001 report. Don't repeat all of that. Okay?

DR. MARKS: So you would --

DR. HILL: Can we back up?

DR. SHANK: (inaudible) reports malic acid and that's not the ingredient.

DR. HILL: Can we back up a step and discuss the appropriateness of combining succinates with malates with tartrates? I'll be curious to see what Dan thinks about this because as both an organic chemist and from a biochemistry perspective, nobody considers, that I know of, malic acid as a hydroxysuccinate. Nobody that I know of considers tartrate as a dihydroxysuccinate. I was bothered by including these in the same report. I'm just asking.

DR. MARKS: That's why I brought up the issue of the ingredients to begin with, just because that. If there were differences in chemical structure or whatever. So -- and then we'll come back to Ron Shank.

So Ron Hill, your concern was including malic acid and tartaric acid?

DR. HILL: Yes.

DR. MARKS: Just those two?

DR. HILL: No. Any of the tartrate esters. Any of the malic acid esters in the same report as the succinate diesters. I guess they're

all diesters. Right? I don't -- I highly question the appropriateness of combining these three sets of ingredients.

MS. BECKER: So you would get the top half of the ingredients on page 1. I guess page 10.

DR. HILL: Well, I'm just -- where are we, page 1?

MS. BECKER: Page 10.

DR. MARKS: Page 10. Yeah, that's where -- that's what I referred to at the beginning. I always go to the ingredients and make sure we're happy that we aren't putting an ingredient in, even though this doesn't have to be a no- brainer but at the same time we should feel like chemically they're similar. And actually, that's what you're raising.

DR. HILL: Well, I'm raising because I said there are big data gaps for the esters. And then there's some missing alcohols, but I think we actually have data on one or two of those alcohols that don't show up in that appendix. So I was just thinking in terms of -- I doubt there's

any tox issues with any of these period, but I was just thinking in terms of tartrate monoester or a malate monoester as opposed to succinate monoester and thinking that I don't know why we'd expect those to be biologically anything alike. Like I say, from both an organic chemist perspective, as well as anything I've ever read on the biochemistry, I mean, especially malate, that's part of Krebs cycle, part of Shevils, part of, I mean, it's pervasive in human biochemistry. Succinates, too.

MS. BECKER: It's too bad Bart's not here because this was his combination.

DR. HILL: He signed off on this combination.

MS. BECKER: He developed this combination.

DR. MARKS: And that's Bart?

DR. HILL: And I'm just wondering, you know, on what basis he chose to do that because I wouldn't have.

MS. EISENMANN: So are you comfortable with calling this hydroxyl succinate?

DR. HILL: No, because nobody thinks a

malate is a hydroxyl succinate. And nobody thinks a tartrate --

DR. SHANK: That's driven by the dictionary, I suspect.

DR. HILL: I guess.

MS. EISENMANN: No.

DR. SHANK: No?

MS. EISENMANN: I mean, the ingredients are listed.

DR. SHANK: Malates.

MS. EISENMANN: Yes, they're malates.

DR. SHANK: Then don't refer to them as hydroxysuccinates.

DR. HILL: Yeah, I don't like that reference because, like I say, except for the artificial stereoisomer, the (inaudible), malic acid is so pervasive in human biochemistry, at least the parent, that that's very different. And actually, succinate is there as well.

DR. MARKS: So Ron Hill, how would you proceed? Would you just change -- I say this casually.

DR. HILL: I know you did. I'm going to answer casually.

DR. MARKS: Would you just change the title and include the same ingredients or can we change the title so chemically you're satisfied with it and then decide what we're going to include? I mean, what would be the lead chemical? I have here diisostearyl malate as the lead.

DR. HILL: Okay. So if I ran the zoo there will be three reports -- malates and -- malate salts and malate esters, tartrate salts and tartrate esters, succinate salts and succinate esters. One report. I would have three reports if I ran the zoo and I don't run the zoo.

DR. MARKS: Well, you contribute to it. What we're going to do is decide how we're going to go with your suggestion.

DR. HILL: Alan won't like it because he likes bigger groups rather than small ones. I'm sure that the group -- I mean, obviously the group relates to the frequency of use which drives what we actually review. I don't know what precedent we've established for it, if we were to split it in three reports.

DR. SHANK: So just call it dialkyl --

DR. HILL: We don't have any succinate

esters in here at all.

DR. MARKS: So how do you -- so there we go, back to the title, Ron Hill, as I say. You suggest just calling it dialkyl malates.

DR. SHANK: Malates and tartrates.

DR. MARKS: Malate and tartrates. Does that sound good, Ron?

DR. HILL: Yeah, that's fine..

DR. SHANK: Wait a second.

DR. MARKS: Yeah, and toxicologically --

DR. HILL: I don't like them combined.

DR. MARKS: Okay. Dialkyl --

DR. SHANK: You don't want the malates -- I don't like the tartrates.

DR. HILL: The malates and the tartrates. Obfuscate the toxicology.

MS. BECKER: Could I go get Bart for this discussion?

DR. HILL: What time is it?

MS. BECKER: It is --

DR. SHANK: Quarter to 12:00.

DR. SLAGA: It'd be worthwhile having him here.

DR. MARKS: Sure.

MS. BECKER: I'll go get him.

DR. MARKS: Lillian, we'll keep --

DR. SHANK: Why? Why bother him?

MS. BECKER: Don't say anything important while I'm gone.

DR. MARKS: No, wait. Wait a second. Why bother him, Ron says?

MS. BECKER: Well, he's the one that has the thought process of why this was done.

DR. SHANK: Well, he calls it the semi core.

DR. MARKS: Yes, the succinates core is how in the introduction --

DR. HILL: Well, there is a succinate.

DR. SHANK: Biochemically, Glen wouldn't do it. Maybe chemically okay. Succinate derivatives. But biochemistry is quite different.

DR. HILL: Yes.

DR. MARKS: That's the point you brought up earlier. So let's get back to -- now we're to, okay, we're going to change-- potentially change the title to dialkyl malates and tartrates.

DR. HILL: I'm just asking can we split it into two reports -- tartrates, malates?

DR. SHANK: Males sense.

DR. HILL: I mean, Dan will have thoughts on this but I'm not supposed to ask him.

DR. SHANK: We can handle the dialkyl malates really easy.

MS. BECKER: Okay.

DR. SHANK: From the malic acid report.

DR. HILL: Because we already have a malic acid in the report. Right?

DR. MARKS: And we can't read-across from the malates to the tartrates.

DR. HILL: I think we cannot. My personal thinking is we cannot. And that was one of the things that bugged me. If you use -- that's why I say there are data gaps for the esters. And if you try to read-across I'm totally uncomfortable with reading malate esters, diesters, across the tartrates and diesters, and vice versa because if the biochemistry goes esterase, monoesters, you've got different beasties in between.

DR. MARKS: So Ron Shank and Tom, how

do you like the idea, first of all, changing, which it seems like we're all right at changing the title to the dialkyl malates.

DR. SHANK: Period.

DR. MARKS: Period. And split off the tartrates. Is that right?

DR. SHANK: Yes.

DR. MARKS: Okay. So we're going to do that. And so let me --

DR. SLAGA: Can we have a malate report already?

DR. SHANK: Yes, 2001.

DR. MARKS: I'm going to -- that was Ron Shank's original comment about putting in or leaving out or just referring to that. And we'll get back to that.

So let's go on page 10. So coming down page 10, so the malic acid obviously sodium malate would be included in this report. The calcium tartrate -- tartaric acid would not. So the whole rest of that acid and salt would only be two. The --

MS. BECKER: So we're only keeping malic acid and sodium malate?

DR. MARKS: Is that correct? I want to confirm that with my panel members. Just those two.

DR. SHANK: Yes.

DR. MARKS: And then we come down to the esters. We would have the malate two, three, four. Everything -- we'd have everything on that first column, which are all malate esters. The di -- what is it, dialkyldecil malate we would have. And then we would get rid of the three tartrates. And that would be the composition of this report and then if we wanted to deal with the tartrates the second time in another report we would. So is everybody agreeable with that, that that's the ingredients we would consider?

DR. HILL: That's what I would like to see. Yes.

DR. SHANK: Yes.

DR. MARKS: We all agree with you, Ron. So thank you for bringing it up.

Now, I want to go back to your comment.

MS. BECKER: Just on the vision, we pick our lead ingredient by number of uses. The ones for your second group, the tartaric acid is the

only one that has any significant number of 104 uses, which is well below the 576 we're at now.

DR. HILL: So that's good because there's no data for any of the tartrate esters. That's where I had the data gap problem.

MS. BECKER: Just throw that thought in the hopper.

DR. HILL: So that may mean that they just don't -- is there a tartrate report?

DR. SHANK: No.

DR. HILL: Okay. But it's tartrate.

MS. BECKER: Yes.

DR. HILL: So it's like going back to bed for a while.

DR. MARKS: Where the use table, yeah, I have -- the diisostearyl has over 500.

MS. BECKER: Right. That's (inaudible). That's the one that --

DR. HILL: The malates.

DR. MARKS: The malates, yeah. Okay. With a high concentration, up to 82 percent in leave-on. Okay. So no data on the tartrates.

I'm just going to go over our reasoning. So we split it based on the chemistry.

DR. HILL: I would say the biochemistry (inaudible) say that.

DR. MARKS: Biochemistry. Okay. No data on it. So diakyl -- we'll change it to the malates. Okay. So now Ron Shank, right in the beginning you talked about there are lots of reference here to malic acid here which Dave already (inaudible).

DR. SHANK: Take all of that out and just put in the summary from the 2001 report. Don't repeat all of the data.

DR. MARKS: Malic acid summary.

MS. EISENMANN: So would malic acid and sodium malic, they wouldn't really be in this report, they'd be in the other report?

DR. SHANK: Right.

DR. HILL: Is sodium malate in the other report?

DR. SHANK: That's a pH adjuster for the most part.

MS. EISENMANN: Correct.

DR. SHANK: Whereas the dialkylesters are not pH adjusters.

MS. EISENMANN: So he wouldn't count

them as being in this report at all (inaudible) as being in the other report.

DR. SHANK: Well, the report is going to be on dialkyl malates. And then an esterase product is going to be malic acid. And that we refer to the 2001 report already reviewed, safe as used. And just put in the summary.

DR. HILL: So if the previous report does not include the sodium malate, is that going to create problems for anybody? That you'll have to answer, Carol, because otherwise you'll just wait until the next time it's reopened and then --

MS. BECKER: The greatest support was malic acid and sodium malate.

DR. HILL: Excellent. Okay.

DR. MARKS: And that was 2002?

MS. BECKER: One. And safe as used as a pH adjuster. Sufficient to determine the safety of these ingredients for other functions.

DR. HILL: All right. So now do we have them in use as other functions? I mean, it's malate. Sodium malate.

MS. BECKER: (inaudible) ingredient, pH adjuster, and the sodium (inaudible)

conditioning unit.

DR. HILL: So for sodium, yes. The answer is yes. Then probably we need to leave it in.

DR. SHANK: Leave all of it in?

DR. HILL: Malic acid and sodium malate because you've got all the data here now, right?

DR. SLAGA: There's very little data.

MS. BECKER: Transfer the data over from writing the report, summarized it.

DR. HILL: And you can't tell whether sodium malate is being used just, as you said, it's being used as a what?

DR. MARKS: PH adjuster.

MS. BECKER: No, sodium malate's skin conditioning agent humectant.

DR. HILL: Yeah. Because we don't have concentration of use reported for sodium malate. We just know there's leave-on use and rinse-off use according to the reports, and a deodorant use and hair color use.

DR. MARKS: A procedural question.

MS. BECKER: Mm-hmm.

DR. MARKS: If we include malic acid and

sodium malate in this report, does that mean we reopen the previous one? Or do we not include malic acid and sodium malate in this report and we only include the esters? Because when we went down as to what we would include in this report we said yes to include malic acid and sodium malate, but then that would, in my mind, mean that we have to reopen the previous one and then we would have a new conclusion or whatever because it includes these esters.

DR. HILL: Well, and then the other thing is the use as a pH adjuster results in very small concentrations in finished product. Right? I mean, that's what I'm reading here.

DR. MARKS: Yes.

DR. HILL: But yet these esters are delivered at much higher concentrations. So we really need to know. In other words, I guess I'm saying we can't really fully rely on that old report because I presume the concentrations examined will be a lot lower than what we might be talking about here. I don't know. Delivering the ester is not the same as delivering the acid anyway, so --

DR. MARKS: Right.

DR. HILL: -- from a level, I like Ron Shank's ideas. Just keep the esters and let the others be.

DR. MARKS: So Ron --

MS. BECKER: Let the full report stand.

DR. HILL: And any needed data on malic acid that doesn't fall within the purview of that old report, we just make sure it's in here.

DR. MARKS: So at least procedurally for me we would not include malic acid or sodium malate in the conclusion of this report.

DR. SHANK: Right. It's not (inaudible).

DR. MARKS: Right. Because we've already --

DR. SHANK: We've summarized the data.

DR. HILL: From that report the summary can be repeated here.

DR. MARKS: Right. Right.

DR. HILL: But not all of the individual data because that's all pre-2001 data.

DR. MARKS: Let me see. The final report was actually received in 2000. Accepted in 2000.

When was it published? As you said, 2001.

DR. HILL: That's what I have it.

DR. MARKS: Yeah, it is 2001. Yeah. So let's get back to what's included in this report. We aren't going to include the malic acid or sodium malate as far as in the conclusion. The ingredients are really going to be only the esters. Correct?

DR. SHANK: Right.

DR. MARKS: Okay.

MS. BECKER: Diisostearyl sterile malate through dioctyldodecyl malate.

DR. MARKS: Okay. That's good because when I went in there we would have to deal with malic acid being a strong irritant. Obviously that had been done before.

Okay. So now we're down to the new title will be dialkyl malates. And it's only going to be the esters that we have on the bottom part of ingredients on page 10 as Lillian mentioned earlier. So that's one, two, three, four, five, six ingredients is what I have.

Do we have any -- now that we've settled on that, do we have any needs? And if we get into

the chemistry, Ron Hill, I might call on you. Okay? I'll say that we decided based on the biochemistry split what was proposed.

DR. HILL: We did. It was a handout with additional sensitization.

DR. MARKS: Right.

DR. HILL: Irrigation with diethylhexyls.

DR. MARKS: Yeah, and those were good. The diiostearyl was okay. So there's a lot of sensitization and irritation data which is it's safe. Any other needs or are there any needs I should say?

DR. SLAGA: Well, there's no muted genicity related to genotoxicity because we were -- in the present book it had malic acid as data. The only other was tartrate -- was under there. So we would have no genotoxicity.

DR. MARKS: Well, we're going to split out the tartrates.

DR. SLAGA: Yeah, I know. Is that the only other --

DR. MARKS: So do we need -- if we need that then it'll be insufficient data. So Tom, do

you want to -- should we proceed with an insufficient data announcement?

DR. SHANK: I think so.

DR. HILL: And on the dioctyldodecyl malate, I don't think we have sensitization. And I have a note here, on page 32, suggests that we may need it.

DR. MARKS: I'll let you look at that a second. I wasn't alerted to that.

DR. HILL: I don't know why I was. It's page 32.

MS. BECKER: That's the appendix.

DR. HILL: That's the appendix.

DR. MARKS: So insufficient.

DR. HILL: There are some case reports on the octyldodecyl. Is that the one I was asking you about? No, this is dioctyldodecyl. That's something different.

DR. MARKS: Insufficient data..

DR. HILL: Oh, no, but that's a diester. So, yeah, octyldodecyl dodecanol, there are some case reports. That's the alcohol, not the diester. However, it's suggesting that we might like to have that data. Sensitization on dioctyldodecyl

malate.

DR. MARKS: Okay. So one insufficient. I'm going to go back. Tom, we'll get yours and then we'll come to the -- so Tom, you would like --

DR. SLAGA: Well, we need genotoxicity. To me, if we have to separate it we would also need a 28-day dermal. These are rabbit studies that were short-term ones.

MS. BECKER: They are toxicity studies?

DR. SLAGA: Yeah, there's really no --

DR. MARKS: So 28-day dermal is another insufficient.

DR. SHANK: Because these would be used in a higher concentration.

DR. MARKS: Is that Ron Shank?

DR. SHANK: Mm-hmm.

DR. MARKS: Ron?

DR. SHANK: Mm-hmm.

DR. HILL: Yeah.

DR. MARKS: Twenty-eight dermal.

MS. BECKER: For any year model.

DR. HILL: Enough that we can do reasonable read- across.

DR. MARKS: So genotoxicity, 28 day

dermal study.

MS. BECKER: And sensitization and dioctyldodecal malate.

DR. MARKS: And three is sensitization for the dioctyldodecal? And that was based on the -- what page was that? That was based on the expensive clinical -- a couple case reports.

MS. BECKER: It was based on the appendix on the alcohol.

DR. HILL: The alcohol.

DR. MARKS: And that was a couple case reports on sensitivity?

DR. HILL: Yes.

DR. MARKS: Case reports. Not allergic. What page is that?

MS. BECKER: Thirty-two.

DR. MARKS: Thirty-two.

DR. HILL: Panel Book page 32. Yes, ma'am.

MS. EISENMANN: How do you feel about reading across from fumerates?

DR. HILL: I know why you're saying that.

MS. EISENMANN: Because you reviewed it

and you have some data on some of the -- there are some data on some of the -- I don't remember exactly which ones.

DR. HILL: There's an equilibrium at elevated temperature but I don't think that that necessarily applies to any potential tox findings here. We have fumerate diesters is what you're suggesting?

MS. EISENMANN: Yes. You just finished recently reviewing fumerate diesters. And I just thought that might be -- even if it's not -- I'm hoping to find the other data (inaudible) might help a little bit.

DR. HILL: If all of our toxicologists say that's fine, I guess I'm fine. I don't feel comfortable myself.

DR. MARKS: Thanks for picking that out, Ron Hill.

DR. HILL: I doubt they're going to find anything. That's, you know. Okay. I agree with what Dr. Belsito said last time, that we shouldn't ask for any data capriciously knowing that we're putting the cost on people but --

DR. MARKS: So tomorrow I'm going to

move that we issue an insufficient data announcement on the dialkyl malates, which on page 10 will be limited to the one, two, three, four, five, six esters. And that -- and we'll get into why we split them out with the biochemistry. In addition, we really don't have data on the tartrates. And our insufficient data needs are genotoxicity, 28 day dermal toxicity, and sensitization for the dioctyldodecyl since there are some case reports of sensitization to this ingredient.

Anything else I missed? Good, well, do you want to break for lunch or do you want to skip lunch?

DR. SHANK: No.

DR. MARKS: Yeah, I don't think -- we don't need Bart. Okay, good.

(Whereupon, at 12:08 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:09 p.m.)

DR. MARKS: Okay. Is it 5 after? May we start?

DR. SHANK: Sure.

DR. MARKS: No, no, not at all. I didn't want to leave any of our support staff out. Lillian's here. Okay. We're ready to go, Lillian.

MS. BECKER: Okay.

DR. MARKS: So we're now going to look at the synthetic fluorphlogopite ingredient. And this is the first time the panelists have seen this report. And in addition to that we actually have received a number of additional data, what we affectionately refer to as Wave 2 electrons, and even more some paper data. So is there -- are there needs? Any further needs for these ingredients from a safety point of view? And then I think one of the other questions would be as we reviewed the magnesium aluminum silicate, which is -- didn't -- was found to be -- concluded to be safe as long as it's not respirable in the past. So we came to that conclusion --

MS. EISENMANN: Actually that's not in the conclusion.

DR. MARKS: Oh, isn't it?

MS. EISENMANN: No. The conclusion is safe as used in cosmetic products as long as in the discussion you state the Panel recognized that most of the formulations are not respirable and of the preparations that are respirable the concentrations of the ingredient is very low. Even so, the Panel considered that any spray containing these solids should be formulated to minimize certain inhalation is what you say in the discussion. The conclusion just says safe as used. It does not say formulated to be not respirable. The discussion says to minimize the inhalation. So.

DR. MARKS: Thank you, Carol. That's exactly right. Now that I look on page 96 of the conclusion in our Panel Book it's exactly what you say. So we concluded safe. I was going from the memo on the front here.

Okay. So let's get back to proceeding with do we need any more data? Tom, Ron, and Ron?

DR. SHANK: Does this ingredient remain

as a solid formulation? I got that impression.

DR. SLAGA: That's the same question I got, too.

MS. EISENMANN: As far as I know --

DR. SHANK: I think it's always a solvent. Okay. Then it's unlikely to penetrate the skin. And now you have inhalation data here?

DR. SLAGA: And genotoxicity and some sensitivity, right? A lymph node.

DR. MARKS: Yes. And the local lymph node assay at percent didn't show evidence of sensitivity. In Wave 2, we have 55 percent of this ingredient with a number of animal studies showing that it's -- it's neither an irritant, sensitizer, phototoxic, although I had Lillian ask to clarify it. It talks about a 55 percent paste mixed with water, so I assume it was probably very minimally diluted out.

MS. BECKER: That would be my impression.

DR. MARKS: Yeah.

MS. BECKER: Just enough to make it --

DR. MARKS: Placed on.

MS. BECKER: Right.

DR. MARKS: Okay. That's what I said.

DR. SLAGA: And genotoxicity was and many tested strains of (inaudible) as well as E. coli, but they were (inaudible) basically.

MS. BECKER: Dr. Marks, would you share the papers I just gave you with Professor Hill?

DR. MARKS: Oh, yes. Here. Go ahead. I'm sorry. I didn't realize you hadn't given us all one.

MS. BECKER: Yeah. That came in Friday after I went home. Yeah, I only -- it's 75 pages.

DR. MARKS: Yeah, no, that's fine. So actually going back, Lillian, based on what Carol said and I didn't pick it up, although I have a checkmark next to it, on page 7. That would be important in the introduction to change that second paragraph. To leave that part about formulated to be nonrespiratory.

DR. SHANK: We have inhalation data here.

DR. MARKS: Well, that's --

DR. SHANK: And respirable particle sites.

DR. MARKS: Yeah, no, I was referring

back to the previous report.

DR. SLAGA: That was not in the previous conclusion.

DR. MARKS: I have use tables, skin up to 67 percent; eye 48 percent. There is the potential of inhalation. It's used in products where it could be. So any needs or can we proceed to a conclusion?

DR. SLAGA: I think we can proceed with a conclusion. As long as we're comparing some of it back to the, what's it called?

DR. SHANK: Magnesium?

DR. SLAGA: Yeah, magnesium aluminum silicate. Now that we have several additional data related directly to this name that we need to change.

DR. MARKS: Okay. So we would move forward with issuing a tentative. Is that right? Is that the next step, Lillian? Tentative report?

MS. BECKER: Yes.

DR. MARKS: With a conclusion that it's safe. Any caveats in that conclusion? Hearing none.

MS. BECKER: How about discussion?

DR. HILL: So how are we dealing with the face powder again?

DR. SHANK: We have inhalation toxicology data in the new Wave 3.

DR. HILL: Okay.

DR. SHANK: And the particle size was point two or three or something like that, micrometers.

DR. HILL: Actually, given the chemistry I was looking for things like mouthwashes but I didn't see anything along those lines. Very small incidental oral exposure for fluoride or lasic given there's a stability issue.

MS. BECKER: It's not used where fluoride would be the formulated (inaudible)?

DR. HILL: Well, and I think the amounts would never reach anything where toxicology would be a concern. I just -- I was looking for anything. I didn't see anything.

DR. MARKS: Okay. So is there anything we need to -- I guess, Lillian, you'll just proceed with the usual discussion. Nothing to specifically highlight in this other than Ron

Shank, do you think we need to talk about the inhalation a little bit since the previous report that we'll refer back to with the aluminum -- the magnesium aluminum silicate is in that previous report and has --

DR. SHANK: To say in the discussion that we have inhalation data for (inaudible).

DR. MARKS: Okay.

MS. BECKER: Inhalation boilerplate.

DR. SLAGA: Also in the discussion, since we only had bacterial mutagenicity, but we had mammalian related to the magnesium aluminum silicate. You'd have both so I think we're fine there, too.

DR. MARKS: So we have human carcinogenicity. Tom, is that human?

DR. SLAGA: No.

DR. MARKS: No?

DR. SLAGA: When are we -- mammalian mutagenicity?

DR. SHANK: Mammalian.

DR. MARKS: Mammalian. Yes. I thought I heard human. Mammalian.

DR. SLAGA: You only do that in prisons,

right?

DR. MARKS: Yeah, I was going to say. Mammalian. In this one the only thing we had you said was genotox.

DR. SLAGA: Yeah. In the new data.

DR. SHANK: Well, bacterial. We had mammalian in the magnesium (inaudible).

DR. MARKS: Okay. So Lillian, you've caught that how we --

MS. BECKER: Mm-hmm.

DR. MARKS: -- used the previous data as a read- across so to speak? Okay. So we have the genotox is taken care of and then we have the inhalations taken care of. We'll talk about that in the discussion.

DR. SLAGA: And you need penetration because it's a solid salt.

DR. MARKS: Penetration. Solid..

DR. HILL: I really thought there was very little of any data that was need other than to make sure it didn't cause problems if you put it in a powder and inhaled it.

DR. MARKS: And three is inhalation.

DR. SLAGA: But it's nice to have extra.

DR. HILL: It is, but it just --

DR. MARKS: And this'll be the discussion. Okay. Anything else? I'll move that a tentative report be issued on the synthetic fluorphlogopites and that it's safe as used. In the discussion we'll talk about the lack of penetration because it's solid. We have genotox covered with this ingredient bacterial but we also have the previous mammalian and then we have inhalation data to support its safety, too.

Anything else? If not, let's move on to the ammonium hectorites.

DR. HILL: And you can give that back.

DR. MARKS: Thank you.

MS. BECKER: If you're all done I'll take it for the next -- Belsito's.

DR. MARKS: Here you go.

MS. BECKER: Thank you.

DR. SLAGA: Here's the other one.

MS. BECKER: Thank you very much.

DR. MARKS: So this is the first time we're seeing this. Is that correct?

MS. BECKER: Yes.

DR. MARKS: And Tom and Ron, any needs?

We refer back to our previous CIR reports on hectorite and lithium. Are there lithium --

MS. BECKER: Wave 2 filled in quite a few gaps on the dihydrogenated tallow.

DR. MARKS: So I guess we could go on page 7. They aren't on a table but the ingredients in this report are the disteardimonium, the dihydrogenated tallow, et cetera, here. What is that?

MS. BECKER: There's four.

DR. MARKS: Do we like these four? Should any of them be eliminated?

DR. HILL: I mean, I question the benzyl one but then I couldn't think of any good reason to ditch it, so.

DR. SHANK: Quatermium-18 hectorite and stearalkonium hectorite, safe as used. I think those can cover the other two.

DR. SLAGA: Why do we have quatermium-18 hectorite up when we already reviewed it? If you look, the second line after the introduction.

MS. BECKER: Right. The idea is we're rectifying the previous mindset of doing only one or a few ingredients at a time and bundling so that

the next time they come up everybody's together.

DR. MARKS: So it gets back to are we -- that's kind of interesting. Are we reopening them?

MS. BECKER: We haven't been considering it reopening, just folding in.

DR. MARKS: Well --

MS. BECKER: I mean, we've been --

DR. MARKS: So is the conclusion going to have all four of these cosmetic ingredients?

MS. BECKER: Yes.

DR. SHANK: It would seem easier to reopen the old one. Mark as old ones -- reopen them, too. And then these are no-brainer add-ons. We already discussed that and decided that's --

MS. BECKER: Well, when they decided that they were doing it, that was mostly Bart and Halyna. I'd been -- the trigger was the one that wasn't one of these two and it has a high number of uses. And when searching for similar ones we found the ones that hadn't been reviewed. The mindset has just been folding them in.

DR. MARKS: Okay.

MS. EISENMANN: But --

DR. MARKS: That doesn't mean we can't propose that tomorrow even though we aren't the team that's going to make the motion. I kind of like -- well, I guess there we reopen. We can rename the report however we want? It can be the ammonium hectorites.

REPORTER: Can I ask you all to keep you voices up. We can all hear the drilling (inaudible) --

DR. MARKS: Right.

REPORTER: I'm having a tough time hearing what's being said.

DR. HILL: And I'm wondering how necessary that drilling is because given the fact this hotel is hosting this conference it seems to me that --

REPORTER: They can turn it off.

DR. HILL: Yeah, well, to not do that while we're meeting, in my humble opinion, unless it's an emergency.

DR. MARKS: So how would the team prefer? It seems to be a little messy not to proceed as reopening the prior report without, you know, you generate a new report and kind of acknowledge the

old one.

DR. SLAGA: When was the old one done?

DR. SHANK: One was done in 2000. That was the stearalkonium hectorite and quatermium-18 was done in '82. So that must have been re-reviewed already.

DR. MARKS: Re-reviewed.

DR. SHANK: Okay.

DR. SLAGA: Well, they could potentially come up for re-reviews so maybe it would be best to open the old one up and combine them all.

DR. MARKS: Right.

DR. SLAGA: And we'd have to re-review.

MS. EISENMANN: So would you also include quaternium-18 because the original report was quaternium-18 and quaternium-18 hectorite?

MS. BECKER: And bentonite.

MS. EISENMANN: So there were three ingredients in the original report. So right now you're just pulling --

MS. BECKER: Whereas the stearalkonium hectorite was our standalone.

DR. SHANK: Oh, that's probably why.

DR. MARKS: Thanks, Carol. Okay, so are we just going to proceed as presented here? It still to me seems a little messy because now we're going to have ingredients as a standalone. Stearalkonium hectorite. And we're going to have an ingredient safety assessment in this report. We can wait and see what happens tomorrow.

DR. HILL: Are they making the motion?

DR. MARKS: They're making the motion. The other would be just reopen stearalkonium hectorite. But you still have quaternium-18 hectorite.

DR. SHANK: Good point.

DR. MARKS: Okay. So at any rate we could proceed at this point to have a tentative report. Is that correct? Safe?

DR. SHANK: Yes.

DR. MARKS: Skin is okay. Okay. Tentative report, safe.

MS. BECKER: Okay. What would you like to discuss?

DR. SHANK: Smectites. Who needs them?

DR. HILL: Geologists. Doesn't that

explain everything? (Laughter) That wasn't on the record. I have friends who are geologists.

DR. MARKS: Okay. Discussion? As Lillian mentioned, obviously part of it's going to be that these were previous -- two of these ingredients were previously reviewed and safe. Is there a lot of carryover to the other two ingredients in this report from the previous reports?

DR. SHANK: Yes.

DR. MARKS: Anything else? It looks like it's going to be a short discussion, Lillian.

MS. BECKER: Yeah, it sounds like.

DR. MARKS: Okay. Shall we move on? Thanks, Lillian.

MS. BECKER: You're welcome.

MR. MARKS: Okay. I have next the galactomannans. You're laughing here, Dr. Hill. These are legume polysaccharides. This is the first draft of this report and the first time we've seen them. So we're back to -- I find that some of the nomenclature are a little bit -- thank you, on page 3 of the book, where we talk about the gums and then the extracts, so they are both

botanical names and more lay names in here. The guar gums, the locust bean gums, the tar gums, which have extracts below in botanical. And then you have ingredient definitions here. So it's got even more complex. Therefore, the trigonella foenum-graecum seed extract and hydrolyzed do not belong in this report with a focus solely on polysaccharides. Can you help with this?

MS. EISENMANN: Do you want me to help with it?

DR. MARKS: Yeah, let's go -- where should we go to the ingredients? I mean, you're saying --

MS. EISENMANN: Table 1.

DR. MARKS: Table 1. Can we go to page 8 and look --

MS. EISENMANN: I prefer Table 1.

DR. MARKS: Okay, what page is that, Carol?

MS. EISENMANN: Twenty-eight, Panel Book 35.

DR. MARKS: Thirty-five.

MS. EISENMANN: And then the ingredient of concern is on page 31.

DR. MARKS: You like to see the chemical structures.

MS. EISENMANN: No, I would like the definitions from the dictionary to be in the table -- from the Cosmetic Ingredient Dictionary to be in the table. These aren't those definitions. Other definitions -- it's okay to put other definitions there but I would like to see the cosmetics -- because in this case, trigonella foenum-graecum seed extract is defined in the dictionary as usual. The extract of the seeds of trigonella foenum-graceum. It's an extract; it's not a gum.

So this definition is wrong. I mean, this isn't the right definition. This is a definition of a gum but the material that's being used in cosmetics at this point is an extract. And the CAS number here is the CAS number for the gum; the CAS number the supplier gave is different. And so the CAS number for the --

DR. MARKS: That's why I -- this was a memo from today.

MS. EISENMANN: Right. Right.

DR. MARKS: So you're on page 38 if I

look at it, where you're talking about, where underneath at the top it says foenum-graceum gums and then underneath it talks about the seed extract. And it's really an extract, not a gum.

MS. EISENMANN: Correct. The cosmetic ingredient -- I mean, there is a gum that's made from the seed but it's not a cosmetic ingredient at this point. So the hydrolyzed ingredient is also --

DR. MARKS: An extract?

MS. EISENMANN: Right. Right. It's an extract. The dictionary defines it as an extract of -- a hydrolyze of the extract, not of the gym.

DR. MARKS: Extract.

MS. EISENMANN: So those two need to come out. But all of the definitions, it would be nice to have the dictionary definition. And then if another definition would be helpful, that would be included, too. But because you're reviewing cosmetic ingredients, even though sometimes the dictionary definitions are very -- are not very specific, they probably should be in here.

DR. HILL: Well, they definitely need

to be in here.

MS. EISENMANN: Okay.

DR. MARKS: So if we go -- so you picked that specific one but let's go back to page 8, Carol, at the top of the page in the introduction. It has a number of ingredients there of which a number of them have gum. And then obviously on page 3, the ingredients in the table there are this guar gums. So how would this be reconstructed in terms of going down here? What would you -- just based on a definition --

MS. EISENMANN: You just need to take off the two ingredients because the other ingredients, they have gum in the --

DR. SLAGA: Just the two extracts take out.

MS. EISENMANN: Correct.

DR. MARKS: Okay. That's what you're saying. So if we go on page 8, you would take out the -- on the right hand side the trigonella foenum-graceum seed extract. Is that right?

MS. EISENMANN: Correct.

DR. MARKS: And then what is the second one here? The hydrolyzed form.

DR. SHANK: The hydrolyzed extract.

DR. MARKS: And where is that?

DR. SHANK: It's third from the bottom.

DR. MARKS: Oh, yeah.

DR. SHANK: Third down.

DR. MARKS: Yeah, third from the bottom. Yeah, third from the bottom. Okay. So you would delete those, too. Okay. Because they're totally different than these gums.

MS. EISENMANN: Right.

DR. MARKS: Okay. So then we get back to maybe now the whole -- from your vantage point the rest of this we're talking about the same -- obviously they're not the same material but in terms of the way they're made, so to speak. The guar.

MS. EISENMANN: They're all polysaccharide based.

DR. MARKS: Right. Okay. Anything, Ron, Ron, and Tom, when you look down this list that you would --

DR. SHANK: No. They're all very large molecules, unlikely to penetrate skin. So there's no systemic toxicity concern. We have an

HRIPT at 2 percent. That's the maximum legal concentration. Two is negative so I'd say they're safe when formulated to be nonirritating.

DR. MARKS: Yeah. My concern where the case reports and series of what appear to be an IgE mediated rhinitis and anaphylaxis. And then I guess my questions from that would be -- and maybe going through with an insufficient -- what portion of these gums cause that IgE reaction?

DR. HILL: Which page are they listed? This reaction page?

DR. MARKS: Page 14, 15 -- 13, 14, and 15.

DR. HILL: I was trying to find it because I think (inaudible).

DR. MARKS: And they're occupational.

DR. SHANK: And they're (inaudible).

DR. MARKS: Yeah, 13. Let's go to 13. I normally do the Panel Book, so 13, 14. Is that it? No? Okay. So let's go to -- here we go. It's actually Panel Book page 20. It's the report page 13.

DR. SHANK: Book page 14?

DR. MARKS: Yes. Panel Book page 20.

It's under the title of allergenicity. And these are all occupational exposures rather than one got after eating. And they're all IgE-mediated so I would be concerned if I applied this topically. What component -- I don't normally think of polysaccharides causing anaphylactic reactions. I assume there's a protein in there.

DR. HILL: They're almost all the same (inaudible), right?

DR. MARKS: No, they're different. Three different gums.

DR. HILL: Yeah, but one of them is a trigonella foenum-graecum seed powder, so that one can go. So then I think we're down to cyamopsis tetragonoloba -- I can't say that one. And then one is the mixture with the seratonia.

DR. MARKS: So can the seed powder go. We didn't -- would that be the same as a seed extract.

DR. HILL: So the trigonella foenum preconceived powder, no.

DR. MARKS: Do we have any trigonella in it now at all in this report?

MS. EISENMANN: We have the

hydroxypropyltrimonium chloride. So you might want to -- that is probably gum. So maybe you would leave that in because of criminal use of it but it's not the ingredient itself. It might be related but the rest of the -- I think the rest of the data on the foenum- graceum extract probably can go.

DR. MARKS: So that was my concern. Could any of the -- whatever is causing this in these, mainly occupational exposures, could that portion of these gums be carried over to the cosmetic ingredient if you had a highly sensitized individuals? Could you end up -- and of course there are cases of topical and small amounts of material and end up with an anaphylactic reaction, a systemic reaction.

So that was my -- Ron, Ron, Tom, did you -- is my concern looking at data -- I was actually quite concerned about it.

Carol, can you elucidate? Is there in the final product, do they talk about we don't know what's causing this reaction?

MS. EISENMANN: It's occupational exposure. I mean, marginal inhalation exposure

in an occupational setting.

DR. SHANK: You wouldn't have that same level of exposure in the cosmetic.

DR. MARKS: Well, except there are definite reports (inaudible) and it's very, very rare, but bacitracin, a topical antibiotic, there are cases of anaphylaxis after exposure. Now, of course, that's to a wound. One might say you aren't going to be putting this on a wound. There's breakdown of the barrier. Maybe a little bit more but I had difficulty handling this potential toxicity.

DR. HILL: You know, and the question is why those two? Because I don't see anything, at least in the structures of the gums, that --

MS. EISENMANN: And I don't know if there would be any protein. I mean, maybe those ones are more or less going to have a little protein residue.

DR. HILL: That's the question.

DR. SHANK: Can we have -- and if you find out what level is the exposure, the occupational as well? Because this is where, you know, you find this gum was used to adhere dye to

the fiber, to me that would have to be an extremely high level, wouldn't it? I don't know, even if it would be relevant, the small amounts that would be in the skin.

DR. MARKS: And here they have one. Cyamopsis was a life-threatening, immediate-type hypersensitivity after a mucosal application of a local anesthetic gel that contained the guar gum.

DR. SHANK: These are case reports. You don't know what else was in that gel.

DR. MARKS: Right.

DR. SHANK: And to blame it on the gum?

DR. HILL: Unless they went back and, yeah.

DR. SHANK: So I don't put too much weight in those. The only one that I thought was possibly pertinent was this one 38-year-old man who had an allergy prick test, apparently with (inaudible) powder. Doesn't say what was tested. And then again that's compromising the barrier function of the skin.

DR. MARKS: Mm-hmm. So in that first, if you look on page 20 of the book, it says -- this

was 162 employees at a carpet manufacturing plant where the gum was used to adhere dye to the fiber. IgE sensitization, the guar gum was between 5 percent. Eight of 162 subjects is assessed by skin test; and 8.3 of 11 assessed by major serum IgE antibodies. So I assume they did RAST test on them to this. I'm not sure. I didn't look at the report. But obviously exposure much different there than to the cosmetic. And even though we have HRIPT tests, which were okay, that's obviously a very -- I'm not sure. In fact, HRIPT is not designed to detect IgE mediated immunity. So having a negative HRIPT would not help me..

How do we want to proceed? Should we do an insufficient and ask for more -- I'm not sure we'll get much more but ask more about -- raise the concern of this IgE sensitivity? Or Ron, do you feel -- Ron Shank, do you feel comfortable just saying this is probably -- this is not applicable to skin application and just proceed?

I have in here concentrations of use up to 93 percent. So it's pretty high.

DR. SLAGA: Yeah, it's pretty high.

DR. MARKS: And over 800 uses. So it's a lot of products.

MS. EISENMANN: It's also in a lot of products in food, too.

DR. SHANK: Half of these are grass.

MS. EISENMANN: Probably higher exposure includes the cosmetics. And 93 percent is a hair product, not a dermal product.

DR. HILL: Well, I mean, I tested positive to acacia-type gums when I was allergen-tested way back when. So some things I'm not supposed to eat. And that was skin prick. But I don't know what I was reacting to. No idea. I just don't think of these sorts of things as being allergenic. So intact skin, no problem. But wounds, abraded skin, mucous membranes, I don't know.

DR. SHANK: I would bet that the purity of the gum used for carpet manufacturers is somewhat --

DR. MARKS: I would agree.

DR. SHANK: -- less than cosmetic grade.

DR. SLAGA: Well, hopefully, anyway.

DR. HILL: A 38-year-old male, he was

an employee of a pet food processing company where he frequently inhaled guar powder.

MS. EISENMANN: Okay. Page 33, the specification for gum in foods and drugs, acacia is less and protein is less than 7 percent. It's listed here, the percent protein.

DR. SHANK: Well, I will defer to you, sir. It's not a concern to me but --

DR. SLAGA: It wasn't a concern to me either.

DR. MARKS: Well, that's why I brought it up for discussion. I wasn't quite sure how to handle it and I wanted to get your input. So I think -- and the other question I had were impurities. I think that's on page 12. They talk about dioxin and PCP and metals. So that's on Panel Book page 12, up in the one, two, three, fourth paragraph down. Originating from India with dioxins and PCP. Do we need to say anything about that?

DR. SLAGA: I don't think so..

DR. MARKS: The heavy metals? Okay. So my sense is we would then go ahead and issue a tentative report and safe.

DR. SLAGA: Do we need the boilerplate for inhalation? Because it is powders. So I think we need to add the inhalation boilerplate in the discussion.

DR. MARKS: In the discussion, okay. Inhalation. Boilerplate. Okay. Anything else in the discussion for Wilbur?

DR. SLAGA: Do you want to put anything about impurities?

DR. SHANK: I don't think so..

DR. SLAGA: I mean, not that it's a problem. But the fact that we mention that it's listed but felt it was not a concern.

DR. MARKS: And the reason?

DR. SLAGA: The levels.

DR. MARKS: Okay. So I'll put that on here. Levels of impurities not a concern.

DR. SLAGA: The ones that you mentioned.

MR. JOHNSON: The PCP and the dioxin.

DR. SLAGA: Yeah. I mean, dioxin scares people. So to have a little bit in the discussion.

DR. SHANK: It's everywhere.

DR. MARKS: Okay. So inhalation -- impurities not a concern. I'm going

to say here something to the effect that IgE allergenicity is not a concern with skin exposure. Are there any uses orally? Was there any mucous membrane? I've got to go back. Where is the use table? Page 46.

DR. HILL: Page 42 of the Panel Book. Yeah.

DR. MARKS: Just to be complete in case that comes up. Twelve mucous membranes with (inaudible) 21. Look at the cool. And am I reading this correct, the guar hydroxypropyltrimonium chloride 179?

DR. SHANK: Does mucous membrane use mean oral?

DR. MARKS: Just relating back to that one where you're exactly right. The case report didn't say what it was in there that caused the IgE. So, maybe just not mentioning it is better. I don't know. I'll put a question mark here and think some more about it.

Okay. Safe, tentative, and then we're going to remove two of the ingredients that are the seed extract.

DR. SHANK: Was it two or three?

DR. MARKS: It was two.

DR. SHANK: Two?

DR. MARKS: Yeah, two. Trigonella foenum-graecum seed extract and hydrolyzed. Those two that Carol pointed out. Two ingredients. Okay. Anything else?

MR. JOHNSON: Dr. Marks, with respect to the discussion, did you want to say anything more than that the IgE allergenicity is not a concern with respect to skin exposure? I guess a reason why that statement is being made?

DR. MARKS: I'm debating in my own mind whether I even want to include it at this point. Let's just delete that.

Okay. Anything else? So we'll probably be seconding a motion that a tentative report be issued on galactomannans with the ingredients minus 2 listed here are safe. Anybody else? We'll see if the Belsito team gets concerned about the IgE.

MR. JOHNSON: They are concerned. They're concerned about it. (inaudible) that may have been due to protein contamination.

DR. SHANK: That's what I think.

DR. MARKS: Yeah, what my comment was is in here was then if it is a gray protein, how do you prevent it? You know, do you say, Carol, if you said it's less than 7 percent protein, how do you say what level of protein is safe? You can't. So -- pardon?

SPEAKER: Maybe it should be in the discussion.

DR. MARKS: But then if it's in the discussion, then how do we determine it's safe? That's the key. We can say we noted that IgE allergenicity occurred in case reports and series but why aren't we concerned about it? And that's what Wilbur just brought up. Why aren't we concerned about it? And it's actually not just skin; it's skin and mucous membrane.

DR. SHANK: Okay, but there's been long widespread use as a food applicant or food additives without a problem.

DR. MARKS: Maybe that's --

DR. SHANK: Why I'm not concerned.

DR. MARKS: Okay.

DR. HILL: Yeah. But on the other hand, oral protein is digested before you --

DR. MARKS: Probably go through the mucous membrane.

DR. HILL: Mouth.

DR. MARKS: Yeah. To me that's very reassuring.

DR. HILL: Yeah.

DR. MARKS: This would be not a problem in food allergy as food additives. So we wouldn't expect it to be a problem as far as a cosmetic ingredient. Does that sound the way we're going? Okay. We'll see how -- I like that. Okay. I have a feeling there's going to be more discussion about that tomorrow. Thanks, Wilbur.

MR. JOHNSON: You're welcome.

DR. MARKS: I'm glad I brought it up. At least it wasn't --

MR. JOHNSON: Absolutely.

DR. MARKS: So we aren't sort of surprised. Okay. The next one is polyquaternium-22 and -39.

This is the first time we've seen these ingredients. We have this report in front of us. I can tell you Alan isn't here but Alan was concerned that the structures of the -22 and -39

were so different that he wondered whether or not we should actually combine these.

DR. SHANK: Well, they're both huge molecules and mighty charged so they're not going to be absorbed. So there's no systemic toxicity. HRIPT is negative..

DR. MARKS: Correct. Yeah.

DR. SHANK: So based on the fact that they're very large, charged molecules I'd say they're safe for cosmetic use.

DR. HILL: There was concern because there's no data on -39.

DR. SHANK: In Wave 2.

DR. HILL: That's where I was looking, in Wave 2, because I mean, by the time Wave 2 arrived --

DR. SHANK: It was a little late.

DR. HILL: Well, given what was on my plate between that point and here.

DR. MARKS: Well, let's go back to -- that's interesting. So we have Wave 2.

DR. HILL: I have it right here but I couldn't digest it.

DR. MARKS: So he didn't -- so Alan felt

that structurally, chemically, these didn't go together but you're not worried, Ron Shank, you're not concerned that there may be structural differences? You have no problems?

DR. SHANK: Right because basically there's no exposure. And we're not relying solely on these. We're going back to a couple of older reports where the monomers are the same. When I read the report that we received I had all kinds of insufficient (inaudible), all of which were answered in Wave 2.

DR. MARKS: Yep.

DR. HILL: Or both.

DR. SHANK: So for both Q-22 and Q-39.

DR. MARKS: Wilbur, on Wave 2, you saw there were a number of studies on Merquat 280 polymer.

MR. JOHNSON: Yes, mm-hmm.

DR. MARKS: Did a lot -- this material was okay for ocular irritation. Didn't cause that. No skin irritation. I wasn't quite sure of sensitization. In your cover memo you said sensitization. Maybe I missed that.

MR. JOHNSON: Yes, there's a human skin

irritation in sensitization studies.

DR. MARKS: Okay, that's good..

MR. JOHNSON: Involving 150 humans.

DR. MARKS: I was probably like Ron Hill when I saw Wave 2 come through. I tried to go through it. But now, is the polyquaternium-22 that was used in all this, was this at 100 percent, the concentration? I wasn't quite sure.

MR. JOHNSON: Actually, it's, you know, it's as supplied and it's defined as an aqueous copolymer of 65 moles percent diallyldimethylammonium chloride and 35 moles percent acrylic acid. It also contains the preservatives methyl and propylparaben.

DR. MARKS: Right. But presumably this material would be quite, again, you thought the sensitivity and irritation studies were fine. They were fine. I just want to be sure we're at a concentration we know. Okay.

DR. SHANK: That's part of Wave 2 and I don't --

DR. MARKS: Yeah.

DR. SHANK: I didn't write down the concentrations.

DR. MARKS: Yeah, that's what I had. Basically, they used this material and that's what they did all the testing with. Merquat 280 --

DR. SHANK: Sixty-five percent.

MS. EISENMANN: Dr. Marks.

SPEAKER: Dr. Marks, someone from the audience.

DR. MARKS: Yes.

MS. VERGNES: Hi.

DR. MARKS: Oh, thank you.

MS. VERGNES: I'm Jane Vergnes from International Specialty Products, Ashland. And basically one of my responsibilities is to provide specifications in manufacturing or in qualifying materials from other suppliers that may be making these. And to be honest, what usually drives our assessment is not the molecules themselves but what processing solvents are going to be used and how much is going to remain, as well as the residual levels of the amines and the monomers.

DR. HILL: Yeah, that was my question. I wrote monomers.

MS. VERGNES: I mean, that's

really -- in looking at all the polyquats across the spectrum, I mean, those are the things that really drive the assessments. And for us it's really important to determine or to benchmark against what do we know about what has been safely used in the market and what the residual levels are in those products. Because we certainly don't want to introduce anything or have manufacturing standards that provide any less than that. And I'm sure you know that for some of these monomers, like when we're talking about the PQ-39 and the PQ-22, were you have the DADMAC and acrylic acid in PQ-22, in the PQ-39 you have the acrylamide, which is common with your PQ-7.

MR. JOHNSON: Yeah, 10 and 11 I found in my notes. They're not relevant. We probably should ditch those. They're different monomers but seven definitely.

MS. VERGNES: So, I mean, in looking at all of these though, again, it's really not -- it's really not the material itself that is driving our safety evaluations and our qualification procedures and specifications. It really is solvents, processing solvents, and

residual monomer levels that we're concerned about in safety assessments.

DR. HILL: That would have been my expectation, too. I'm glad to hear it from somebody who's working in the area.

DR. MARKS: So issue a tentative report on polyquaternium-22 and -39, safe?

MR. JOHNSON: I just have one question, whether or not the actual, I guess, level of acrylamide monomer in the polyquaternium-2 and polyquaternium-39, trade name materials. Is that information available? The monomer content of both of those trade name materials..

DR. HILL: Twenty-two and -39?

MR. JOHNSON: Yes.

MS. VERGNES: I would need to go back and see whether it's publicly available. For some of these things we have internal specifications but I will need to go back and check. Have we submitted any of that information?

DR. HILL: No.

MS. EISENMANN: Another company submitted information on those two ingredients. I don't know if that was in their facts. And then

this company just recently purchased the ingredients from another company. So.

DR. HILL: The company that sent you the info recently purchased?

MS. EISENMANN: Mm-hmm. From somebody else. Yeah, so.

MS. VERGNES: And that's largely our situation as well.

MR. JOHNSON: And I know the technical datasheets on both of those materials were submitted but I don't recall whether or not the monomer content was stated in those.

DR. HILL: Do we have those sheets? Are they in Wave 2?

MS. FIUME: They are Davis supplement page 360 is for the polyquat-39.

DR. HILL: Okay. Page 360 is in Wave 2. All right. So here we go.

DR. MARKS: So is there any reason given this question about the monomer content not to proceed with a safe?

MR. JOHNSON: Let me just say this also. I know in 2005, CIR published a safety assessment on polyacrylamide and the limit on the monomer

content is established at 5 ppm.

DR. HILL: Also, that takes care of one of the three monomers but not the other two. Is it -39 that has all three? Sorry.

MR. JOHNSON: Yes, it's -39.

MS. EISENMANN: And that was (inaudible)?

MR. JOHNSON: Yes, for polyacrylamide.

DR. HILL: So, yeah, the DADMAC. Really, the one glaring note I wrote on my notes was need monomer info. I felt like that was an insufficiency but I didn't have Wave 2 at the time I wrote that note. So page 360 you said.

MS. FIUME: And it's 264.

DR. HILL: Two-sixty-four is the one?

MS. FIUME: It's polyquat-22.

DR. MARKS: Here you go. That's the one I had. There's the -22.

DR. HILL: Okay.

DR. MARKS: You can see what I have underlined there, Ron. That was what Wilbur quoted earlier about the moles.

DR. HILL: You don't have anything underlined on here. Where am I looking?

DR. MARKS: Right, oh, sorry. Right in here.

DR. HILL: All right. Yeah, but those are the monomers when it's polymerized and then no percents in the finished polymers. So the question is -- and it doesn't speak to impurities at all -- and how about this one? It doesn't have impurity spec on here either. So I don't see impurity spec on any of them.

DR. MARKS: Now, which is the main toxicity on this? Are you concerned about sensitization from the monomers?

DR. HILL: Yeah.

DR. MARKS: And I would say this material is what's being used for the HRIPT and it's negative.

DR. HILL: Do we know that that's the HRIPT?

DR. MARKS: Yeah. Yeah. If we have HRIPT and it's negative, then that would indicate to me that no matter what the monomer content in there is it's not enough to draw sensitization.

DR. HILL: Well, all right. So then if this is the only vendor that's fine, but if there

are alternative vendors for -22 and -39, then how do you write the report to reflect that? Do you say formulated to be nonsensitizing?

MR. JOHNSON: I think that with respect to the polyacrylamide report that that limit was based on carcinogenicity.

DR. HILL: Sure.

MR. JOHNSON: For the polyacrylamide.

DR. SLAGA: And what was that, 5 ppm?

MR. JOHNSON: Five ppm.

DR. SLAGA: That's pretty conservative.

SPEAKER: Huh?

DR. SLAGA: That's pretty conservative.

DR. HILL: So it's in the finished product.

DR. SLAGA: We get (inaudible).

DR. HILL: Yes. It is conservative. For something mostly dermally applied. Yeah. I would think sensitization for a dermal product would be the greater concern.

MS. VERGNES: And just I think as a benchmarking exercise, there are a number of global supplier of these materials. Right now some of the drivers, particularly for global

supply, are done in Europe for cosmetic ingredients. The limit right now with acrylamide is the big 1 ppm. And I believe they're taking it down to 1 ppm. And then again --

DR. HILL: So what you're saying, at least for that one is, if they're manufacturing to meet European specs then it's going to be well below anything we might be -- but that's that one monomer. So what about acrylic acid and DADMAC?

MS. VERGNES: Well, again, for those, for the DADMAC, certainly, you know, with all of the amines, it's always about -- the assessments are frequently complicated when new molecules are being developed or when you're trying to manufacture something that's already existing in commerce. It's what do you use as the benchmark for how much of the amine is going to be okay and is not going to create an issue. And for that, again, we searched the literature. We tried to benchmark against what's existing in commerce and has been safe. And that's currently what we're doing as we're working with these two materials.

For a number of the monomers, just because of the way the REACH regulation is phrased,

there is a great deal of pressure on all monomers in materials that are used in personal care of polymers. The pressure to keep those monomer levels very, very low, as close to non-text is possible is significant just because of the way the regulations run. So that's going to be why you see things like a 1 ppm on acrylamide as opposed to a higher value.

DR. HILL: But that's mainly driven by production concerns, right? I mean, you said whose specs are that low?

DR. SHANK: The Europeans.

DR. HILL: Okay. But that was for a criminal matter. I mean, I can see where you have something which is clearly a known carcinogen that you keep those levels low but dimethyl diallyl ammonium --

MS. VERGNES: Great. And again, for that it would be mostly a pragmatic point of view, benchmarking against those materials that are in commerce that have been demonstrated to be safe.

DR. HILL: Sure. So you know you don't race across -- yeah.

MS. VERGNES: Or looking at the

literature on the monomer and determining how much information, if there is any information, that can also guide you as to what might be a safe level.

MR. JOHNSON: Your name, please..

MS. VERGNES: Jane Vergnes, V-E-R-G-N-E-S.

MR. JOHNSON: Thank you.

DR. HILL: Thank you.

DR. MARKS: Yes, thanks. So Ron Hill, how would you like to proceed with dealing with the issue of the monomers? We're at this point of perhaps saying that these two ingredients, issuing a tentative report that they're safe. Do we handle this in the discussion?

MR. HILL: That seems reasonable.

DR. MARKS: Ron Shank and Tom?

MR. SHANK: Well, it's not in this book but the Wave had a lot of information -- innoculator, skin sensitization, Genotox, et cetera -- on the product. And it was all negative. So if there were toxic levels of monomers in that you would have a positive response.

DR. HILL: Yeah, but all I'm just saying is if you have that material coming from a first rate company where they're extremely rigorous about driving down those monomer levels because they're trying to meet the most rigorous European specs, then you won't see anything; whereas if you have just sloppier manufacturing at higher levels you might. So if you have all of this testing on the very best available material but then you have products that are not formulated with the very best, the question is how do you deal with that? We have this come up every time we have polymer-anything, quite frankly. And I don't know how --

DR. SHANK: You'll have to send (inaudible).

DR. HILL: That might be a little difficult for some of these.

DR. MARKS: Absolutely. We could, again, getting back to in the discussion, just state what you said, Ron, the discussions concerning about monomer levels occurred and with all the testing that's been done that in the products that these -- that doesn't address multiple

manufacturers but it addresses that we did consider the monomer issue and the safety data we have indicated -- I don't know if you would -- Ron Shank, what do you think about that? Because it is a carcinogen issue. It sounds like sensitivity in my mind isn't an issue with -- although it would be the same issue -- is would it be sensitized? I think if you had -- I think if you had diethyl diallylamine at high enough concentrations you would see sensitization.

DR. SLAGA: Yep. Well, obviously, I mean, there's data on its carcinogenicity but even that it's not a carcinogen that would scare me like some others.

DR. HILL: Like you say, we get more French fries on (inaudible).

DR. SHANK: It's really weak, you know, so I don't -- I think what Ron said in the discussion, the products that we observed here were negative.

DR. MARKS: Yeah. Do we even need that in the discussion?

DR. SLAGA: Yeah, I think we can discuss it but I don't think we need to set any kind of

limits.

DR. HILL: Yeah, I think you're right. I think if you say we considered the possibility of sensitization due to monomer or any other toxicology, be it monomers.

DR. SHANK: Yeah, or irritation related to --

DR. HILL: Extensive testing on materials from one vendor did not show any -- I don't know if you can say from one vendor but something along those lines. Did not show any signs of problems.

DR. SHANK: I don't recall from Wave 2, were all of those data from one study with one supplier?

MR. JOHNSON: Well, basically you have polyquaternium-22 and -39. And I think one you had two trade name materials identified as polyquaternium-22. And I think one identified as polyquaternium-39.

MS. EISENMANN: But it all came from one supplier.

DR. SHANK: I think just say that these tests are negative in all of these different

parameters, one which gave us confidence that the levels of unreactive monomers were too small to produce adverse effects. When you talk about a sloppy manufacturer, I mean, that would apply to any.

DR. HILL: Yes, it would. We've talked about that before and there's no way to deal with that.

DR. MARKS: So I'm going to let Wilbur craft it. But basically, since we're proposing this again it will be a tentative report. These two ingredients are safe. In the discussion we'll mention we considered the issue of (inaudible) toxicity but found no problems with the data submitted and everything was tested.

DR. HILL: The last time I remember -- I don't remember what it was right at the moment but it's coming to me. We ended up with a question about propylene glycol impurity in something or other.

DR. SHANK: I think it was one of the -- it should have been one of the PEGs. Yeah.

DR. MARKS: Okay. So.

SPEAKER: Speaking of PEGs.

DR. MARKS: Okay. Do we need to take a break?

DR. SHANK: No.

DR. MARKS: Okay, good. Okay. Now we're into the sulfosuccinates, a Pink Book.

So an insufficient data announcement was issued in September of this year. We needed dermal absorption, mammalian genotoxicity and inhalation toxicity. We did get a number of -- we did get a number of -- we did get some data and the question is whether we have our own sufficient data needs met.

So Tom and Ron, what did you feel?

DR. HILL: Yeah, I'm looking at my notes. Give me a second..

DR. MARKS: No genotox effect without micronucleus. Is that it, Tom?

DR. SLAGA: Well, it's what we asked for.

DR. MARKS: Yep. So the mammalian genotox is okay.

DR. SLAGA: There's plenty of bacterial mutangenicity.

DR. MARKS: No inhalation tox data but

the highest potential use in spray is 2 percent. Is the inhalation toxicity insufficient data really still an issue? And we received no dermal absorption.

MS. EISENMANN: Do you really need dermal absorption based on the (inaudible)?

DR. SLAGA: I don't think you do.

MS. EISENMANN: And the actual practice, aren't these charged? And isn't that partly how they function or (inaudible)?

DR. SLAGA: I don't think we need any additional. What about (inaudible)?

DR. SHANK: It depends on the pH whether they're charged.

MS. EISENMANN: Certainly you would have some kind of nonirritating in your conclusion.

DR. SLAGA: Yeah.

DR. HILL: I'm referencing page numbers here in my notes that don't seem to exist. September Panel Book page -- that's nothing. It's the wrong page numbers.

MS. EISENMANN: Try the -- I think you're in the September --

DR. HILL: I referenced the September book. I just have page numbers that don't make any good sense. So I think -- I'm in the September book at the moment.

DR. MARKS: You're in the right one. It says December. And I think Wilbur actually has captured your concerns, Ron Shank, quite well in the last paragraph on page 86 under the discussion that addresses that issue of the dermal penetration.

But Tom, you were a little less concerned about dermal penetration, so we would proceed with a tentative report. The question is, is it going to be insufficient and our one data need is dermal absorption?

DR. SLAGA: Well, I, to Carol, it's polarity in that in that the molecule I don't think would be absorbed.

MS. EISENMANN: To use primarily a rinse-off products, so if you want to limit it to that you'd get most of the products at least that way.

DR. HILL: Looking at my notes because I remember I had mentally come to rest on these

the last time. My issues were more with what's written. Like on Panel Book -- I'm in September's book so never mind. I can't remember, let's see. So it should show up again.

DR. SHANK: It's in the Pink Book.

DR. HILL: Yeah, I'm in the Pink Book now. I'm just trying to find the same -- it's in the summary.

DR. MARKS: So inhalation is okay at this point? I just want to be sure that we're okay with that.

DR. HILL: Yeah. So it's a statement. I'm on Panel Book page 85. And it say something to the effect that if these ingredients have the ability to penetrate skin then first level metabolites would likely include corresponding alpha PEG ethers and sulfosuccinic acid and I wrote, "Without evidence I disagree with the veracity of this statement."

I think it's the statement that bugged me more than -- there's no evidence to suggest that that would be true.

DR. SLAGA: Well, Wilbur has in his draft discussion that the LD50 for oral is

extremely high. So to me --

DR. HILL: So my point is --

DR. SLAGA: -- there's no way you're going to get that (inaudible).

DR. HILL: This is like the other one we looked at earlier. If the metabolism what's written there is speculative and doesn't even -- I doubt that this is what would happen. Then we'd just take that out and remove that concern.

MR. JOHNSON: So delete that statement about the --

DR. HILL: That was in the summary but I'm assuming that may reflect something that was in the actual sections. So toxicokinetics.

DR. MARKS: So Ron Shank, we have somewhat conflicting on the discussion, the third paragraph and the last paragraph. I know the last paragraph is what you're concerned about. Are you reassured by these --

DR. HILL: No.

DR. MARKS: -- oral animal studies? And Ron Hill, the same question with you. Are you reassured? Are you concerned about having dermal absorption at this point?

MR. HILL: Well, for reproductive and developmental toxicity we have no data, only the statement that according to an internal (inaudible) that there are no data available. So that's not satisfying.

MS. EISENMANN: Does it help that there's a -- I mean you reviewed at some point diethylhexyl sodium sulfosuccinates. There's a three gen study on that..

SPEAKER: And why (inaudible)?

MS. EISENMANN: Well, it's a related ingredient; it just doesn't have the pathoxilation on it.

SPEAKER: The diethyl sodium sulfosuccinates is what you're (inaudible).

MS. EISENMANN: Mm-hmm.

DR. MARKS: And what you're suggesting, Carol, the reproduction and development on that is clean and we could ride it across?

MS. EISENMANN: I presume it's clean enough. I don't know the details of the doses or anything like that. But there is a -- I looked at the report briefly and there's a --

DR. MARKS: And that was a safe?

MS. EISENMANN: I think so. Yes.

DR. SHANK: The compound you just mentioned --

MS. EISENMANN: You have a previous review on it.

DR. SHANK: It's the same thing but without the (inaudible).

MS. EISENMANN: So it's -- the new name would be diethylhexyl. So it's --

DR. SHANK: Diethylhexyl's succinates. So it's not a PEG.

MS. EISENMANN: Right. It's not a PEG.

DR. HILL: Correct.

MS. EISENMANN: So if it would help with maybe the sulfosuccinates as part of the molecule.

DR. HILL: I think it does. And maybe we -- and we don't have anything about that in here. Correct?

MR. JOHNSON: No, we don't. But I think there has been some discussion regarding that but, you know, that's not an exfoliated compound.

DR. HILL: Right. I remember there was. I was trying to remember if we actually took it

out back in June. We took something out somewhere along the line in developing this.

MR. JOHNSON: At least internally that was discussed.

DR. HILL: Okay. I thought I remembered actually explicitly considering something.

DR. MARKS: Well, I think we're still into the need for dermal absorption, aren't we? Unless we can use that.

MR. JOHNSON: We do have data on the, I guess, reproductive and developmental toxicity of laureths summarized in the report text.

DR. MARKS: What page are you on?

MR. JOHNSON: Page 9 or 10 on 83.

DR. HILL: Yeah, because it was on that basis that that was there that I wasn't as worried about that as otherwise because that -- without that I didn't think we had anything to go on. So actually, the data that we're looking for is on the top of page 84.

DR. SHANK: That's (inaudible).

DR. HILL: Carcinogenicity. So what were you looking for?

DR. MARKS: Reproductive.

DR. HILL: Oh, no, we don't have any of that.

DR. MARKS: Other than what Wilbur mentioned.

DR. HILL: Well, now wait. It says repro tox and it's checked. So where is it? It should be in here.

MR. JOHNSON: Well, it's a material (inaudible) issue.

DR. HILL: Oh.

MR. JOHNSON: And it just says there are no data available (inaudible). So I wouldn't give that much weight.

DR. HILL: So we might need that data you're talking about.

MS. EISENMANN: To help cover the sulfosuccinates prior to (inaudible).

DR. MARKS: Ron, would you feel comfortable with that?

DR. SHANK: So I'm just reviewing under laureths what is here. Laureth 9.

DR. HILL: Well, there's no sulfosuccinate moiety on it basically, so those can be just PEGs basically. ALCO PEGs. Laureth

is an ALCO PEG, right? So I actually think if there's concern about repro tox, the only way we can address that is either insufficient or if we decide we can read-across the non-PEG version.

DR. SHANK: Can you convince me there's no absorption across the skin?

DR. SLAGA: Well, no, I can't..

DR. HILL: That's why we were looking for absorption data because from a log P standpoint, molecular weight, you can't rule it out.

DR. MARKS: Okay. Well, unless we hear -- I guess the question is whether we could see that other report by tomorrow. Carol, you can scan or Wilbur scan it and get it.

MR. JOHNSON: Which report? It would be disodium without the sodium sulfide?

DR. MARKS: Yes, that's the one.

MR. JOHNSON: Okay. And will that substitute --

DR. MARKS: Yeah, and then (inaudible), would that be satisfactory, Ron, do you think?

DR. HILL: Didn't you say it's dioctyl?

MS. EISENMANN: Well, that was an old

name. It was diethylhexyl. They used to call everything octyl..

DR. HILL: Well, okay, the question is whether it's esterified on both ends or not.

MR. STEINBERG: Diethyl.

DR. HILL: It is.

MR. STEINBERG: It's a diester.

DR. HILL: That's what I thought. Yeah, I'm real familiar with that. Yeah. So none of these are. These are all monoesters. These are all half esters.

DR. MARKS: So you wouldn't be comfortable reading across?

DR. HILL: Of course if that one was clean, in all probability. I think it's designed whether we agree that we don't have dermal absorption, I'm pretty sure it would hang in the stratum corneum and not go in.

DR. MARKS: So let's just go with issuing a tentative report on the alkyl PEG sulfosuccinates as insufficient and we need the dermal absorption. Is that correct?

DR. HILL: Or repro tox.

DR. MARKS: Insufficient. Dermal

absorption or reproductive development tox. Okay. And we already addressed -- now, the inhalation we got no new data but are we okay?

DR. SHANK: Well, the boilerplate's in the discussion.

DR. MARKS: So we'll do the boilerplate. Okay. We're happy with that? Highest potential use in sprays is 2 percent.

DR. SHANK: If you do thermal absorption my suggestion was to do it on the disodium laureth sulfosuccinate because there are a whole bunch of (inaudible) and I think that's the leave-in, the most used ingredient.

DR. MARKS: So disodium --

DR. SHANK: Laureth sulfosuccinate.

DR. MARKS: Okay. It would be the lead if they're going to do dermal absorption, unless they had reproductive and development toxicity. Okay.

DR. SHANK: Right.

DR. MARKS: So tomorrow I'll move that we issue a tentative report on these sulfosuccinates; that there's insufficient data and it's insufficient to conclusion and what we

need is the dermal absorption or reproduction and developmental toxicity. In the discussion we'll point out that it's the disodium laureth sulfosuccinate would be the lead one if we're going to do dermal absorption. And the mammalian genotox is okay now and the inhalation tox we're going to address with a boilerplate.

DR. SLAGA: And even if we got the dermal and it wasn't absorbed we'd still look at the concern they would have to be formulated to be not irritating.

DR. MARKS: Oh, yes. Thank you. Formulate non- irritating. And I guess if it goes out as an insufficient with the formulate to be non-irritating at that point would be in the discussion, but if we ended up getting the dermal then it would go into the conclusion. Is that right? Yeah?

Okay. The next one I have is the citric acid group. Pink Book. Is that wrong?

SPEAKER: You missed one.

DR. MARKS: Which one did I miss?

DR. SLAGA: I've got alkyl glyceryl ethers. Is that correct?

DR. HILL: I wanted to get ahead. Oh, yeah. That's why -- I've got alkyl glyceryl.

DR. MARKS: Yeah, that's right. My pages stuck together.

DR. HILL: Your pages were wishful.

DR. MARKS: You got it. So in September a tentative report with safe as used conclusion was issued and now we're at the stage of issuing a final report on the alkyl glyceryl ethers with a safe conclusion. And the ingredients are listed on Panel Book page 59. Any comments?

DR. SHANK: Conclusion is okay. I have one comment on the discussion.

DR. MARKS: So Wilbur, do you want to comment input from a supplier that it's coming separate? Did you want to comment on that, Wilbur, on your memo? A copy of the draft final? Then there's this tentative report comments from Schuelke.

MR. JOHNSON: Yes. Yes. Basically, we had initially received a summary of the repeated dose toxicity study, an oral study on ethylhexylglycerin but it wasn't clear to me, you know, as to whether or not that NOAEL established

was from the primary reference or was it from Schuelke. But that has been clarified and the NOAEL is determined for ethylhexylglycerin in that study. And NICNAS, an Australian group actually considered the 50 mg/kg for their doses in LOAEL. So both viewpoints are included in that summary. And we also received the first 10 pages of the primary reference. So basically, that will replace the summary information that we had initially received from Schuelke.

DR. MARKS: Ron Shank, you were making comments. Did you want to react to that or you just had some editorial things?

MR. SHANK: Editorial.

DR. MARKS: Ron Hill, you abstained?

DR. HILL: Yes. And I'm still not having my concerns resolved. For one, the glycerol allyl ether, which is structurally dissimilar to the rest of them and has that nice ally moiety on the end; and two, there's no metabolism data so no solid basis for read-across on the isostearyl and the isodecyl. So one of the comfort levels was that these kinds of molecules with natural sort of carbon chains on them are apparently

relatively abundant. Actually, not apparently because that information is abundant in natural sources. But as soon as you put that branching on the end it's not as abundantly clear to me that given that there's no metabolism data, that these will be handled in the same say as the other compounds. So I'm still -- basically, I wrote a big note that said I don't buy read-across for those three ingredients.

MR. JOHNSON: Okay. Which three again?

DR. HILL: Isostearyl, isodecyl, and the glyceryl allyl ether. We don't have any direct data on any of them. I think it's a glaring deficiency that we don't have any direct data on any of those three. And I know people are tired of me saying if it's branched, it's different. But if it's branched, it's different..

DR. MARKS: So Ron, tomorrow, the Belsito team will be making the motion. I'll be seconding it. Do you want me to ask you to comment again?

DR. HILL: Yeah, because I'm going to go on those three unless something comes along stunning between today and tomorrow.

MS. EISENMANN: But you are okay on that?

DR. HILL: I'm okay with all the rest.

MS. EISENMANN: Because the other ones, the ones that are used --

DR. HILL: I'm perfectly comfortable.

MS. EISENMANN: -- that's isostearyl is currently used. Well, isostearyl is the only one that has a few uses.

DR. HILL: Yep. My vote will be exactly that. I'm good with all of them except those three.

DR. MARKS: Okay. Ron Shank, okay.

DR. HILL: Yeah, I had in my notes still needs chronic dermal toxicity. Is that what you wanted, those three?

DR. MARKS: Yes. And then I'm not going to -- you'll elicit which three you have problems with tomorrow.

DR. HILL: I will.

DR. MARKS: I assume Wilma will go around and ask for it but if she doesn't --

DR. HILL: I'll make sure.

DR. MARKS: Ron Hill comment. Okay,

next. The decyl glucoside group. Another Blue Book..

So in September we issued a conclusion, a tentative conclusion, that these ingredients were safe when formulated to be nonirritating. There are 19 of these ingredients. They're listed on page 35. It'll be Panel Book. And now we're at the point of issuing a final safety assessment. Are there any comments about that? Monice. Ron, Ron, Tom?

SPEAKER: The conclusion is fine.

DR. MARKS: Conclusion is fine. Okay, good. I just had, Monice, a couple editorials. And these are really rearranging. You'll see it in my book, bringing all the skin together up here. There is this one paragraph which I brought up and then when the issues are sensitization, the Panel knew that I wouldn't even -- I'd just delete that. This is editorial stuff. You'll pick that up. I don't even need to mention that tomorrow.

DR. HILL: Yeah, I raised a concern about, again, we didn't have -- there seemed to be a trend towards sensitization in the long chain molecules with branching at the end. There was

data suggesting that trend and we don't have any sensitization data addressing that.

I have to go back to last time's book to see exactly which ones were flagged.

DR. MARKS: Yeah, I didn't know that. A comment that you abstained from the vote this time.

DR. HILL: I don't remember what I said last time. It could be I was beaten to death by Lynn and Justin.

DR. MARKS: Ron, I would never beat you to death. I want you to --

DR. HILL: No, somebody who had a higher level of expertise with dermal sensitization than me apparently --

DR. SLAGA: Well, the two that you commented on were the branch streams were really not being used right now, too.

DR. HILL: Well, that might --

DR. SLAGA: Which would be handled that way, too.

DR. HILL: Yeah, it was --

DR. MARKS: Well, it's either Don or I in terms of beating on you Ron. And it wasn't me..

DR. HILL: Yeah, okay. No, I remember the specifics now. Sorry, I'm just reading notes. It was specific to the LLN One C12-C18 glucoside and one C18 branch glucoside, C14 glucoside and with smaller concentration for that C18 branch glucoside was the one that concerned me because it was at 43 percent whereas the others were up above -- well above 1 percent. They were 8 and 6 percent. That was.043 for the C18 branched.

MS. EISENMANN: But if you look at the description of that one in the table, it says that all concentrations for irritants -- there was not a third dose responsive to stimulation index versus concentrate. So it may not have been as clear as being a real sensitization reaction. But I thought you might want to put something about that in the discussion that, you know, this might be a little bit more. It might have a bigger potential for sensitization.

DR. HILL: The hits only came -- the hits only came from the local lymph node assay but there seemed to be an SAR sort of emerging out of that. And that's what caught my attention.

MS. EISENMANN: And that was the C18

branch?

DR. HILL: The C18 branch was the one --

MS. EISENMANN: So there's a guinea pig maximization test that shows not an irritant or a sensitizer on Panel Book page 45.

DR. HILL: Okay. Maybe that was what -- somebody brought that up last time. It might have been you or it might have been somebody. That was it. Yeah. And then I decided that was debatable. And in re-reviewing it --

MS. EISENMANN: Because it was also a human test, too.

DR. MARKS: Yeah.

DR. HILL: I didn't see that in the minutes.

DR. MARKS: So should we say safe, formulate, nonirritating? Just some editorial I have in the discussion otherwise.

Okay. Ron, is that okay?

DR. HILL: Yeah.

DR. MARKS: Good, thank you. Let's move on to -- now we get the citric acid.

DR. HILL: Well, those were pretty straightforward, weren't they?

DR. MARKS: Okay. Let me see. In September, the Expert Panel issued an insufficient data announcement requiring NHRIPT on citric acid concentrations of 35 percent. Inhalation toxicity, if available. So we're a little -- we have received the HRIPT and that was fine. Do we need anything as far as inhalation since we set it available or can we move this forward?

MS. FIUME: Dr. Marks, I just want to clarify something in the use table, the highest known use concentration of inhalation for the trihexyldecyl citrate is actually 4 percent. We know that that 14 percent is not inhalation. So I just wanted to make (inaudible).

DR. MARKS: Thank you. Okay.

DR. SLAGA: Safe as used.

DR. MARKS: Safe? Kay?

DR. HILL: Yeah.

DR. MARKS: Okay. So we would issue a tentative safety assessment. Safe. Okay.

Is there -- do we have anything that we need to include? Draft, discussion? Okay. You addressed the toxic effects.

Okay. Very good. Is that it? Ron Hill, you're still reading.

DR. HILL: Yeah, I am. No, I just had noted on here that we didn't have any repeated dose dermal toxicity. All the other evidence suggests that toxicology shouldn't be a problem. Systemic toxicology shouldn't just be a problem.

DR. MARKS: Okay. Citric acid. Safe. Next is ethanolamine. And again, what we have before us is a draft tentative amended safety assessment of ethanolamine and ethanolamine salts.

We'll take a one minute break. Maybe two minute break.

DR. SLAGA: Could be longer.

DR. MARKS: Could be longer. I have safe when formulated to be nonirritating.

Draft conclusion. So we move that a tentative amended safety assessment be issued.

Do you want to stretch again?

MS. EISENMANN: I have a comment in the discussion.

DR. MARKS: Sure. Go ahead.

MS. EISENMANN: I have a problem with

the word "itself." Diethanolamine itself because in Europe diethanolamine itself is not permitted so the levels of diethanol in the products are really driven by addition of other ingredients. And when you -- I thought at the last meeting you discussed -- you referred to the levels as discussed in the diethanolamine report which included levels when cocamide DEA are put in products.

DR. SHANK: I don't see what the problem is.

DR. MARKS: You're talking about the last paragraph?

MS. EISENMANN: You're using the word "itself." Yes, "itself." Because diethanolamine is not added to products.

DR. MARKS: Stated in the amount of three, diethanolamine available must be limited to the present practice of use and concentration. Oh, I see what you're saying, of diethanolamine itself. You're saying that sentence implies that it's actually used as a cosmetic ingredient?

MS. EISENMANN: Very rarely because it's not permitted in Europe to be used that way

but you can -- I mean, it can be in products because you're adding cocamide DEA or some other (inaudible).

DR. MARKS: How would you change that sentence?

MS. EISENMANN: At a minimum, delete "itself." But another option is just refer to the -- you would discuss -- at the last meeting I thought that you were referring to the DEA report because I provided trace and use information for that report. That was based on levels of DEA in products in which the DEA could then (inaudible).

DR. MARKS: Actually, if you get rid of "itself" it kind of answers it. Right?

MS. EISENMANN: That would be the minimum.

DR. MARKS: Okay. That's straightforward.

MS. EISENMANN: Okay.

DR. SHANK: You don't use (inaudible) normally.

DR. MARKS: Yeah. Any other changes to that sentence, Carol, that you would suggest?

I'll let you and Monice kind of wordsmith that.

MS. FIUME: I'll word it like it is in the TA report. I, for the life of me, don't know why I didn't --

MS. EISENMANN: (inaudible) has its own persona.

DR. MARKS: So Ron, Ron Hill, tomorrow I'm going to move that we issue a tentative amended safety assessment of ethanolamine and ethanolamine salts as stated on Panel Book page 27. Safe as long as formulated to be nonirritating. Okay?

DR. HILL: Yeah. Good.

DR. MARKS: Okay. Let's move on to the next one then. Unless did you have any other --

DR. SHANK: In the discussion..

DR. MARKS: Okay, good.

DR. SHANK: I think I would like to see it mentioned specifically that the safe for use in rinse-off only and that we do not include leave-on in this even though the table doesn't list, if I remember correctly, leave-ons. It's in the list here. Everything is just not reported. I think it would be better to say that we concluded

that these ingredients are safe for use as used in rinse-off because that's what we had considered, I believe.

DR. MARKS: If that's the case, shouldn't it be in the conclusion?

DR. SHANK: The table lists leave-on but then this kind of ambiguous not reported -- not reported doesn't mean that it's not right. It's just another way of saying no data.

DR. MARKS: Yeah. So you're concerned about leave- ons?

DR. SHANK: Well, our review with the current uses and the current uses that are listed in the data are rinse- off. Should we say in the discussion? I don't know that you have to say it again in the conclusion. Not a big thing. Okay.

DR. MARKS: Tom. Ron Hill.

DR. HILL: Yeah, I mean --

DR. MARKS: It's clear. I see what you're saying, Ron. It's clear in the table we don't -- it's not being -- we don't have uses in leave-on.

MS. FIUME: It's stated in text in the use section but I'd be happy to reiterate it in

the discussion if you want it there also.

DR. SHANK: I would just do that because it's a voluntary reporting system. In fact, what's not reported doesn't mean it's not in the leave-ons. And our review was based on rinse-off.

DR. MARKS: Okay.

DR. HILL: Yeah, and I mean, if it was just the MEA component, what bugged me about this whole report is that I'm not sure in some of these that the toxicology is necessarily driven by the MEA. And so, yeah, that helps spread that concern for me.

DR. MARKS: So Monice, you'll repeat that again in the discussion just so there's no -- do I need to bring that up tomorrow?

DR. SHANK: I don't think so.

DR. MARKS: Okay. Good.

DR. HILL: And we eliminated some on that basis but I'm not sure we got rid of everything that that might be true for.

DR. MARKS: The next Pink Book is the ethanolamines. And at the September meeting we reopened the safety assessment and added a number of ingredients. So page 17. We have a list of

the ingredients. That's Panel Book page 17. Are we happy with all those ingredients as listed?

DR. HILL: No. I'm trying to figure out how some of those got in there.

DR. MARKS: That's why I asked the question.

DR. HILL: This is the first time we've seen the mono - mono ethanolamine amides group after splitting, correct?

MS. FIUME: It came last time and split into two reports under one cover.

DR. MARKS: Right. And we really --

DR. HILL: Right.

DR. MARKS: And we really didn't address these. We just decided to split them out and now we're seeing it. So that's why I brought as the first issue is do we like all these ingredients that are grouped together on page 17?

DR. HILL: Maybe we didn't discuss them but I think I marked a bunch of these in the last book. I thought we had had a discussion about that but apparently not because they're all still in there.

DR. MARKS: So the isostearamide MEA,

myristamide MEA, and stearamide MEA were reviewed by the expert panel in '95. And it was concluded these were safe for use in rinse- off products. And then there was a limit placed on leave-on products to have no more than 5 percent free ethanolamine. But the maximum concentration, 17 percent for the isostearamide, myristamide and the stearamide MEA.

So, the following additional 47 ingredients are being included in a re-review of iso, myrista, and stearamide. Myristamide. So Ron, you immediately said I don't know this list..

DR. HILL: No, I don't.

DR. MARKS: So can we pair down some or did you want to add more?

DR. HILL: We have data that would allow us to read- across on simple MEA amides and when I say simple, I mean that can be fairly elaborated on the left. But some of these are not MEA amides at all. So if you wanted to look at the table of structures I can tell you which -- I mean, basically starting on page 27 because there's a lot on the next page that should certainly be kept. Everything on Panel Book page 27 ought to get out

of there in my opinion.

DR. MARKS: How about page 26? Those are all okay?

DR. HILL: Yeah.

DR. MARKS: Okay. And everything on 27 you would delete?

DR. HILL: Yep. Because they're no longer mono ethanolamine. You've got -- now we're at tertiary amines. Singling out the mono ethanolamine moiety in those doesn't make any good sense from a biological perspective.

DR. SHANK: They're not all tertiary amines.

DR. HILL: No, okay.

DR. SHANK: Yes, the second and third one are not. I think it just was because what was to the left was so structurally dissimilar from all these other --

DR. HILL: Let's go back to Ron Shank and Tom. Do you -- using the tertiary amines as a dividing point, do you like that idea? Just eliminate tertiary amines when we look at these?

DR. SHANK: Well, they're certainly different.

DR. MARKS: Okay. So let's go -- you said, Ron Shank, so the hexyl -- what is that? Hexyloxodecanamide. That's the number two compound there. That one's okay to include? Would you include that Ron?

DR. HILL: See, I wouldn't because those are beta -- it's an amide of a beta keto acid -- branch beta keto acid. I don't know how one should think about those but they're nothing like the rest of them. And I would suggest biochemically without having any data on anything that looks like that to read-across, which I think is where we're at. No reason to believe that those would necessarily be handled the same way as the others which would undergo a mega hydroxylation, rounds of beta oxidation, chopping down to something. These would result in something very dissimilar. I'm not sure what without any information but --

DR. SHANK: Yeah, based on beta oxidation of those compounds these don't fit the rest.

DR. HILL: I'm not sure what you'd be left with without having some metabolism data

but --

DR. MARKS: Okay. So everything on page 27 is eliminated. How about 28?

DR. HILL: So on 28, the only one I took out was myristol -- let's see. Similar structure. It's about halfway down. It's myristoyl/palmitoyl/oxostearmide/arachamide MEA.

DR. MARKS: Yep, okay. Ron Shank, eliminate that. Okay. And that's, again, because it's structurally dissimilar in the way it'd be metabolized is your concern. It doesn't -- I agree, it doesn't look like anything similar to the other ones. Okay. So that one. Any others?

DR. HILL: Yes. I wasn't sure quite how to think about the pantothenamide MEA. I wasn't sure that we'd be able to do read-across with the other MEA amides.

DR. MARKS: Pantothenamide. So that's the second one from the top?

DR. HILL: That's the second one from the top.

DR. MARKS: On page 29.

DR. HILL: On that one I feel a little

less strongly about taking it out but I'm not sure why -- on what basis we'd leave it in either.

MS. FIUME: Dr. Hill.

DR. HILL: Mm-hmm.

MS. FIUME: Just, is the fact that there is a (inaudible) acid, does that play a role in the decision?

DR. HILL: Not without knowing whether that's even relevant..

MS. FIUME: Okay.

DR. MARKS: So we, again, if we're going to err we want to err on the safe side. So remove that one, Ron Shank? Tom? You didn't say -- you didn't say --

DR. HILL: To me it's not a no-brainier. If we want to go back to what the rule is supposed to be but we've passed that point.

DR. MARKS: Yeah, well, if it's a no-brainer it's easy. We get rid of it. Okay. Because that's exactly right. If there's any question at all we remove it.

DR. HILL: All right. The other one on this -- there are two more on this page I wasn't sure how to think about either. One, two, three,

four, five, six. The sixth one down, which has got the MEA moiety as stearified with stearic acid on the opposite end.

DR. MARKS: So is that the stearamide MEAs?

DR. HILL: Stearamide MEA stearate. If we had direct toxicology data on that of some sort, any sort, I'd be all right with that, but I'm pretty confident we do not.

DR. MARKS: Okay. And then you mentioned one more.

DR. HILL: And the one right below it. Yeah, the one right below it is not a MEA amide at all.

DR. MARKS: Okay.

DR. HILL: And I took out the whole next page because they are also not MEA amides. Those are all -- I think the use of these is all different as well. These are probably low concentration emulsifying surfactants only would be my guess. But again, the rationale is there. They're not MEA amides.

DR. MARKS: Okay. So that's whittled it down dramatically. Tom and Ron, you're, okay,

again with that last page. We'll make those no-brainers. So the ingredients, I need to go to page -- what's that -- 26 through 30. Just to be, Ron, to make sure I heard what you said, basically everything on page 27 is eliminated. One ingredient on 28, the myristoyl (inaudible), et cetera; 3 on page 29; and then the entire page 30.

DR. HILL: Yeah, because then we're left with a list. And I think we have things that we can use for read- across in a biochemically reasonable and toxicologically reasonable fashion.

DR. MARKS: Okay. Ron and Tom.

DR. SHANK: That's fine with me.

DR. MARKS: Okay. And then in terms of do we -- since this is simple add-on no-brainers, when we reopen this can we just read-across and the data we have, do we need any more data to reach a conclusion that's safe or safe with limitations?

DR. SLAGA: Safe when non-irritating.

DR. MARKS: Mm-hmm.

DR. SHANK: Well, I would put some concentration limits based on (inaudible)

sensitization. Pardon me. So they're all safe as used except stearamide MEA, which is safe up to 5.27 percent because that's what was tested. What's used in deodorant is 15 percent.

DR. MARKS: Anything else?

DR. SHANK: That's it.

DR. MARKS: So the stearamide MEA safe up to 5 percent. Non-irritating. Formulated to be non-irritating. Formulate non-irritating.

DR. HILL: Now, I need to raise an issue but we don't have any reproductive toxicology on any of these.

DR. MARKS: Can you use --

DR. HILL: And we don't have biotransformation -- I mean, if we had even biotransformation data that suggested what happens to these is the amides are cleaved and we get fatty acid and we have plenty of data for those but I don't see that we have that data and I'm not sure that I think that that's what would happen anyway.

DR. MARKS: Can you use from the original report --

DR. HILL: That's what I was looking

for.

DR. MARKS: Page 49 of the Panel Book?

DR. HILL: So what's written up out here is the teratogenicity. It seems to be just dealing with the MEA itself.

DR. MARKS: There's no data. That would be an insufficient.

DR. HILL: There sure are a mess of uses.

MS. FIUME: Dr. Marks, I don't know if it's useful at all or not but in the DEA amide report, the diethanolamides, the reproduction data were also missing. And in that one there wasn't the same paragraph with discussion that's in this discussion referencing -- it's Panel Book page 25 if you accepted it there. I don't know that it will apply here to just the amides as well but right in the middle of the page about the lack of reproductive and developmental toxicity, that paragraph is accepted in the DEA amide discussion.

DR. HILL: For me that resulted in nothing. I mean, if you had something to hang your hat on in terms of what might happen metabolism-wise that would be one thing. I'm not

sure how that on the DEA amides report how that slipped past me, quite frankly. Because if that's what it says in the other report I'm not so comfortable there either.

DR. MARKS: So Ron Hill, you would prefer that this would go out as an insufficient conclusion and that we don't have the reproductive and developmental toxicity?

DR. HILL: Are we making a motion tomorrow?

DR. MARKS: No, the other team is making the motion but that doesn't change what we've concluded. So the question is do we go with this formulate nonirritating, the stearamine MEA at 5 percent limit? And then, of course, that was with a safe conclusion. Otherwise, it would be insufficient and we need reproductive and developmental toxicity to move forward with safe. And I don't -- it sounds like it's going to be difficult since this paragraph that Monice referred to talks about ethanolamine and then with amidases and skin these amides would be converted to ethanolamine and therefore that would address the issue.

MS. FIUME: I think that came from Curt, my recollection.

DR. HILL: So I don't know. Yeah, I mean, I don't know why that escape clause would have been used for the others because amidases probably don't even cleave those diethanolamine amides. I mean, all the evidence was that whatever biotransformation occurs happens at the other end of all those molecules or its conjugation, which is probably what happens here, probably removed by -- whatever penetrates probably gets removed by glucuronidation and billiary renal excretion depending on the lucidity and the size. It sure would be nice to have information to that effect.

And I don't know. We researched this a little bit. I don't remember what we concluded about amidases and the skin. Mostly in humans they're in litter and not much of anywhere else but I think there are some in skin. I just don't remember if we had any SAR data to tell us what might likely happen here.

MS. FIUME: I think this is something we've done a search on in the published

literature --

DR. HILL: You couldn't find anything pertinent. That's what I thought I remember. This isn't the first time I've asked about this I'm pretty sure.

DR. MARKS: So Ron --

DR. HILL: I kicked the can down the road.

DR. MARKS: Yeah. Ron Shank, do you have a way you would lean? Do you want me to just bring it up tomorrow as an issue?

DR. SHANK: (inaudible) aren't likely to metabolize this, then we need reproductive toxicity data.

DR. MARKS: Well, why don't I tomorrow, depending -- well, it doesn't depend on what the other team -- they'll make the motion and then I'll just respond to it. If it's safe, I can bring up the issue we have. We were struggling with. We discuss insufficient versus safe as a conclusion and we had difficulty dealing with a lack of reproductive toxicity data and then see how the discussion takes us. Does that sound like a reasonable way to move forward?

DR. HILL: Yeah. You can bring up the amidase, too.

DR. MARKS: Yeah.

DR. SLAGA: I just vaguely remember --

DR. MARKS: Skin amidases.

DR. HILL: Yeah, and I brought a paper with me but I need to reread it.

DR. MARKS: And let me see. That paragraph that you so cleverly put together was -- that was on page 25 where you talked about the --

MS. FIUME: The lack of reproduction data?

DR. MARKS: Yes.

MS. FIUME: Yeah. It's pretty much right in the middle of the page.

DR. MARKS: Yeah, right in the middle. And then you mention also the amidase is in there. So, yeah. It's on the second, so that's page 25. So we're -- so basically ingredients are the first issue that we're going to -- we're going to reduce the number of ingredients. And then once we get to that point then the question is the issue of this tentative amended safety insufficient

because of reproductive toxicity data versus moving forward with safe, formulated as nonirritating, and with a limit on the stearamide MEA at 5 percent.

Okay. Anything with (inaudible)?

MS. EISENMANN: (inaudible) insufficient data announcement first? I don't know (inaudible) review it's --

DR. MARKS: Well, no. Oh, yeah, it won't go to safe if we can't get over the hurdle.

MS. EISENMANN: I mean, does it go directly to tentative insufficient or do you --

MS. FIUME: I was going to check with Alan how it goes since it's a re-review.

MS. EISENMANN: I know. I would think it would go to an insufficient data announcement though.

DR. MARKS: Oh.

MS. EISENMANN: That reports directly to the tenant.

MS. FIUME: Probably but I didn't see anything since I needed to run it.

DR. HILL: Well, because, I mean, most of these are add-ons. Right? All but three.

DR. MARKS: Correct. Although doesn't this reproductive toxicity data apply for those original three?

DR. HILL: Yes.

DR. MARKS: We can, in terms of procedurally, we can, in terms of procedurally we can let Alan make that decision tomorrow. Sometimes he likes to move forward just putting out the report. We did that the last time with the use concentration that we moved forward rather than tabling it.

Okay. So we have that conundrum which we will resolve tomorrow. Okay.

DR. HILL: And it occurred to me, Monice, that the search might need to be done using lipases instead of amidases because it could be -- what could do that cleavage would be light pages that could handle amides and substrates, albeit with a substantially rate. But I'm not sure.

MS. FIUME: Okay.

DR. MARKS: We're back to the Buff Books and the aerosol inhalation toxicity. The boilerplate which, actually, Ron, you referred to

multiple times. And there were comments about that back and forth on the e-mail. Any other -- anything else in terms of -- and this was, yeah, Ivan, you're here. Good.

SPEAKER: What you did this morning by way of comments.

DR. SHANK: Just where there was a lack of inhalation data, we said we would use the boilerplate (inaudible) because it was variations from one report to another as to how the lack of inhalation data was handled. Now we're going to have a formal boilerplate statement for that.

DR. MARKS: Anything -- no, go ahead. I see editorial comments here. I'm going to capture those from Dr. Shank.

DR. SHANK: Okay. What's here my understanding is, different comments depending on where in the report it is placed.

MR. BOYER: We do have some suggested verbiage for the cosmetic use section. And then there's some variation depending on whether the report is tentative versus a final -- tentative with a request for any available inhalation data

versus tentative without that request. And then the final, suggested language gives a lot of examples. And those -- that kind of language would be captured in a final report, at least that's the intent with (inaudible).

For the final report and re-review summaries, so this is page 52 and 53 of the Panel Book. It seems to me there's more detail than is necessary and basically what we could say is that these particular issues would be handled on an ingredient by ingredient basis or case by case basis rather than trying to have so many fill-ins, I guess, whatever you call these.

DR. HILL: Fill in the blanks.

DR. SHANK: Yeah, probably having all of this fill in the blanks. This would be handled on a discussion of a particular ingredient rather than trying to create something that's applicable to everything.

The second comment I had was it's still, I have a feeling, we talk a lot about the effects of inhaled -- pardon me, respired particles and the effects on the lungs. And I get the feeling that we are not giving proper attention to the

nasal pharyngeal tissue --

SPEAKER: Or the bronchial.

DR. SHANK: Or the bronchial tissue. They are susceptible to adverse effects. Case in point, formaldehyde. All right. Very serious effects on the nasal pharyngeal tissue. So maybe you pair back at least a couple of sentences saying that just because a particular deposits in the nasal pharyngeal area doesn't mean there's no problem that's going to be sneezed or coughed or swallowed. Now, there may be a local reaction.

And I don't know where to put it but when we keep talking about the particles, we tend not to think of the chemistry of the particles. And it's more than just a particle of a certain size or aerodynamic property. Of course, that's very important for a deposition, but then once there's a deposit, the chemistry of the particle is important and I would like to see a little more emphasis on that. But it's a great document in coverage of the importance of coverage of the importance of inhalation toxicology. Very well done.

DR. MARKS: How do you want to proceed

tomorrow with this? Do we want to just say, Ivan, you've captured Dr. Shank's comments here today and we'll incorporate that in the next revision?

DR. SLAGA: I think we have to discuss it.

DR. SHANK: Is this going to be a panel discussion, Ivan?

DR. MARKS: It's in my notes here.

MR. BOYER: It's actually going to be brought forward to the beginning (inaudible). And the chairman --

DR. MARKS: No, it's actually -- well, if I'm looking at the right Tuesday, it's other discussion items. That's the first one. It's the second to the last.

MR. BOYER: There's going to be a motion to move it up to June 1st. And also there's going to be a suggestion to keep things very brief.

DR. MARKS: Motion to move it up. I think Wilma and Alan can do that without a motion. Let's see.

MS. BURNETT: It was discussed as the chairwoman's prerogative.

DR. MARKS: Pardon?

MS. BURNETT: The chairwoman's prerogative.

DR. MARKS: Yeah, (inaudible).

MS. BURNETT: That's what you call it.

DR. MARKS: Where's Kevin? I'll give him the feedback. Every time I see Dr. (inaudible) title as chairman, I keep wondering what he's trying -- what we're doing there. I prefer chair or chairman as you did, Monice. I forget to give Kevin feedback on that for the website.

I think Wilma is probably so immune to that now, she probably wouldn't, but I will for her. So at any rate it'll go up front. So then were there any other embellishments? What I'd probably do is say, Ron Shank, you would you give me your editorial comments. And unless Tom or Ron Hill want to say anything more --

DR. SLAGA: Well, we had that discussion about the (inaudible) in the past. And it's brought in here but there's still a concern about those areas. I agree with Ron.

DR. MARKS: Ron, but you can't wait five minutes?

DR. SLAGA: I'll try.

DR. MARKS: That's sensitive to you. It'll be -- let me see. If we start out -- yeah, I know..

DR. SLAGA: It's still going to be a shot discussion.

DR. MARKS: Well, it'll be even shorter if Ron is asleep. Ivan, you've heard this first. Let me see. This is -- probably get going around 8:30 I bet.

DR. SLAGA: It's 5:30 a.m.

DR. MARKS: Yeah, 5:30.

DR. SLAGA: West Coast time.

DR. MARKS: West Coast time.

DR. SLAGA: It's 5:30 a.m.

DR. MARKS: Yeah, 5:30.

DR. SLAGA: West Coast time.

DR. MARKS: Ron Shank, okay. I'm going to put you to make the comments. Thank you. You obviously can do it much do it much better than I can.

MS. EISENMANN: One comment we're going to bring u on page 55 of the Panel Book. It's about this paragraph. It says however characterizing a particle distribution from finished powder

products that are sprays. It comes from one of Dr. Roth's slides. It really did not concern about powder products in general and the methods of measuring sizes of powders, changes to powder, so it doesn't really reflect what the powder is. That's what the (inaudible) trying to get across. So if you disperse -- to measure a powder you have to just burst in a solvent or you disperse it through a nozzle to measure it, so that changes it. That was the point. It did not concern spray powder products. Was that useful?

MR. BOYER: That was my misinterpretation of what you said.

DR. MARKS: So are you going to mention that tomorrow?

MS. EISENMANN: Yeah, it's in his comments, so I don't know if that means we mention it when we provide comments this morning.

DR. MARKS: Okay.

MS. EISENMANN: I gave them to Ivan. And so -- I don't know how much they have to be considered. And then the other concern that was mentioned is that in the first paragraph in the boilerplate in the U section, it doesn't really

distinguish -- I don't know if you want to distinguish -- you're asking me at times to collect is it a pump spray or is it an aerosol spray? Well, maybe you should distinguish that the pump spray has a smaller tail versus the aerosol spray. If you want me to collect that information. I can distinguish. Maybe I should just be collecting spray products. But it would be nice if, you know, it might be useful to distinguish between the two types of sprays. Right now it doesn't in that paragraph.

DR. HILL: It seems to me we should because a manufacturer might choose in a case where there was some problem with inhalation, they might be able to get around that by using a pump spray where you didn't have droplets that could penetrate deep into the lungs even though it would be a small amount. I don't know.

MS. EISENMANN: That's what the committee suggested in our comments that it would be good to distinguish between. To let them know that there is a difference between the two types of sprays.

DR. HILL: Oh, yes.

MS. FIUME: Are you going to bring that up tomorrow then, Carol?

MS. EISENMANN: If you want me to. I mean, it's in our comments, written comments.

DR. MARKS: As long as it's captured. Thank you, Ivan. Well done. Okay. Anything else about the aerosols? And then last -- am I right? Lastly, the re-review summaries in the other Buff Book that has memo at the top. The bottom three reviewed summaries, are there any editorial comments about these? That's page 21 and 23. Any comments? None?

DR. HILL: They both look good.

DR. MARKS: Looked good?

DR. SHANK: Just change "while" to "although."

DR. MARKS: Okay. And who is -- Monice --

MS. FIUME: It's Alan's but I will forward -- what was the comment? I'm sorry, Dr. Hill.

MS. HILL: On page 23 -- it happens all the time, I keep putting my little comments in red. But on glutaral, under discussion, "while the

number of uses," et cetera, it's actually "although." "While" implies time comparison, and then he says it again, "Additionally while glutaral." It should be "although." It's not a big deal.

DR. MARKS: Did I miss any ingredients? Any discussion points?

SPEAKER: No, you did great..

DR. MARKS: Okay. Thank you everyone for your input. We are adjourned.

(Whereupon, at 3:46 p.m., the PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

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

(Signature and Seal on File)

Notary Public in and for the District of Columbia

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