125th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

BREAKOUT SESSION

Washington, D.C.

Monday, December 10, 2012

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P R O C E E D I N G S

DR. MARKS: We're going to being with Lou Brook safety assessment of tin oxide as used in cosmetics. Before us we have the Duryea final report on tin oxide and that's the IV valent tin oxide.

And our conclusion was that this cosmetic ingredient was safe in the present practice of use and concentration. We're at the point now of issuing a final report on tin IV oxide.

Comments, move forward, any editorial comments? Tom?

DR. SLAGA: Um, just related to the abstract. Overall, a great report. There was a sentence that got in here in the abstract. Expert concluded that poor (inaudible) is.

MR. JOHNSON: We're going to correct that.

DR. HILL: Cut and paste is always dangerous.

DR. MARKS: Any other comments? That's an editorial one, obviously. Proceed forward to issue a CNL report with a safe conclusion.

DR. HILL: I have a general kind of comment. I know we're trying to move along but this is applicable here and it's applicable to a number of things. Had a look at page 16 under the summary and there's a sort of one sentence paragraph. It says, "Tin IV oxide is greater than 99 percent pure."

We sort of see those kinds of statements on a more or less regular basis and I mean tin IV oxide is 100 percent pure but it might be 99 percent pure or 92 percent pure or 97 percent pure depending on the source, the supplier and the particular lot from that supplier. So, like I say this isn't the only report that that kind of sentence appears in but philosophically I'm wondering if we need to change the way that we make statements like that. Qualify it in some way to say -- I don't know how to qualify it. Or if it were up to me I would remove that statement.

And I don't know why we need specific gravity in there. I think it was just trying to incorporate something from chemical properties after the summary but I don't even know that that sentence needs to be there. But in general I think

when we make any statements about purity what's implicit is whose the supplier and, you know, how is it lot to lot?

Cause tin IV oxide is 100 percent tin IV oxide. That's it. You know? But in the real world that's not how it comes to us.

DR. SLAGA: But it does give you an idea that what the --

DR. HILL: Say cosmetic and --

DR. SLAGA: -- level of impurities you're potentially looking at.

DR. HILL: I get the point, okay and so if we're talking about the ingredient tin IV oxide, again, I still say this sentence sounds weird as written.

DR. SHANK: You could call it cosmetic grade tin oxide.

DR. HILL: That would be fine.

MR. ANSELL: Or what we would typically say is typically.

DR. HILL: Typically?

MR. ANSELL: Typically 99 percent pure or --

DR. SHANK: That doesn't work..

MR. ANSELL: -- which reflects it's not really a specification but, you know, reflects the commercial grade.

DR. HILL: Well, we don't have to make that decision today but I would just ask that that sentence be changed somehow to reflect reality.

MS. GILL: But, Ron, I think what you're getting at is the cosmetic grade of tin oxide should be 99 percent or greater or this cosmetic grade? The statement should reflect the cosmetic grade of tin oxide.

DR. SHANK: Right.

MS. GILL: As opposed to tin oxide that's a hundred percent pure.

MR. ANSELL: But we don't want to establish a cosmetic grade.

MS. GILL: Well, that's what I'm trying to clarify. If you say that and say should be --

DR. MARKS: So --

MR. ANSELL: But I don't think that's --

MS. GILL: Then you've established the requirement.

DR. MARKS: What we say in the conclusions it's safe in the present uses and

concentrations so I think deleting the sentence is better rather than trying to define --

DR. HILL: Right.

DR. MARKS: -- and then we have an impurity. So, I'd just delete the sentence.

DR. HILL: What would we lose by deleting the sentence is what I guess I'm getting at and this isn't the only report where I'll have a similar comment. But I just, philosophically, we need to pay a little more attention.

DR. MARKS: Yeah. Another other comments?

MR. JOHNSON: Yes. If that sentence is deleted, should there be any statement, you know, relating to the absence of information on impurities? Cause I know they probably aren't even expect to given the greater than 99 percent purity. But should there be any statement relating to impurities added to replace this deleted statement?

DR. HILL: So, what you're getting at -- maybe I just didn't catch this. So, we really lack some impurity information here? I thought we had --

MR. JOHNSON: None other than that statement about purity, we don't have any impurities data in the report. Excuse me.

DR. HILL: No, you have a section called impurities and it's a one very short sentence.

MR. JOHNSON: Yes.

DR. HILL: And what's the reference again? I'm sorry. It's a strange 1982 tin and its uses reference. So, I'm not sure even that that reference backs up that statement. So, I'm sorry that I didn't catch this before. It's kind of like peeling off layers but --

DR. MARKS: So, Ron Shank or Tom, do you see any difficulty in just deleting that sentence?

DR. SLAGA: If we do there's nothing under impurities.

MR. ANSELL: Well, there is it's just not in discussion.

DR. SLAGA: We need to put something. Huh?

MR. ANSELL: There is a lot of discussion. That 99 percent shows up in --

DR. SLAGA: Yeah.

MR. ANSELL: -- manufacturing methods. It shows up in impurities --

DR. SLAGA: Right.

MR. ANSELL: -- it shows up throughout the report. I think the objection was --

DR. HILL: The one in the summary. That's where I was objecting is the one that's written in the summary cause it just -- if somebody reads that without having read the -- I mean that's the problem but it just sounds strange in the summary.

MR. JOHNSON: Okay.

DR. HILL: It didn't hit me so strange on page 2. The other question I have in the -- are we done with impurities or you were going to move past it?

DR. MARKS: No, go ahead.

DR. HILL: All right this is in the discussion --

DR. MARKS: -- other edits..

DR. HILL: I cringed when we talked about creating, this morning when we talked about creating another boiler plate because I mean they're intended to be modified ingredient. So,

under discussion it says "the panel noted that 95-99 percent of droplets, particles was (inaudible) to any appreciable amount."

Maybe we can add in, "on the other hand the potential for inhalation toxicity is not limited to -- there seems to be, and like more importantly at which -- coupled with small actual exposure in the breathing zone and the concentrations of which the ingredients are used, along with the highly insoluble nature of tin IV oxide," that ought to be inserted in there. The available information indicates et cetera, et cetera, et cetera. The boiler plate, I think, is intended to be adapted to also the specifics of particular ingredient or ingredient categories in that.

MR. JOHNSON: So, let me just make sure that --

DR. HILL: So, what I was suggesting is two changes. One is we have the sentence "the panel noted that 95-99 percent", after appreciable amount I would put "on the other hand the potential for inhalation toxicity" because otherwise there's a sort of a transitional

disconnect. And then after "however coupled with the small actual exposure concentrations at which the ingredients are used along with the highly insoluble nature of tin oxide, tin IV oxide."

I guess that may be open to debate but I think that's an important one to capture there because --

DR. MARKS: Ron Shank, how's that sound?

DR. SHANK: I have no problem with that.

DR. MARKS: Okay. Ron and Ron, so is this important tomorrow to bring up for the edits?

DR. HILL: I think it's editorial but unless somebody --

DR. MARKS: Well, for the other team to hear it or just know? Okay.

MR. JOHNSON: I had accidentally I guess failed to include the website for the inhalation boiler plate so that will be inserted..

DR. MARKS: Right. Good. Any other comments? Okay, let's move on to blue book and this is a re-review on M. para-phenylenediamine and M. para-phenylenediamine sulfate. And the safety assessment was published in 1997 and the conclusion was safe as used in hair dyes at

concentrations up to 10 percent. We'll get to the self-testing issue in a minute.

But is there any need to reopen this, Rons and Tom? Do we have any data? I didn't see a reason to reopen it but I ask for your input.

DR. SHANK: I don't see reason to reopen either. The conclusion won't change so I don't see any reason. We're not going to add anything to it so I don't see any reason to reopen the document.

DR. SLAGA: All there is is it's being used less --

DR. MARKS: Less and the use concentration is one percent. So, it's well below what was in the safety assessment prior. I guess when we do the re-review statement under it the reason, obviously, is that we don't see any new safety data that would suggest it needs to be reopened. We will include the epidemiology boiler plate we do with all the hair dye ingredients now.

That's been developed since the original report back in '97. And then I think the self-testing is open at this point. I didn't get

a sense from that that we were going to proceed with a document. It's federal law..

Is that correct, Jay, or regulation that's at least at this point, so we're not going to change that in the CIR?

MR. ANSELL: Well --

MR. MILSTEIN: It is in section 601A, (inaudible) revisions of the NE.

DR. MARKS: Right. So, I think it was interesting what's going on in Europe and this attempt to refine what self-testing is. And acknowledging that it's not validated there, perhaps, could be active sensitization and the testing methods varies greatly but I don't know that as a panel we should be addressing self-testing.

Should we? What's your feeling, Tom, and Ron and Ron?

DR. SHANK: Well, I don't think we should address in a particular ingredient document. If you want to make a general discussion on the philosophy of self-testing, that should be independent of any one ingredient.

DR. MARKS: Right.

DR. SLAGA: I totally agree.

DR. MARKS: And do you feel that we should, going forward, develop our own CIR? We have a boiler plate now. It's not right, it was referred to what the CIR has commented but that was in accordance to the North American Group and that's really testing by dermatologists. So --

MR. ANSELL: I think your point was most relevant that perhaps considering the incidents and that we wouldn't recommend spending a lot of energy on this.

DR. SLAGA: Yeah.

MS. GILL: I just -- I was just going to say I just have one comment. Did you hear anything as a presentation this morning that reflected comments on some testing, whether or not it increased sensitivity? Anything changed based on what you heard this morning?

DR. SHANK: Well, I didn't understand how the allergy alarm test prevented a person becoming sensitized to hair dye. It's a different test but isn't the risk the same? That in order to determine sensitivity one risks inducing sensitization?

What I would like to hear is industry making an effort to find other chemicals for hair dye use that don't sensitize? Just find a way to get rid of this issue about sensitization. But if the incidents is so low there's not going to be a stimulation for that.

DR. SLAGA: Yeah.

DR. HALL: How often are there fatalities from this?

DR. SHANK: Zero.

DR. HALL: That's what I thought. So, back to the ingredient itself about, I'm sorry I didn't go back and look up the identity of the ingredient. But we had an ingredient that we reviewed that was part of an oxidative hair dye system where we captured some of the chemistry of what goes on. And that raised the question of what molecules are being generated under the conditions of use and then furthermore we had a presentation from industry. Was that Julie Skare's presentation? I'm not sure.

DR. SHANK: I think so.

DR. HALL: I think it was. But we looked at time courses of what chemicals were formed or

how fast the loss was occurred and because I had asked a question. Here's a small molecule under the conditions of use generating other small molecules that based on molecular weight and physicochemical properties would be highly likely to be absorbed into the skin.

We didn't capture anything like that here. Nor did we capture anything along those lines in the 2-amino 4-nitro 6-chorophenol report. No chemical function in the hair dye. What sorts of things might be formed, none of that's captured in the report. And the reason I ask that is if this is going to be published re-review I'm not satisfied with what we've got based on what we heard in that presentation. And, you know, basically meta phenylenediamine is being changed to other things. We're not capturing the toxicology of that and I'm not sure we're capturing --

MR. ANSELL: The question on the table is whether it's important enough to reopen to --

DR. HALL: Well, if we don't reopen it -- I didn't expect that we would be reopening it.

MR. ANSELL: Okay.

DR. HALL: But we're going to publish a re-review summary whether we -- or it won't be. Do we publish a re- review and we don't reopen?

MR. JOHNSON: Right. We do publish --

DR. HALL: You do publish a summary.

DR. MARKS: So, the summary that we publish is relevant to the concerns and issues. So, if there's anything perhaps with, and there I would say it's the self-testing issue but I'm not sure we want to address that in this --

DR. HALL: Here's why I raise the issue because this isn't the only time I'm going to say this. All the toxicology data is for meta phenylenediamine itself. If it's changed in the conditions of use which it is, it absolutely is, we're not capturing the toxicology of what it's changed to at all. And I'll just put that out there for food for thought at the moment on the basis that we're talking about publishing a re- review summary. And I submit that and a key component in the safety information was never captured in the '97 report.

DR. MARKS: Um --

DR. HALL: I'll have the same exact comment on this 2-amino 4-nitro 6-chlorophenol.

DR. MARKS: I would presume that the studies that were in here like sensitivity studies, that if there is a metabolite that was sensitizing it would have been captured in a toxicologic studies looks at sensitization. I assume that would be also applicable to other areas.

So, even though we may not know the exact, we don't have specific studies on the metabolites, we have the starting compound and then we have end points that show that it is safe. Is there --

DR. HALL: I'm not talking about metabolites. I'm talking about under the conditions of use because when it's using an oxidative hair dye it doesn't stay meta phenylenediamine. It gets converted to other chemicals.

So, if you just study sensitization to meta phenylenediamine you're missing whatever other chemicals are formed under the conditions of that use. Sensitization, toxicology, all of

that, now yes grant you if people are sensitized to whatever it's changed to under the conditions of use, that's going to show up as a sensitivity reaction. Is there any other toxicology that's important?

I can envision some that aren't necessarily systemic but might be in skin types of toxicology.

MS. LORETZ: I think what Julie Skare's presentation showed was and it was looking at reaction products in general across hair dyes and how short lived they are. And how --

DR. HALL: They weren't that short lived and some of them stayed there in the hair. Of course, if they stayed in the hair encapsulated then they aren't really a problem. But some of them weren't that short lived. I think what we got out of that -- what I got out of that was that time courses were not necessarily as expected, that some of them, I mean there was a definitive time course for loss of the -- in this case it would be meta phenylenediamine and formation of other chemicals in that all was within the time frame of somebody actually doing one of these

procedures. And so, was significant that those other molecules were formed.

We really never followed up on that with the particular ingredient that we reviewed. But I think it's a general issue that, at least in this report, there's nothing about what this thing actually does in the hair dye under the conditions of use. And maybe that varies dye to dye to dye but in general I think it's going to be doing a similar sorts of thing.

MS. LORETZ: Yeah, I think her presentation was trying to address that as an overall --

DR. HALL: It was. It was. And it was a very impressive presentation with some loose ends that they were -- my understanding was they were going to continue to work on. So, I don't know what we need to do at this juncture, if anything, but for the future in these kinds of chemicals I think that thought has to be there. That we need not only worry about meta phenylenediamine but whatever it might be changed to during the time course of the hair dying procedure and what that might do toxicologically,

both sensitization and anything that might be going on on the skin.

Facilitation of psoriasis or something like that, I'm just throwing something out there to be a little marginally facetious but because I didn't want to say tumor promotion one more time.

DR. MARKS: Uh, not reopen what you're suggesting --

DR. HALL: And I agree, yes. Not reopen.

DR. MARKS: That there perhaps should be something in the discussion of the re-review summary that the problem I see is how do you address that. Did you compose something that we could look at? And perhaps in the future if you could because if you say it's going to be applicable across multiple hair dye ingredients we maybe should see it. And then as a team and as a panel say this is what we sign off on or not. Almost like another boiler plate.

DR. HALL: Well, what I would like is that in the future any time we consider an ingredient that's in an oxidative hair dye that we capture the chemistry, which we did in that one

report. That's part of what raised it is that we captured the chemistry of what goes on enough to get some sense of what might be formed, what we know is formed, whether the time course is, what the actual exposures might be like and that's a whole other level that maybe that science isn't being done in industry and needs to be. Or, you know, I don't know that answer. But I think it's -- I'm posing that out there on the record to be considered for the future.

DR. MARKS: Okay. Ron, Tom? Ron Shank, Tom? Any comment or --

DR. SHANK: I think that's the generic issue for all oxidative hair dyes.

DR. HALL: It is.

DR. SHANK: And I wouldn't, for this specific ingredient open that question.

DR. HALL: For this one and for the other one that we'll look at today I agree with you that those concerns, for me, are substantially less. But going forward in the future there are other ingredients where there would be much greater concerns.

DR. MARKS: Okay. So, conclusion is not

reopen. It's going to be minimal discussion. In the re-review summary there's no pressing points in a re-review summary. We just attest to its safety.

MR. JOHNSON: Is there anything in particular that you might want to --

DR. MARKS: No. We aren't going to do this in metabolites. We aren't going to do the self-testing. So, it's going to be short and sweet.

MR. JOHNSON: Okay.

DR. MARKS: Okay next is a pink book methyl glucose polyethers and esters and depending on your short memory back in September, so just a few months ago we issued an insufficient data announcement asking for skin penetration data on the polyethers. And if absorbed, of course, the systemic toxicity. Gina talks RIPT on the methyl glucose dioleate and details the RIPT on the methyl glucose sesquistearate. And we did get some of this.

So, let's start with the skin penetration. Basically, we got a memo from Wilbur in wave two indicating a molecular weight is

around 722, so it indicated to be low penetration. Is my interpretation, Ron, correct?

DR. HALL: Well, I disagree with that. 722 is well within the penetrable range. I know it would depend on log P in conjunction with that and also affected molecular radius cause all of those would play in.

DR. SLAGA: Well, it would be, it's lower than if it was smaller molecular than that.

DR. HALL: Right. I think another thousand can penetrate the skin and then if you get a log P anywhere between maybe two and seven or eight, that was going to get at least into the skin, if not systemically through it. So, I mean that's --

DR. SLAGA: Well, it can get into the skin but it's the relative amount that crosses the barrier that we're worried about.

DR. HALL: I'm not very excited about anything in this agreed at category, quite frankly, in terms of toxicology, so, I'm not that worried. But I just -- I get irritated -- well 722 so it has a low potential to penetrate the skin, baloney. Baloney.

DR. MARKS: Ron Shank, do you think that's insufficient data, is -- are you concerned enough with the skin penetration that we do need a repro and a developmental tox or?

DR. SHANK: I think we need skin penetration data, real data not just --

DR. MARKS: Not real data.

DR. SHANK: -- an assumption based on molecular weight. Leave on use is up to 10 percent. So, I think we really need the absorption data.

DR. MARKS: Okay. So, that remains insufficient. How about the gene tox, Tom?

DR. SLAGA: I thought that was sufficient that they gave.

DR. MARKS: Okay.

DR. SLAGA: I mean it was only on, you know, one of the -- I think the PEG-120 but --

DR. MARKS: So, for the repeat insult patch, I thought that was okay. Now, the HRIPT was okay at zero point five percent and then the use on leave ons is zero point six percent. So, I thought that was close enough even though there had been some case reports of allergy to this particular ingredient, I thought the RIPT was

reassuring.

And then we also did get more details on the MG sesquistearate. So, I thought that was fine. So, I think we're down to one insufficient need. Is that correct then, Ron, Tom and Tom? We need the actual skin penetration data of the polyethers.

DR. SHANK: And then if it is absorbed --

DR. MARKS: Right.

DR. SHANK: -- either reproductive developmental tox or metabolism of the parent ingredient.

DR. HILL: Yeah, I'm a little irritated with myself. I mean, I don't know it's probably just a function that I didn't suggest separating out the PEGylated ones from the others and looking at them separately but too late now.
So -- consider them together.

DR. SLAGA: I didn't hear that, Ron.

DR. HILL: I said I'm a little irritated with myself that I didn't suggest back at the beginning separating out the ones that are PEGylated from the ones that are not so that we could look at these disparately but it's kind of

too late now and I think we just should keep on going forward..

DR. SLAGA: Penetration data, what do we want it on? We better be a little bit more specific.

DR. MARKS: We can't just say polyethers?

DR. SLAGA: The smaller one?

DR. SHANK: The one that has the maximum use?

DR. SLAGA: Yeah.

DR. SHANK: Which is 120 you said?

DR. SLAGA: PEG-120.

DR. SHANK: PEG-20 sesquistearate.

DR. MARKS: PEG-20.

DR. SHANK: Methyl glucose sesquistearate is used at percent in leave ons.

DR. MARKS: Which page are you on?

DR. SHANK: Panel book 38.

MR. JOHNSON: Now, Dr. Shank, that one is just classified as an ester in the table. In table 1, the methyl glucose sesquistearate.

DR. SHANK: In table 1?

MR. JOHNSON: Yes, uh-huh.

DR. HALL: Right and so we have updated use tables in wave 2 and sesquistearate which is not PEGylated I see up to four percent in leave ons. That's the highest of not five percent, well no, here's four percent in face and neck creams, lotions and powders and here is okay. Yeah, four percent in face and neck creams, lotions and powder, barley hand creams. It's the wave 2 supplement of page 185 in case you happen to have to have it. I don't know who has --

DR. MARKS: 180.

DR. HALL: 185 was in the supplement, the wave 2 that we got. It was updated usage data. So we have dioleate used in hair conditioners and foundati -- let's see. I don't know about hair conditioners, whether these were leave on or not. Doesn't say here but it's four percent. And the sesquistearate is four percent. Face and neck cream is et cetera, et cetera.

DR. MARKS: So, which polyether?

DR. HALL: It's not polyethers, that's the point. Just esters. The first -- if you look on that table in panel book page 3, the first five, six, seven, eight, nine, ten, ten ingredients are

not polyethers. They're not PPG's. That why I say I'm a little irritated with myself that somehow I missed this. Or I didn't miss it but it was okay.

And then there's no systemic tox of any kind. Only got human sensitization on one of them.

DR. MARKS: Right.

DR. HALL: We've got acute oral tox on two of them. Take back what I just said. We don't have any chronic tox. We don't have any chronic tox or sensitization except for one, two.

DR. MARKS: So, let's get back to the skin penetration data what's in our first draft report we said polyethers in general. And then Ron Shank, you specifically picked out --

DR. SHANK: The one with the highest use concentration in leave ons.

DR. MARKS: And that was --

DR. SHANK: That's PEG-20 methyl glucose sesquistearate according to table 4.

DR. MARKS: And that was page --

DR. SHANK: Panel book page 38.

DR. MARKS: 38. Okay.

DR. HALL: Let's see. We got some new genotox state in wave 2. Which one was that on again?

MR. JOHNSON: I didn't see any new genotox data, Dr. Hill.

DR. HILL: There is or there isn't?

MR. JOHNSON: No, no. Just acute oral tox, popular irritation and skin irritation and sensitization data for wave 2.

DR. HILL: Okay. I was thinking it was -- yeah I mean the ones that PEGylated, that's why I say the ones that are PEGylated, the chances of them having any sensitization are extremely low unless there would be impurities. But the other ones, let's see. We're going to have to do read across from the sesquistearate and the dioleate and those are clean, right?

DR. MARKS: Any other, so you're still processing, Ron. I was going to move forward to say what I would move tomorrow is we issue a, nail a tentative report on methyl glucose polyethers and polyesters with an insufficient conclusion that we need skin penetration data on the polyethers. Specifically we could use PEG-20

methyl glucose sesquistearate as our lead compound in that.

Now, do we -- another way is we could say that these ingredients are safe other than the polyethers. Is that correct? And it's insufficient for the polyethers? Or should we just put it all together?

DR. SHANK: Well, we don't have absorption data, skin absorption data. So, I think we need that. And if you don't want to do the PEG-20 methyl glucose sesquistearate, the methyl gluceth-10 and 20 also have high leave on concentrations.

DR. MARKS: Now, Ron Shank, was there concern that you divided the esters from the ethers that the esters would not be toxic absorbed? Is that --

DR. SHANK: No. I didn't separate it.

DR. MARKS: Oh, okay. So, in the report here it really should be you want dermal penetration data on these ingredients not just the polyethers.

DR. SHANK: Correct.

DR. MARKS: Okay. And if you have the

methyl gluceth-10 or gluceth-20 would you feel comfortable then or --

DR. SHANK: I would.

DR. HALL: So, I guess going back to this methyl glucose sesquistearate has a molecular weight of 460 dums. Like I said, I don't have any big toxicology concerns quite frankly, but the sesquistearate caprylate, the ones that are just esters, that I would be concerned would have any systemic anything. And you were looking at concentration of use but we didn't have this updated table which shows the couple of these. Sesquistearate has molecular weight of four point two and is used up to four percent in leave ons.

Dioleate up to four percent in hair conditioners and here's the mark of the (inaudible).

DR. MARKS: So, can we -- can I move forward tomorrow on that issue with a tentative report on these and the units that the data is insufficient and we need skin penetration. And if there is penetration then we need the appropriate toxicologic studies including reproductive, developmental, et cetera. Does

that sound -- and then if they ask for a lead compound we can discuss that. It looks like there are now perhaps three candidate lead compounds, the MG- 10, the MG-20 or PEG-20 MG sesqui.

DR. SHANK: Fine.

DR. MARKS: Okay. Any other comments, Tom or Ron?

DR. HILL: Well, again, I ask the question we seem to be talking about a PEGylated one as a lead compound and I'm asking about the ones that are simple esters. So, the first in the table on page 3 are not PEGylated. I say PEGylated, I mean PPGylated. They're not polyethers or PEGylated. Just simple esters with many cases molecular weights that would allow for dermal absorption and do you have any toxicological concerns..

DR. MARKS: So, you're talking about the methyl glucose caprylate --

DR. HILL: Methyl glucose caprylate down to methyl glucose sesquistearate. And it appears that the two that are in common use are the ones that are checked there on oral acute toxicity which is mainly the dioleate and the

sesquistearate.

If you look at the, I guess, I didn't -- when I looked at this before I thought I can't dream up any good reason to worry that they're toxic but I'm not a toxicologist by original education. Let's put it that way.

DR. SHANK: Well, is it known that methyl glucose does not interfere with glucose metabolism?

DR. SLAGA: There are glucose derivatives that definitely have effect on glucose metabolism but I don't know about the methyl glucose.

DR. HILL: I think that came up in here. So, you know, I think it would be in concentrations much higher than delivered from dermal use of these but -- to get that amount of methyl glucose delivered even assuming those esters hydrolyzed which we don't know because we don't have data.

DR. MARKS: So, Ron Hill, do you have any problem with moving forward tomorrow with issuing this tentative report with an insufficient data in skin penetration?

DR. HILL: No, and then we can discuss what we might or might not need maybe in conjunction with the toxicology expertise on the other side of the table.

I just know we have no chronic tox of any kind.

DR. MARKS: Okay. So, insufficient data conclusion. Any other comments? Okay. Next is PEGylated oils.

In the September meeting we issued a draft final amended safety assessment of the PEGylated oils with a conclusion as safe as long as formulated to be non-irritating.

Any problems with that conclusion?

DR. SHANK: No.

DR. MARKS: Okay. Then I think that at your editorial comments, there's a huge number of ingredients on page, or large maybe not huge. A number of ingredients on page 22 and 23. I wanted to be sure in my notes, the aerosol inhalation framework, Ron, did (inaudible) put in the discussion, Ron Shank and Ron Hill, did that look fine from your perspective? I know you read through it. So, other than minor editorial

comments is there anything that needs to be done with this report?

DR. HILL: Well, the concern I raised last time that we under category, take, for example, toxicokinetics and acute toxicity. So, if we wanted to look, go on page 17 and say something like, under toxicokinetics, toxicokinetics data were available supporting the safety of alkyl PEG ethers and castor oil as summarized in table 2. And my comment again is that that's totally irrelevant. Same under acute toxicity. We've got alkyl PEG ethers and castor oil and so what?

So, it's kind of the truth in advertising that those are not components that are likely to be liberated. They are not -- I don't see how those support the toxicology of this group of compounds at all and so, we could mention that in the discussion. But in terms of toxicokinetics, acute toxicity, reproductive, developmental and genotoxicity we're talking about toxicology for castor oil and PEGs and alkyl PEG ethers. So what?

Again, to me that doesn't support the

toxicology of this group in any way. At least convincing way, compelling way, useful way. And I don't think it's needed and it don't think it detracts from the report but it's like false advertising as it sits right now.

DR. MARKS: Well, I would say, Ron Hill, if I look at this and deleted those that from the repro and the gena then I'd say what, how can you say it's safe if you don't have something under those sections. So --

DR. HILL: Because there is. Because it says the genotoxic, if you look at genotoxicity we drop down. We have the PEG-60 hydrogenated castor oil. And there is a genotoxic study. I mean we're doing massive read across but I guess that doesn't trouble me in this case.

DR. MARKS: Ron, Tom?

DR. SLAGA: I didn't have any trouble.

DR. SHANK: I had one comment on the discussion page 21, panel book 21 paragraph, the fourth one down. It starts with "while the safety assessment," which should be "although the safety assessment." The second line says, "the group of ingredients includes PEG-4" which is a mixture of

which includes PEG-2. And I think the impact of that needs to be pointed out. Add right there after PEG-2. PEG-4 was found to be safe as used in cosmetic formulations.

So, if PEG-4 if safe, PEG-2 should be safe.

DR. MARKS: Okay. Ron Hill, so tomorrow when we vote on this there will be an opportunity for discussion. Do you want to make that point again tomorrow? I'll defer to you when Wilma asks for comments.

DR. HILL: Sure. I'm just trying to struggle with looking at the structure of these polymers why those would be relevant. That's all I was getting at.

DR. MARKS: Okay. Any other comments? So, I think those just couple of editorial comments that Dr. Shank mentioned.

Okay, so let me see. I assume tomorrow I'm going to second the motion that these ingredients are safe as long as formulated to be non-irritated.

Next, let's see.

DR. SHANK: Nylon?

DR. MARKS: Nylon. Let's see what we have. So, of course in carrying concentrate of 35 percent. So, in June of this year the panel issued an insufficient data announcement on the safety assessment on the ingredients. The first was the need for irritation and sensitization of nylon 12 at use concentrations. We now have that I believe and so, I think that data has been met.

We have I think a 35 percent HRIPT. So, I thought that was okay. Other relevant toxicologic data and genotox and none of those two data needs were met the best I could tell. So, Tom, Ron, Ron, comments? Seems like we would proceed forward with a tentative report with insufficient data. Does that sound?

DR. SHANK: Yes.

MR. ANSELL: The genotox data was provided in wave 2.

DR. MARKS: Was it?

MS. BURNETT: For dodecanolactam. But not for --

MR. ANSELL: For the --

MS. BURNETT: -- for yeah. But they're asking for nylon-12 and we didn't receive a lot

of that data still.

DR. SHANK: For the ocular irritation we have data for up to five percent nylon-12 but it's used in eye products up to 25 percent. Nylon-6 is used up to 20 percent.

Jim, there's a difference between five percent and percent. Impress you?

DR. MARKS: The numbers impress me. I guess the lack of case reports of problems --

DR. SHANK: Fine, fine.

DR. MARKS: I was I think having the irritation and sensitization up to 35 percent is reassuring to me. So, 35 percent is obviously greater than 20. So, insufficient --

DR. HILL: Well, the case I tried to make the last time is that I don't know why you would need information like genotoxicity on the nylon itself based on the characteristics of the molecules. And I was after, which was provided at least in the case of two of the monomers, the dodecanolactam, is that it?

DR. SHANK: Yes.

DR. HILL: Yeah, dodecanolactam and also the amino and decanoic acid which I'm not

sure we have comfort level. That's a nylon-11 monomer which is, there's a new insertion on page 27. Again, we're now down to the limits of my toxicology expertise in terms of what does it mean in this particular species of rats and it, male not female. Yeah. And IARC on that one determined not classifiable.

But then, you know, we're talking hypothetical concentrations of monomers within the polymer. So, effectively we're looking at impurities rather than the nylon itself. But I don't know why we would believe that there should be any problems with the nylons themselves because they're really stable. We wouldn't expect them to diffuse around the body. I can't even come up with a way that they would get into the body.

DR. SLAGA: We do have carcinogenicity on two of the monomers --

DR. HILL: Yes, yes. So, the nylon-6 monomer is good and what's the epsilon caprolactam, the nylon-11 monomer indeterminate but it's the kind of concentration we might expect for them to arise, I doubt there's any problem

there. But again, that's, I feel like that's not for me to say. And now we have new data on the dodecanolactam that suggests we're okay there. No genotox. I think that's an HPV chemical.

DR. MARKS: So --

DR. HILL: The nylons themselves, I'm just -- I don't know why there should be any worry.

DR. MARKS: So, it's the monomers.

DR. HILL: Yeah, the potential for monomers. Which for me, even with this one question mark, for me that's still resolved.

DR. MARKS: So, Tom, what do you feel about that?

DR. SLAGA: Well, I think we obviously, if we have carcinogenicity we don't need the genotoxicity. The only thing we don't have is the dodecanolactam one, right?

MS. BURNETT: In the wave 2 there was the HPV report that had data that indicated that genotox was not needed.

DR. SLAGA: Was not. Okay, I didn't catch that.

DR. MARKS: That's what Jay was mentioning earlier on the wave 2 so --

DR. HILL: IN case you want to look at that later the supplement page is 223 where the memo is. And then, I think the reference --

DR. SLAGA: If we have that then that to me, we don't need genotoxicity.

DR. MARKS: So, in this case there wouldn't be an insufficient data.

DR. HILL: I don't think it is. I'm satisfied.

DR. MARKS: Okay. And how about other rele -- there was this very -- I guess you would say other relevant toxicologic data. And all that is repeated, those that's all relevant to its carcinogenicity. So, it's really, there wasn't other things like repo or development or anything. So, actually it sounds like we could move for a safe.

DR. SHANK: Safe.

DR. MARKS: -- rather than insufficient. Is that correct?

DR. HILL: As long as nobody's troubled by the --

DR. SLAGA: Six percent right?

DR. MARKS: Pardon?

DR. SLAGA: What only safe as used or set a limit?

DR. MARKS: From an irritation sensitization I'm happy with as used even with the caveat that Ron mentioned with the eye. But do you have any problems with any of the other to set a limit?

DR. SHANK: I do not.

DR. MARKS: Okay. Well, let me change for the record of this team meeting, I'm going to change that initial conclusion of insufficient. Tomorrow I will move that this -- we issue a tentative report on nylon of safe as used.

Okay. Good. Whoever has a watch can tell me how close we are.

DR. SHANK: It's a quarter after eleven.

DR. MARKS: We got plenty of time.

DR. SHANK: We got more time..

DR. MARKS: We can get through this stack. Next, 6-hydroxyindole. So, this is your favorite group of chemicals, Ron Hill. It's the oxy beta hair dyes.

DR. HILL: Yeah.

DR. MARKS: And you were --

MS. BURNETT: Dr. Hill?

DR. HILL: Yes?

MS. BURNETT: I pulled up, when you were talking about the presentation that we had last year --

DR. HILL: Yes.

MS. BURNETT: I pulled up the report that referred to it. If you'd like to see what we wrote in that report, you're welcome to.

DR. HILL: Yeah, in fact --

DR. MARKS: Why don't you just go around?

MS. BURNETT: I can come to you..

DR. MARKS: Okay. So, this is a draft report on 6- hydroxyindole. This is first time we reviewed this oxidative hair dye. And the first time we've seen this report. And so all these -- and this is going to be Ron Hill's opportunity moving forward to address the issue of metabolites. But at any rate, were there any needs, Tom Slaga and Ron Shank?

DR. SLAGA: I had none.

DR. SHANK: No. No needs.

DR. MARKS: No needs.

DR. HILL: Me neither, but I would like the nitrosation expert to comment on the fact that this is not a secondary amine nor is an arylamine. And so, in terms of writing the chemistry we need to fix all of that. The not indoles nitrogen stand alone. It's a nitrogen containing hetero cycle specifically 6-hydroxyindole. And I'm not sure how, I mean we shouldn't have language that said, hey this is secondary amino. It behaves like one because it certainly is not.

DR. SHANK: But this is not nitrosable?

DR. HILL: It is nitrosable but it is secondary amine and I don't know how indoles when they nitrosated behave toxicologically. So, we need to capture information that's very specific, not boiler plate but very specific to 6- hydroxyindole in terms of what's known about nitrosation and toxicology flowing from that.

Not even saying hydroxyindole or 5-hydroxy. It's specific to 6-hydroxyindole. What happens if you nitrosate that? Or we just say we make sure this doesn't happen.

DR. MARKS: So --

DR. SHANK: It says the majority of n

nitrosive compounds that have been tested for carcinogens are strongly positive.

DR. HILL: Yeah, I mean on the safety but I mean erring on the side of safety, the precautionary principle, I totally agree with you. Yes. I mean -- I'm not saying we should take that out. I'm just saying that we shouldn't rely on secondary amines as an index because this is not a secondary amine nor is it an aeromine. I bring your laptop back in there. I'll let you retrieve it in a second.

DR. MARKS: So, before we get -- is there anything, Ron Hill, when you're bringing up that issue of the nitrosation that's going to prevent this from moving forward --

DR. HILL: No, sir.

DR. MARKS: Okay. So, we would issue that I presumably am going to second is issuing a draft tentative report on 6-hydroxyindole with safe as used.

DR. HILL: With again, the caveat that I don't know what happens to that sucker in oxidative hair dye conditions and it would have been nice to capture some chemistry so we know

what things are being formed and what the time courses are.

DR. MARKS: So, this is the first time we've seen this and it's going to be issued as a draft tentative report. So, we're moving forward. We aren't amending or going back. So how --

DR. HILL: For me that would be an insufficient data. For me it's an insufficient data whether it becomes sufficient when the literature search is captured in there which I did not do at home. I apologize.

MS. BURNETT: Sir, I'm confused. What's the sufficient, insufficient?

DR. HILL: I don't know what happens to 6- hydroxyindole when it's used in an oxidative hair dye and what molecules might be born and whether we've captured the toxicology of that. I don't know if that information is publicly available or not because I didn't do that search before I left home.

DR. MARKS: And as I understand it, Ron Hill, your concern is that just testing 6-hydroxyindole without having it oxidated or in the --

DR. HILL: This is what I'm asserting.

DR. MARKS: -- similar form in which it's applied to the hair and subsequently having scalp exposure, there may be something else going on there. We aren't --

DR. HILL: That's what I'm getting at, yes. Absolutely.

DR. MARKS: So, Ron Shank, and Tom Slaga, do you have the same concerns?

DR. SLAGA: Well, I have no concern about the parent compound.

DR. SHANK: Me neither.

DR. SLAGA: We have sufficient genotoxicity, irritation, carcinogenicity. Now under oxidative conditions I don't know. I can't, I can't argue if something would happen but --

DR. SHANK: Well, we know --

DR. SLAGA: If it does it's probably a small amount, right?

DR. HILL: You know if, it probably is not. In fact, it's probably almost completely consumed and if you formed just a bunch of insoluble polymers then who cares? Nothing's going to happen. But if you form absorbable

molecules under those conditions that could sensitization I guess we'd see that. Again, probably isn't going to kill anybody. But again, do you form things that cause a problem in terms of skin biology? That's the question mark that I can't answer in terms of concluding safe.

DR. SHANK: Several years ago we had a presentation to the panel addressing this question because this has been a question for a long time. And the bottom line was that the reaction products are sufficiently reactive to react with the keratin in the hair and in the stratum corneum very, very rapidly. And the amount of free product would be very small.

DR. HILL: That is not what I got from that presentation we had most recently. That's not the conclusion I drew from that at all.

DR. SLAGA: I agree with Ron Shank that's what the last presentation a long time ago was.

DR. HILL: We had a presentation less than two years ago and that is not what the bottom line conclusions were. I thought that was Julie Skare's presentation. I probably have that; I

didn't bring that slide set with me this time. I have been bringing it every time until now and I don't know why I didn't grab it and bring it. But it had time forces in there in the slides and that's not what it shows.

DR. MARKS: Jay?

MR. ANSELL: Well, I think our conclusion from the presentation is similar. They were highly reactive. Reacted nearly instantaneously with the hair, did not penetrate and that it really hasn't been an issue.

DR. HILL: I would ask you to go back and look at that slide set carefully because that's not what it showed. I'm just telling you it's not.

DR. MARKS: So, Jay -- is it possible since what Ron Hill is hearing from the Julie Skare, Skare?

MS. LORETZ: Skare.

DR. MARKS: Pardon?

MS. LORETZ: Skare.

DR. MARKS: Is just ask that very specific question of her, not what she presented on the slides but is her interpretation --

DR. HILL: Is she here?

DR. MARKS: No. I'm going to email her.

DR. HILL: Okay.

DR. MARKS: I mean this is just going as a draft tentative report so we can get that answer --

MS. LORETZ: We can get that in by Friday.

MR. ANSELL: But she's retired..

DR. MARKS: Pardon?

MS. LORETZ: But we can still get that input.

MR. ANSELL: Yeah, we can get that input. It's not --

DR. HILL: Thank you.

DR. MARKS: She's retired did you say?

MS. LORETZ: Julie is retired, yes.

DR. MARKS: Oh, okay.

MR. ANSELL: We'll conference Julie.

DR. MARKS: At any rate, I would suggest that we get specific and obviously it would come from Halyna or you, Jay, as to what the question -- cause this is going to keep coming up again and again and we need to get some sort of --

DR. HILL: And she had multiple ingredients in there but I do not remember if 6-hydroxyindole was one of those that was included. I don't remember it being there but maybe it was and I just --

DR. MARKS: Well, it doesn't -- I think you're asking a much more general question, Ron Hill, is are the oxidative products of these hair dye of concern. And you're mainly how much are they around? How reactive? So --

DR. HILL: And the answer is going to be chemical by chemical because it's going to depend on the chemical kinetics under the reaction conditions in the hair. And we've got to capture that information if you want to conclude safe. That's all I'm saying.

DR. MARKS: Okay. Well, let me see here. Tomorrow, I presume I'm going to be seconding a motion and a draft tentative report on 6-hydroxyindole the issue safe as used and then again when the comments come up, Ron Hill, you can either wait until we get one step further along. Because obviously then we're going to have a draft final report to see, probably at our next meeting.

DR. HILL: Okay. Just say what's written here I do not agree with a hundred percent?

MS. BURNETT: The master --

DR. MARKS: Okay. So --

DR. HILL: What was written in that last report --

DR. MARKS: I presume we'll have the hair dye epidemiology boiler plate, the nitrosamine boiler plate, is that correct, Tom, Ron?

DR. SLAGA: Yes.

DR. MARKS: Christina?

MS. BURNETT: I'm sorry.

DR. MARKS: We have the two boiler plates, the nitrosamine and the hair dye that will move in. And of course we know all these oxidative hair dyes are either moderate to strong sensitizers but they're basically exempt. And did we have a use table in here or did that come in wave 2 and I missed it?

MS. BURNETT: It's only used by the hair dyes so it's written in test.

DR. MARKS: Oh. Maybe I did capture that

then.

MS. BURNETT: It's head over to page 8. It used in 105 hair coloring formulations and its maximum concentration is point five percent.

DR. MARKS: Point five. Good. Because that's what, that's also what the Europeans have said is their recommended limit.

DR. HILL: Where are you on that page?

DR. MARKS: This is panel book page 8.

MS. BURNETT: Top of page 37.

DR. MARKS: Thank you. I must have skipped over that. I was highlighting other things.

MS. BURNETT: When you're used to a low play ingredient reports for lots of tables --

DR. MARKS: Okay. We're face again with self- testing. Now, this one we have the opportunity. Do we want to have anything in the discussion acknowledging that self- testing has not been validated, it varies and it is an FDA regulation? Am I saying that correctly?

MR. ANSELL: Well, required by law in question the --

DR. MARKS: Yeah.

MR. MILSTEIN: It's actually part of the act.

DR. MARKS: Yeah, so it's a law not a regulation. Yeah. I would say no but --

MS. BURNETT: Well, we have it written -- we have the hair dye labeling cause in the report itself.

DR. MARKS: Right.

MS. BURNETT: If you want to add more to the discussion we can.

DR. MARKS: Rons, Tom, as is?

DR. SLAGA: As is.

DR. SHANK: As is.

DR. MARKS: Okay. So, we're going to move forward tomorrow. Presumably, I'm going to be seconding a draft tentative report safe as used.

Next is -- actually it's splitting out. This is the first review of this draft report entitled source amino acids. I'll ask and this of course was split out from the safety assessment of the alpha amino acids when we looked at amino acids as a large group. And now we have three, there will be three safety assessments, the alpha

amino acids, the source amino acids and the hydrolyzed source amino -- I mean source proteins here.

So, did you like the title "Source Amino Acids?"

DR. SHANK: It didn't mean anything to me but maybe to others it does.

DR. MARKS: So, I kind of wondered whether we could put on there and again, I just throw this out. It occurred to me it didn't mean much to me if I were doing a search. Do we put plant and animal derived amino acids? I don't know. That's --

DR. SLAGA: To me that would be better because source, it depends on the source and you know, out where the multiple type is. You know, if it's from silk or it's from this or that. I don't think that source is needed either.

DR. MARKS: So, is this clear? Would you just put it, Tom, as assessment of amino acids or do we have the alpha amino acids? Or would you put plant and animal derived?

DR. SLAGA: I'd say plant and animal derived.

DR. MARKS: Okay that's how I -- we'll see what happens tomorrow in discussion.

MS. BURNETT: The chemist came up with that.

DR. MARKS: Yeah, where is the chemist?

MR. ANSELL: Well, at least in introduction he said he wanted to distinguish that there were not mixtures from various sources but unique sources. But I don't know that that needs to be carried over to the title.

DR. HILL: Well, I think it should say mixture somewhere in the title. I think it should say amino acid mixtures from natural sources or something like that.

MR. ANSELL: Accordingly the group is given the name source amino acids indicating that they came from a specific source. So, I'm just reading from the report.

DR. MARKS: Yes.

MR. ANSELL: So --

DR. MARKS: That's, the two sources are plants and animals. I thought --

DR. SLAGA: I don't think a mixture of amino acids from plant and animal source.

DR. MARKS: Okay, so, we'll let -- that isn't crucial at this point but I was left, Ron Shank, like you. Source just didn't do much for me.

Okay. We'll let Bart defend that some more as he gets over here.

So, Tom and Rons, page 9 and 10, do you like all these ingredients? Add more, delete? Is that a good spot to go? I might just pick panel book page 9 and 10 have a list in table 1 of the ingredients. And I don't have anything on wave in here now. So, Christina, you didn't sneak any other ones in here from --

MS. BURNETT: No.

DR. MARKS: -- from non-plant and non-animal sources, okay.

Do you like all these?

DR. SLAGA: If that's the source.

DR. SHANK: I don't have a problem.

DR. MARKS: Yeah. Okay. So, the ingredients are okay. So the next question would be what needs do we have? I have no irritation and sensitization on anything in here. So, I'd like to see one RIPT.

DR. HALL: So, in terms --

DR. MARKS: But Tom and Ron? Are you happy with --

DR. SLAGA: Formulated to be non-irritating.

DR. MARKS: How about sensitizing? Did I miss it Christina? Is there anything on sensitization or irritation?

MS. BURNETT: No, we did receive a comment from the Counsel that we could carry over just a summary of the findings of the alpha amino acids if you'd be okay with that.

DR. MARKS: So, why did we split them out then if we thought that we could just do the safety on the alpha amino acids and carry it over?

MS. BURNETT: Yeah, I think until we finalize it, I think we were not sure how we felt about the D and the L and anything that isn't an alpha amino acid that is in these.

DR. HILL: To me, that's not the issue at all. The issue is under the conditions of hydrolysis, let's see beyond tryptophan, I'm not sure any of them will be oxidized but there may be hydrolysis. But in many cases we may not have

complete hydrolysis here which is noted.

So, what for me is a major question mark is if we've got a number of small peptides in there or maybe not so small depending on the production conditions, those are the other things where I could see we might potentially have sensitization issues.

MS. BURNETT: You would like to see composition --

DR. HILL: And then also, if it's from an animal source, what are our assurance that we don't have prions in there, you know..

DR. MARKS: Well, that I have prions as a boiler plate.

DR. HILL: Yeah, I'm sure.

MR. ANSELL: Well, it would also be illegal.

DR. HILL: I know it would be illegal but -- and that's presumably --

DR. MARKS: Well, that's -- I have prions as collagen in here, and other animal sources --

DR. HILL: Yeah --

DR. MARKS: -- so do we just put the

prion boiler plate, right? Or if we know it's manufactured in such a way that prions would not be an issue. We went through --

DR. HILL: And the other question I had related to sensitization is there's enzymatic hydrolysis in many of these cases if I understand correctly. Do we remove the enzyme that's doing the hydrolysis? I know in the peptides when the source derived proteins is peptides, the enzyme may still be there in denatured form.

DR. MARKS: So, wheat amino acids are 257 uses up to point three percent. The collagen are 37 uses but up to six percent. So, Tom, you're safe with everything.

Ron, do you want to see irritation or sensitization?

DR. SHANK: In fact, I don't see a need for this report at all.

DR. MARKS: Ooh.

DR. SHANK: We have hydrolyzed proteins and we have individual amino acids. So, why is this intermediary report needed? I just don't understand that. And that comes from the chemist as to why we need -- what's the difference between

hydrolyzed proteins --

MS. BURNETT: In our process of starting the reports and everything, these chemicals were originally grouped with the hydrolyzed proteins group and then we were told don't put them together. So, we decided to review them separately. So, if you want them to go away entirely you can do that. You can combine it with the hydrolyzed proteins report, but you'll probably get some backlash. It's your call.

DR. SHANK: You separated them and reviewed them and I don't see the need to separate them.

MS. BURNETT: Okay.

DR. SHANK: So --

DR. MARKS: So, you would include these two reports, the hydrolyzed -- I'll still use the word source since that's what's on the green cover. You would combine the hydrolyzed source proteins and the source amino acids into one report?

DR. SHANK: I would, yes.

DR. MARKS: That eliminates the sensitization and irritation need.

DR. SLAGA: Gives the other half of --

MR. ANSELL: Well, that's what we would argue is that the data in these other reports is relevant.

DR. MARKS: Yeah.

DR. SHANK: So, why a separate report?

MR. ANSELL: Doesn't come from us.

DR. MARKS: Well, we can make that suggestion tomorrow. We're still in the draft status. So, before we issue a tentative report we could recommend that they be --

So, Tom and Rons, would you like to see these two reports combined?

DR. SHANK: I would, yes.

DR. MARKS: Okay.

DR. HILL: Sorry, but yes.

DR. MARKS: No, no. You don't have to say sorry because now I -- So, combine the two. Let me see who goes first tomorrow because I'm responsible for the hydrolyzed. Of course, it doesn't matter who goes first.

MS. BURNETT: Belsito goes first tomorrow.

DR. MARKS: So, Belsito goes first. Good. So, when he -- we'll see whether he moves.

So, what we would move is combining the two with a conclusion of safe.

DR. SHANK: I would agree with that.

DR. SLAGA: I'm good with that.

DR. MARKS: And then I'll say source proteins for now. We can go over the title. Proteins safe.

Okay. And then, we have prions impurities. I guess we have impurities from, again from the others. In this report, I didn't see much on impurities. But once we combine it, I didn't have a need for impurities there. Sensitization. Do we need boiler plates for heavy metals, pesticides, prions? They're plants and animals so you would think all of those. That's just almost editorial but Rons? Do you want the boiler plates in there?

DR. HILL: Probably so. I guess I'm stuck on are we on the source proteins that we were looking at sort of together now, right?

DR. MARKS: Yeah, and I've opened it up to both now that it sounds like the sense of our team is to combine source amino acids with hydrolyzed source proteins. Make it one report.

The conclusion is safe and now I'm sort of into --

DR. HILL: Right --

DR. MARKS: -- just sort of editorial. What we need to include which, in my mind, would be heavy metals, pesticides and prions and you know, whether we change the title. But otherwise I don't have any needs either.

DR. HILL: Okay, well I want to back up one step then.

DR. MARKS: Okay.

DR. HILL: All right? In many of the cases with the source proteins, and it's probably true of some of the amino acids but it depends, I guess, on the end isolation. You've got enzymatic hydrolysis of proteins. So, what we can presume from that is we've got a lot of small peptides. And also in many of these it seems the terminal production step is we denature the preparation which denatures the enzymes but we still have that protein in there.

I don't think you expect sensitization from smearing this on intact skin but what about mucous membranes?

DR. MARKS: Yeah, I'm not worried there.

DR. HILL: No?

DR. MARKS: Actually, it's interesting. My main concern would be type I reactions which we talked about before. The testing wouldn't, the typical RIPT and such would not pick that up but there aren't number of case reports of anaphylaxis --

DR. HILL: Okay, cool.

DR. MARKS: So, I've -- now the one thing I didn't specifically ask on the panel book on hydrolyzed source proteins, were the ingredients okay in that? That's page 13 and 14 in the hydrolyzed source proteins.

We said amino acid ingredients were okay. Is everything okay? And there's a lot of proteins here in table 1. Is there anything that jumps out? I mean for example, if I look down here brazil nut protein. Well, brazil nuts can cause type I allergies but again, you know --

DR. HILL: Is it the proteins in it that does it?

DR. MARKS: Yeah, probably. But I'm not too concerned about it in terms of in a personal care product.

DR. HILL: Okay.

DR. MARKS: Anything that should be deleted? Is there any protein you don't like in this table? Like royal jelly?

DR. SLAGA: What's wrong with royal jelly?

DR. MARKS: Okay. So, Don, we'll see how this plays out tomorrow. Do you -- heavy metal. Okay.

Any other comments? So, we did two and one. Christina?

MS. BURNETT: I'm sorry. The Counsel provided a memo this morning. I don't know if you've had a chance to receive it saying two points for the hydrolyzed proteins. And this is from the Science and Support Committee that the Japanese Society of allergology has formed a special committee to review the safety of hydrolyzed proteins mostly specific to hydrolyzed wheat protein..

And so, as those documents become available to us and which we can provide, pass them on to you. And then they reiterated the concern for protein derived ingredients that

cause type I allergy. And they provided some references that I can include. If there's any guidance you want to provide for wording since I do have to turn this around quickly after the meeting. So --

DR. MARKS: Yeah. I guess for me it would be what are the case reports of contact anaphylaxis to this and I suspect if there are it's exceedingly rare.

MS. BURNETT: I did do a search for whatever came up, came up.

DR. MARKS: I didn't find any..

DR. HILL: What about ones that are sprayed? Maybe they're not used in anything sprayed?

DR. MARKS: Well, that's -- no, they are because I have -- let me see. Where's -- thank you, Ron Hill, because I had underlined in here. See, that's all okay.

MS. LORETZ: Does the spinal protein, I know none of it taken out but like spinal protein? Does that give anybody conniptions or --

DR. MARKS: What's spinal?

DR. SHANK: Spinal?

MS. LORETZ: Yeah. It's one of the hydrolyzed proteins in the --

DR. SHANK: Really?

MS. LORETZ: It's not used.

DR. MARKS: But, yeah it's -- are you concerned about prions?

MS. LORETZ: Yeah. I mean does that sound like an appropriate cosmetic ingredient, I guess.

DR. MARKS: I guess if it's processed correctly you can --

MS. LORETZ: That's true but --

DR. MARKS: To me I guess it's -- actually if it's processed it means you don't get anything from the CNS, right? Cause you can't destroy prions, can you through processing?

MR. ANSELL: I think that's why they're specifically prohibited materials.

DR. MARKS: Right.

MR. ANSELL: But whether we want to carry that through as guidance or to be formed with that requirement that specifically prohibited materials not be used as source materials. I think our -- the issue that keeps

coming back up is this wheat allergy reaction in topical products which presumably is not because of a topical exposure but inhalation in the shower or -- I mean this is a multi-year program that's ongoing in Japan and they have years of work left to talk about this.

So, you know, some mention in the discussion might be appropriate. But I think I heard that that was the intent..

DR. MARKS: Yes. I would agree with that. And actually, the other question comes up Ron. If you look on the book that has source amino acids in it, in page 12 and 13 there is potential of inhalation exposure with the keratin amino acids. There are four uses and incidental inhalation spray. And then in the wheat amino acids there were six uses. So, do we need to put the inhalation boiler plate in along with the other boiler plates?

DR. SHANK: Yes.

DR. MARKS: Okay. That obviously doesn't address the issue of type I allergy but it does address --

MS. BURNETT: I over -- I didn't for some

reason write about it in the source proteins but it used in aerosols in the hydrolyzed wheat protein.

DR. MARKS: Yeah. Okay. So, combine the two? Safe? We got four boiler plates, heavy metals, pesticides, prion and inhalation and in the discussion we'll talk about this issue of wheat allergy.

And I think this is an example where to my mind the panel is ongoing. So, if the results of the Japanese initiatives in three years are significant we would reopen it.

DR. HILL: Works for me.

DR. MARKS: Okay. Achillea mille. Is that where we're at? Yeah, achillea mille. Pardon?

DR. HILL: I said maybe we can do this one and have lunch.

MS. BURNETT: We have 10 minutes.

DR. MARKS: Oh, we have more than 10 minutes. Who knows? Maybe we'll do two. So --

DR. HILL: I'm going on strike in 10 minutes.

DR. MARKS: In achillea millefolium aka

yarrow was assessed and reported in 2001 with an insufficient data conclusion. In June of this year, we reopened it and in light of having a number of new data. And so, on the memo from Lillian the data needs work. Bulleted on her memo and then the question is are the -- is the new data okay? Can we move forward with a safe or do we still have insufficient data needs?

DR. SHANK: For sensitization, I couldn't find the lymph node assay study. The conclusion says it's okay but I wasn't able to review the study.

DR. MARKS: Yeah. I have 100 percent assay it was okay. So, Lillian -- so, I thought that was the last bullet. Clinical sensitization, repeat insult patch, but I thought the local lymph node assay where it was okay at 100 percent would really would not -- we would not need an RIPT say at that point. So, it would indicate that it's virtually a non- sensitizer or almost non-sensitizer.

Okay, continue, Ron, while Lillian's looking..

MS. BECKER: Okay. The mouse lymphoma

is on panel book 43.

DR. MARKS: No, that's --

MS. BECKER: Oh, sorry.

DR. MARKS: -- a --

MS. BECKER: Oh here we go. I'm sorry. 37. Yeah, local lymph --

DR. MARKS: Pardon?

MS. BECKER: 37. Panel book 37.

DR. SHANK: Okay. That's all there is.

MS. BECKER: That's all they gave us, yes.

DR. SHANK: Okay.

DR. MARKS: That's -- I trusted them. So, that was okay. Particularly in my clinical experience even these have become very common, these botanicals in personal care products. I can't remember seeing that, the yarrow and the case reports would pick up things too. And again, you just don't see much.

DR. SHANK: Okay.

DR. MARKS: So, we'll say the last bullet is okay. How about the UV absorption? It's minimal above 290 it looks like? Is that okay at this point? Do we need --

DR. SLAGA: It absorbs at 360 right?

DR. MARKS: Yeah.

DR. SHANK: Actually, the reference shows a single absorption peak at 190. Nothing at 260. That's on panel book page 32.

DR. MARKS: Yes. So --

DR. HILL: Well, no. There are minor absorption bands at 260 and another one at 330. I mean there's not as -- the e-max is not as high. There's still absorption going on clear out to 390 which I would expect from a plant extract because there are going to be some --

DR. SHANK: But our tech says there was a peak at 260.

DR. HILL: Oh, there is a peak. Well, it's a shoulder at 270, 265, something like that.

DR. MARKS: No, I think what you said, 190 didn't you? It's below 200.

MS. BECKER: Yeah. It's 190. I reworded that, yes.

DR. MARKS: So, are --

DR. HILL: There are shoulders. There's a shoulder at 265 and there's another shoulder at 330ish.

DR. MARKS: Okay, so is there -- even though there's some absorption in the ultraviolet range -- concerns? I think it's small.

DR. HILL: I didn't because the concentrations of use are so low.

DR. MARKS: Right. Okay.

DR. HILL: That was where I landed on that one.

DR. MARKS: How about these other, gross pathology histopath?

DR. SLAGA: There's no histopath of the skin but I don't know if that's needed.

DR. MARKS: This point it --

DR. SLAGA: From repeated applications but I don't have a concern for it.

DR. SHANK: I don't think we need it.

DR. SLAGA: -- toxicity. I don't -- there's oral repeated.

DR. MARKS: Repro development tox?

DR. SHANK: We have that.

DR. SLAGA: We have that.

DR. MARKS: That's okay.

DR. SLAGA: Genotox I think we have.

DR. MARKS: And the geno is okay. So,

it looks like we could move forward to a safe but now we have include the oils, page --

DR. HILL: I was going to say, can we go to page 3 and have a look quickly cause --

DR. MARKS: Yes. That's -- you're ahead of me, Ron, but good. Thank you.

MS. BECKER: 3 in the report or 3 in the book?

DR. HILL: Panel book page 3.

DR. MARKS: 3. So, we have other ingredients in here now.

DR. HILL: Yeah.

DR. MARKS: So, do we want to include and I question the oils.

DR. HILL: I'm not sure why the oil is here. You know, that, to me belongs, if it's truly an oil that belongs in vegetable oils and we had a whole other -- I don't know if we picked that one up back when we did that. Probably not or else it probably wouldn't have landed here but we don't have any data on it. And I question whether it even belonged in here given its dissimilarity from the other extracts I'm almost certain.

DR. MARKS: So, your sense would be that

was what I was questioning. Is the oil the same as a water extract? No. That's what -- So, Ron and Tom, would you include or delete the oil? Because we have the opportunity now to -- and I guess it's an -- if we use that this is going to be an amended report, this should be a no brainer if we add ingredients. And it doesn't like the oil is a no-brainer.

DR. HILL: This doesn't belong with the others from where I see it. If it's truly an oil it doesn't go with --

DR. MARKS: Okay. So, we will have one, two, three, four ingredients.

MS. BECKER: Well, according to the definition it is an oil. It's oil obtained from the herb so --

DR. HILL: All right. So that shouldn't go here in my opinion.

DR. MARKS: Yeah. So, four ingredients. Safe.

MS. BECKER: And what would you like me to mention in the discussion besides the UV?

DR. MARKS: Well, obviously convention. All these things that were safety needs before

that now we feel are met. I think that would be important. Do we have, again, since these are plants, do we have the heavy metals and pesticides boiler plate?

MS. BECKER: Yes, we do. Put that in.

DR. MARKS: Okay. And then I had a question, page panel book 16. And I forget. I should have looked it up but quercitin is one of the ingredients and that just rung a bell. Was there safety concerns in the past about quercitin or not?

MS. BECKER: Don't know.

DR. SLAGA: Yes. It was sold over the counter --

MS. BECKER: It's an OTC drug? Oh, good.

DR. SLAGA: I mean there is some toxological but it's extremely at high doses.

DR. MARKS: Okay. Okay, good.

DR. HILL: That's what I was going to say. And the extracts are used at small concentrations and then amount here is -- I mean none's listed which means that should be small.

DR. MARKS: Right. I had the same. I had hydroquinone as listed as an ingredient and

of course that's a feed pigmenter but it's such a small amount that it seems like that would be un -- that was on page 15. Okay.

MS. BECKER: Would you like me to mention this?

DR. MARKS: What does the team feel? No?

DR. SLAGA: It's such small amounts.

MS. BECKER: Well, that would be why I'd mention.

DR. SHANK: I would just say these minor components are not a concern because of the low use concentration via extract.

DR. HILL: Right. And if we want to pick on something then we should pick on isoartemisia-ketone. When you get down to the --

DR. MARKS: Yeah, so I would probably not mention it. I just wanted to bring it up now to make sure that there weren't any alerts there.

Okay, so let me see. This is Belsito. I will move, I presume he'll move, it will be safe. We want to have the four ingredients, not the oil and this would move on to a final. To a draft amended final report. Okay. Any other comments? Lunch?

(Recess)

DR. MARKS: Okay. Let's go ahead and start the afternoon. And I believe we're up to the ingredients safety assessment of hypericum perforatum, otherwise St. John's Wort. And in 2001 an insufficient data conclusion was reached and in June of this year we reopened that. And had a number of insufficient data needs which many of them are met and let's just go down and make sure that -- where we're at at this point.

So, if you look on panel book page 2, there's bulleted needs and let's just go down there and we have the concentration, current concentration of use data. We have a table now with that. Functions in cosmetics, do we have that?

MS. BECKER: Yes.

DR. MARKS: Okay. I saw the list in there. Photosensitization of phototoxicity, that was still an issue for me since --

DR. SHANK: Me, too.

DR. MARKS: On page, panel book page 15, you see under hypericum and other constituents that there's clearly photosensitization and then

there was even severe prolonged response with ear swelling. So, how do we get around the issue of phototoxicity? And this is being used at this point. There are uses as in page 27 table 4.

DR. SHANK: Well, we have some data on phototox but not photosensitization. And most of the studies are in UVA, UVB not visible. So, I think we still need photosensitization in the physical light.

DR. MARKS: Tom, Ron? Is that -- do you feel the same? Most of the photosensitization when you look at it occurs in the UVA range but when you do photo patch testing you're actually irradiating mainly with UVA. So, I'm not so much, I don't know if --

DR. SLAGA: Well, it's that one study in (inaudible) for photosensitization which resulted, there's a minimal after radiation but --

DR. MARKS: Right. That's right at the top of the page?

DR. SLAGA: -- swollen at all concentrations. That doesn't sound minimal to me.

DR. MARKS: So, would we want -- does it matter, in this case would you want to see it in humans? And is this -- one's an extract the other is the oil and the other one's constituents which I'm not sure what the constituents are there. Do we know? That's again on page 15.

DR. SHANK: Hypericin is the one they tested.

DR. MARKS: Yeah.

MS. BECKER: -- hypericin.

DR. MARKS: So, photosensitization?

MR. ANDERSEN: Jim, you always have the option since hypericin is a constituent of limiting the concentration to a level that wouldn't cause photosensitization. If you didn't exactly know what that level was, and I don't think these data are going to provide it, you could say and limit the hypericin to a level shown to not be photosensitizing. But the monkey back on the suppliers' back.

DR. MARK: Rons, Tom? Do you like that in the conclusion?

DR. SHANK: If hypericin is the only photosensitizing agent that would work. But do

we know that?

MR. ANDERSEN: Whatever is in the oil, which is likely to be one group of things, and then the extract I would think would be another group of things, neither of those were photosensitizers. It's only when we've got purified hypericin that you got a positive result.

MR. ANSELL: Yeah, there's photosensitization on the extract using tape strip skin.

DR. SHANK: Was that invisible light?

MR. ANSELL: 320-400.

DR. SHANK: Okay, so not really.

MR. ANDERSEN: That gets into a discussion of what's visible versus; the 390-400 is blue light. You can see just barely that it's blue. Or violet.

DR. HILL: So the 98 insufficiency specifically said 550-610 nanometer. Do we know why that range was set? I still hadn't been able to sort that out.

MR. ANSELL: There's also photosensitization on the oil.

MR. ANDERSEN: Yeah. And that went up

to --

MR. ANSELL: 290-2500 nanometer.

MR. ANDERSEN: Well, that's the entire spectrum.

MR. ANSELL: Yeah and then the minimal photosensitization in balb c 3 mice, balb c mice --

MS. BECKER: Okay, I'm looking at the --

MR. ANSELL: And that goes up to --

MS. BECKER: Sorry.

MR. ANSELL: -- just under 600.

MR. ANDERSEN: Got the original report here, too.

MS. BECKER: Yeah. I don't see anything in the discussion that said why you picked that range.

DR. SLAGA: Yeah. Why would they pick that range? I had a question about that but that doesn't really make sense.

DR. MARKS: They would be us, is that correct?

MS. BECKER: Yes.

DR. HILL: Okay. I can answer that question. On page -- well I've got the original

report brought with me from last time and it says h. perforatum is a primary photosensitizer in animals because of the photo dynamic pigment hypericin. Hypericin causes photo activated damage by absorbing visible light in the 550-610 nanometer range. Maximum at 585. And so, that's where that -- it's written in the photosensitization section of the original report.

MR. ANDERSEN: So, focus was on that one chemical?

DR. HILL: It was indeed.

MS. BECKER: Right. There we go. Found it.

DR. HILL: And the concern seems to be oxidative damage to capillary walls.

DR. MARKS: So, it's an interesting suggestion. You made, Alan, is can we have the level of hypericin below a photosensitizing phototoxic level or --

MR. ANSELL: Well, since the commercial products look like there's six separate studies perhaps it would be better to point out that when hypericin is isolated it may be sensitizing.

Cause we seem to have human volunteer data, oral data which is hard.

DR. MARKS: Yeah. Where's the human data?

MR. ANSELL: Well, I'm looking at the summary on 34.

DR. MARKS: Yeah, okay. Eight subjects, right, that's with the oil.

MR. ANSELL: And then 48 human volunteers after an oral study but --

DR. MARKS: Yeah. Do we have an idea of how much, because in the hypericin photosensitization studies they were using concentrations up to one to one point five percent? I presume we don't know how much hypericin are in these extract?

MR. ANSELL: Yeah, we do.

MS. BECKER: Yeah, we do. Page 22 of panel book 22.

MR. ANDERSEN: What is it?

MS. BECKER: It's fourteen point five parts per million up to 18,000 parts per million depending on plant part.

MR. ANSELL: Yeah, Carol calculated

that at the maximum use concentration the hypericin concentration would be two, one, two, two ten-thousandths of a percent.

DR. SHANK: Okay.

MR. ANSELL: 0002.

DR. SHANK: And it wasn't photosensitizing at point one percent?

MS. BECKER: Okay?

DR. MARKS: Yeah.

MS. BECKER: All right. Sounds like a fun paragraph in the discussion..

DR. MARKS: So, we'll put that -- so, now we've met that data need that we're not concerned about the hypericin photosensitizing phototoxic effects since the concentration is so low on the final. So, that would be in the discussion.

Gross pathology, histopathology in the skin, sounds like allergist discussing. Is that still an issue?

DR. SHANK: I had no -- no, I have no --

DR. MARKS: Okay. Reproductive developmental toxicity?

DR. SHANK: We have it.

DR. MARKS: Skin irritation sensitization?

DR. HILL: On the oil specifically is what's --

DR. MARKS: Yeah, the oil and now we get into like with the previous botanical. Do we want to include the oil with these other extracts? Which presumably are water extracts, is that correct? Let's see. How do they manufacture this?

MS. BECKER: See what we've got. Ethanol extract.

DR. MARKS: Oh, ethanol.

MS. BECKER: It's like all the other extracts. It could be any of the solid ones.

DR. MARKS: Yeah. So, do we want to eliminate the oil?

DR. HILL: To me that would make very good sense but that's just my opinion.

DR. MARKS: If we do, that eliminates that.

DR. HILL: It does indeed.

MR. ANDERSEN: Well, you've got the phototox study on the oil.

DR. MARKS: Uh-huh.

MR. ANDERSEN: Which, by definition says the oil itself wasn't a photosensitizer.

DR. SLAGA: Right.

DR. MARKS: Yeah, that's just --

MR. ANDERSEN: When you added light it didn't sensitize so --

DR. MARKS: Eight subjects, is that enough?

MR. ANDERSEN: Well, it's not a lot of one that's for sure.

DR. MARKS: What about the actual idea of including the oil with these other extracts?

DR. SHANK: I think it's all right because --

DR. MARKS: Okay.

DR. HILL: But there is no toxicology other than that phototox? I guess my only comfort would be that if the concentrations of use are -- where's that? They're really low, aren't they?

DR. SHANK: Yes.

MS. BECKER: Yes. They're incredibly low.

DR. HILL: Yeah, that's -- point zero zero zero zero five percent.

MR. ANDERSEN: It's hard to keep track of all those zeros.

MS. BECKER: Yes.

DR. HILL: That's pretty low..

MR. ANDERSEN: I think the intent here, because the original safety assessment addressed the extract and the oil, I think that you can't bucket --

DR. HILL: Want to keep it --

DR. MARKS: Okay. Now, I still have, there's not much on sensitization other than these phototoxic which are small numbers. There's not a RIPT. There's no local lymph node assay is there? Let me see.

MS. BECKER: There's --

DR. SHANK: We have naked photosensitization. Doesn't that cover it?

DR. HILL: Interesting.

MS. BECKER: We've got dermal repro and developmental. We've got one human irritation test.

DR. MARKS: I guess if I put a hair dye

on eight subjects and didn't see a reaction I would say that's not a sensitizer? Well, we'll see what Don says. I still would like to see -- I don't think it is a sensitizer.

MR. ANSELL: On the oil or --

MS. BECKER: On the oil.

DR. MARKS: Anything. Do we have any big numbers on any animal? Let me see here.

MR. ANSELL: We've got 16 humans topical. We have oral, whatever.

DR. MARKS: Yeah, oral.

MR. ANSELL: And dermal, mouse dermal coupled with the guinea pig 10 animals.

DR. MARKS: Okay. So, the backs of guinea pigs with tape supply. Was that at -- but was an adjuvant. There was no adjuvant added to that as guinea pigs. It wasn't a maximization?

MR. ANSELL: It says it was.

DR. MARKS: Does it?

MR. ANSELL: Well, I'm looking at the summary. An unpublished guinea pig maximization study, two sites.

DR. MARKS: Oh, okay.

MR. ANSELL: One point one percent

extract at ten percent dilution for reduction and point one and one diluted in challenge. No sensitization. One site at induction given UVA.

DR. HILL: So, I'm looking at the -- maybe I'm looking at the wrong one. I'm looking at the original report and there's a section on sensitization and it has, not in humans but it has hypericum perforatum extract and let's see, in guinea pigs. Bueller test and then they have the oral tested maximization test in guinea pigs.

DR. MARKS: And that's, okay. And that was negative.

DR. HILL: Yes.

DR. MARKS: Okay.

DR. HILL: But I don't know why it wasn't captured in the --

DR. MARKS: In this.

MS. BECKER: We don't put the old data in the new reports.

DR. HILL: Okay.

DR. SLAGA: But the old report had genotoxicity for some -- this report doesn't have it. So, that's not a concern.

MR. ANSELL: But your summary as it includes the data includes all the data not just the new data or?

MS. BECKER: At the beginning of the report I got a summary of the old data and then the summary has a summary of the new data.

MR. ANSELL: But the letter you sent on page 34 was just the new data that was submitted?

MS. BECKER: Right.

DR. HILL: Okay. Yes and it just has that one sentence in the original safety assessment so --

DR. MARKS: Okay. So, we have guinea pig.

DR. HILL: Guinea pig.

DR. MARKS: Okay. I think that's sufficient. There aren't a significant number of case reports that would raise a flag so --

DR. HILL: Concentration's really low.

DR. MARKS: Yeah. Concentrations are low so.

DR. SLAGA: Also, in the old report there was mixtures containing the extract and the oil were not irritants or --

DR. MARKS: Sensitizers, yeah. Okay. Looks like we've met all the needs, ocular irritation so, proceed with a safe?

DR. SLAGA: Okay.

DR. MARKS: And this would be a draft final amended report.

MS. BECKER: In the Counsel comments, they suggested that we should take out the callus culture extract. It's collected and processed differently than the rest of it and with probably does that really belong here?

DR. SHANK: Okay.

DR. MARKS: Okay.

DR. HILL: There were no reported uses either, right?

MS. BECKER: Right.

DR. HILL: Not that that matters but --

MR. ANDERSEN: Jim, since you're reporting on hypericum, this -- you should be approving a draft tentative or a tentative amended because it does need to go out for public comment. It's not a final.

DR. MARKS: Okay. Because what I have, the memo says this is a draft tentative amended.

And so, it's --

MR. ANDERSEN: So, all your removing is draft.

DR. MARKS: Okay. Thank you. Any other comments? I'll move tomorrow that we issue a tentative amended. So, then once this goes out is it going to change from the draft final report?

MR. ANDERSEN: We take all of the editorial comments. Put them in. Remove the callus ingredient.

DR. MARKS: Right.

MR. ANDERSEN: So, it will be tweaked. But not changed.

DR. MARKS: So, a tentative amended report with a conclusion of safe. And with removing the callus culture extract.

MS. BECKER: Right.

DR. MARKS: The hypericum. Okay. Any other comments? Since Alan is here I'm going to go back and for our team, I have a comment that Alan made on an ingredient we already reviewed and I didn't bring it up when we reviewed it. Under the hydrolyzed source proteins, what we decided to do, Alan, was our team decided we want to

combine the amino acids with the proteins and make it one report.

Alan raised a concern that the possible addition of bioactive peptides to cosmetics, that in the reference under the hydrolyzed source proteins, refers to ACE inhibitory antithrombotic surface tension antioxidant properties in the psilo protein hydrolysates. And of course, personal care products should not be bioactive.

Did, Tom or the Rons, did that happen to -- did you think of that and, Alan, did you want to expound --

DR. SLAGA: What do you mean by bioactivity?

DR. MARKS: Did you want to --

MR. ANDERSEN: I think that my concern from the get- go was that polypeptides were going to have questions about safety that are separate from amino acids just because they're poly. And one of the issues is some six, ten, twelve amino acid molecules are functional. And seeing the one report in here of the soy protein hydrolysates having ACE inhibition, antithrombotic,

antioxidant doesn't bother me so much.

But those are biological activities about which I'd like to know more. And that was part of the reason why I was pushing so hard to keep these separate. I didn't want those questions dragging down amino acids.

DR. SHANK: But the polypeptides are not likely to be absorbed across the skin.

MR. ANDERSEN: Even six to ten?

DR. SHANK: Probably not. It would be difficult.

MR. ANDERSEN: Then I really don't care.

DR. HILL: And the other thing that came up I think is do we know is that source amino acids that we're hydrolyzed down to only amino acids with no contamination by di and tri peptides which we don't have that information. So, I think that was were --

MR. ANDERSEN: No, that's coming at it from the other direction.

DR. HILL: Yes, it is.

MR. ANDERSEN: I think I was rather more comfortable with that we were going to get the how to (inaudible). I don't know that I can point to

a piece of data. So, I get your point. And that's another reason to support combining them.

If you're not going to be concerned about systemic effects that I withdraw my objection in combining them.

DR. MARKS: Okay. Good. It was opportune that you were here, Alan, now to redis -- bring that back up. I didn't want our team not to hear your concerns about that in the notes you sent me, Alan. Okay.

MR. ANDERSEN: Good. Thank you..

DR. MARKS: You're welcome. Next is the modified terephthalate polymers and this is our first time seeing this draft report. I think the first thing always is, Ron and Toms, on page, panel book page 18 are figure 2, are the ingredients in this report. Do these all look like they belong in this report?

DR. HILL: The only one that raised any question for me potentially was the one with the sulfate. Excuse me sulfonate. No data on it. But I thought I'd just toss that out and see if anybody else had this similar question. I thought in terms of the potential for sensitization that was

the one that jumped out at me. And there was no data.

DR. MARKS: Yeah. That didn't -- I felt there was enough both irritation and sensitization data that I was not concerned about the ingredients.

So, needs? Any needs for these compounds?

DR. SHANK: I think as long as these polymers, the cosmetic grade is chemically equivalent to the medical device grade. These are all seen as used. So, that's what I would put in there.

DR. SLAGA: That would at least end the discussion. The only question I had was the goitre (inaudible).

DR. HILL: So, Lillian, do we know if that sulfoisophthalate is used in medical devices?

MS. BECKER: That one in particular, not that I've found. So, we don't want to -- so, you're not comfortable depending on the read across for that one?

DR. HILL: No. But only if there was

a monomer related issue.

DR. MARKS: So, in the -- Jay can you comment at all in terms of it is reasonable to think that the cosmetic grade of these terephthalate polymers are similar to the medical grade?

MR. ANSELL: I don't know that..

DR. MARKS: Yeah. And do you feel comfortable if we say, Ron, and Tom, if we say in discussion they should be? Then we could move forward with a --

DR. SLAGA: Yeah. As long as we discuss it yeah.

MR. ANSELL: Well, at least in terms perhaps of monomer residue. I mean, we would need to be sterile. But you know, I don't know what the medical specs are. I think to identify an element which is a concern perhaps, residual monomer or could be something we would look at. But you know --

DR. MARKS: I guess the other way you could word it isn't -- would it be that we come to a safe conclusion based on data from the medical grade and that we would expect these

cosmetic grade polymers to not be significantly different. Something to that effect?

MR. ANSELL: Yes.

DR. MARKS: How does that sound about wordsmithing?

MR. ANSELL: I think that's good.

DR. MARKS: Do you like that, Ron?

DR. SHANK: I do like that.

DR. MARKS: Yeah, okay.

DR. HILL: It's okay but just -- and again, I ask if it terms out that that sulfoisophthalate is not used in any medical devices then what are we saying in that particular case? Cause that's my only source of concern in terms of -- and there's no data to support at very different one --

MS. BECKER: Right.

DR. HILL: -- in terms of testing.

MS. BECKER: Right. Also, point that out. We don't have anything specifically on that particular ingredient.

DR. HILL: I don't think there's anything on impurities either in that case.

MR. ANDERSEN: One strategy for

tomorrow, since you're making the motion here is to suggest that that one be deleted.

DR. MARKS: Yes. That's --

MR. ANDERSEN: But what the other one is.

DR. MARKS: Yeah.

DR. SLAGA: Good.

MR. ANDERSEN: I kind of like the language that you negotiated in the back and forth with Jay but I didn't want to let it go to remind you that you have in the past, and the ingredient escapes me. It was an acid violet dye that also is a food, drug and cosmetic color. You said, looks safe to us as long as it's identical to the approved color.

DR. SHANK: Right.

MR. ANDERSEN: Which is a wonderful way around it. Basically said it has to be the approved color. So, it has to be identical to the approved medical device. We've done it once before for another thing..

DR. SHANK: But the --

MR. ANDERSEN: I liked the language better that finesses it. But you've done it once

before.

MR. ANSELL: If the other applications were relevant to cosmetics, I think an implacable hit might not be --

MR. ANDERSEN: Probably less so --

MR. ANSELL: Yeah.

MR. ANDERSEN: Addressing the rather extensive review of safety questions the devices did to approve these; you're at least partially relying on that. But the way it was phrased that you recognized that those data exist and you don't expect that the cosmetic grade material is going to be significantly different. That's a fine way of finessing it.

MS. GILL: But is the -- heard the language here? It's the same grade as the medical grade used in the medical devices and not the same material?

DR. MARKS: Hopefully Lillian took notes on what I said.

MR. ANDERSEN: Do it all (inaudible) but none of us could remember it.

MS. GILL: Safe as used as the medical grade. Same as used in the medical --

MS. BECKER: Not very different.

DR. MARKS: Yeah, not significantly different.

MR. ANDERSEN: Yeah.

DR. MARKS: Allow that it might be somewhat but not --

DR. SHANK: Should be chemically equivalent.

DR. MARKS: Yeah, there you go. Chemically equivalent. Lillian, we'll get you to -- we'll react to it the next time and I'm sure have lots of discussion as to how it's worded. So, Tom, Rons, you had no needs then?

DR. SHANK: I have no needs.

DR. MARKS: So, what did you think about, let me see, page panel book 75. I have 75 but that can't be right. 76. That David Steinberg wrote this letter to Alan that he was deeply concerned about the PET ingredient which where is the use tables. 15. That's the number one. That's -- we don't have a concentrations on panel book page 15, the polyethylene terephthalate has the largest usage. Has 98 uses reported in the eye area.

We don't have a concentration and we

have this concern that there may be some sharp edges that can get caught in the eye. Yet all the data in here on eye irritation is okay. I actually, Lillian, you have notes from the ophthalmologist that you talked to. I talked to our Chair of Ophthalmology at Penn State and he was aware of no problems with this glitter material. And --

DR. SLAGA: It should be --

DR. MARKS: -- there were no case reports. Is that correct? Pardon?

DR. SLAGA: It should be discussed.

DR. MARKS: Oh yeah. I'm not saying it shouldn't be discussed but were there any case reports I missed?

MS. BECKER: I went through Sci Finder and Pub Med. Could not find anything. Google Search got popular articles. That's how I found Dr. Glasser and he just happened to be right across the street from us which was very convenient. And his concern is loose glitter more than glitter in the makeup. And there is loose glitter out there to be used for makeup that comes in little jars. You take the lid off it, you put your finger in it and you wipe it over your eye.

Or whatever body part and --

MR. ANSELL: His letter says he doesn't see this as a problem. That it's dermatitis of the eyelid.

MS. BECKER: Right.

MR. ANSELL: So basically, we have a single note from an esteemed colleague that he thinks it's a concern. Yet the other people --

MR. ANDERSEN: Jim, if I can go retrieve a piece of (inaudible).

MR. ANSELL: -- had interviewed said they don't see it as a problem. The only data we have says it's not a problem. If we think it is a problem, it would be nice to have a study that we could cite.

MS. BECKER: Right.

MR. ANSELL: And I hesitate, we've written -- you wrote more about it than the introduction than all of the data that's in here. And let's speculate on a mechanism that may or may not be true. So, we think that discussing the potential problem is legitimate although it's far from clear that it is a problem and certainly far from clear that the mechanism is jagged edges.

And you know, it's just -- it seems a legitimate issue that, if necessary, should be researched and kind of thoughtfully addressed.

MS. BECKER: Right. That's why we're going for a thoughtful address right now. Although, he did that it will damage the eye if you do get a piece of glitter in there and if it does get embedded you do have to have a doctor remove it. You can't do it yourself and wipe it out. It's just going to cause more damage.

So, and also that it's the glitter in hairsprays is his problem. Not actually spraying it on the hair but once it's in the air, walking through it and then getting the glitter in your eye. That's in the interview.

MR. ANSELL: Right. But the ophthalmologist, the College of Ophthalmology says, American Academy, "If you tend to have dry eyes, makeup that flakes and gets into the tear film can increase irritation. In such cases you should discontinue the use of powdery eye shadows and glitter makeup." And then be especially careful of glittery eye makeup. And we think perhaps citing the American Academy would be

entirely appropriate and not necessarily Dr. Steinberg's letter.

DR. MARKS: So, Tom and Rons, are you concerned at all? Would you like this picture published of those nice little (inaudible)? Actually when you Google it, I did Google it. There's some pretty interesting shapes but that clearly that couldn't have been what was tested in the eyes. I mean there are moon shapes and all sorts of things that on glitter but what was tested here wasn't a problem.

MS. BECKER: Right. For that type of use, for stuff that made -- for glitter that's in the makeup.

DR. MARKS: Right.

MS. BECKER: I think you ought to at least address glitter that's not in the eye shadow but just glitter. I don't know that it's a problem. That's up to you but I think that's something that needs to be at least discussed. That's all.

DR. MARKS: So, we don't need to -- so, Tom and Rons, safe?

DR. SLAGA: Safe.

DR. HILL: So, the question is, I mean

besides the source that Jay cited what do you cite for sources? I mean you can cite personal communications I guess. But everything is anecdotal. I'm not sure how well that goes into a scholarly paper.

DR. MARKS: And that's the difficulty I had. All the science is pointing to it's safe and then we had some theoretical issues but we have nothing -- not only, you know, I would expect it would have appeared in an ophthalmology literature as maybe a mini epidemic of corneal abrasions, this material. Just hard to believe that if this was a significant medical issue that there wouldn't have been some case reports or a series so.

MS. BECKER: Right. But since it was brought to our attention I think we --

DR. MARKS: Yeah.

MS. BECKER: -- it deserves a couple of sentences from us.

DR. MARKS: Oh, I agree. I agree. We can put that in the discussion. So, let me see. I'll be moving tomorrow that we issue a tentative report for the modified terephthalate polymers.

Am I saying that right? Terephthalate? Polymers, that they are safe as used and we have the caveats that the cosmetics, since a lot of the tox data it's based on medical grade polymers, that the cosmetic grade should be equal to it or --

DR. SHANK: Chemically equivalent --

DR. HILL: And actually there's already language in this report under the impurities section, by the way, that basically says what you said. Just, yes.

DR. MARKS: And then we are going to delete the sulfoisophthalate ingredient. So that was the second one on the list of ingredients. Anything else?

MR. ANDERSEN: Jim, I found what I went looking for. I don't know if it helps the situation or not. When David Steinberg gets ahold of something he digs. So, I have here an almost 30 year old recall action that FDA took against a manufacturer of glitter. And it's most notable because it seems to be more of a fight between the Consumer Product Safety Commission and FDA on, you handle it. No, you handle it. No, you handle it.

But FDA did issue a class 2 recall notice to the manufacturer. And the manufacturer responded back by saying, screw it. It's not enough of our business. We're going to withdraw the product.

MR. ANSELL: What was the cause for the recall? Micro? Illegal color? Glitter is a very complicated regulatory --

MR. ANDERSEN: Yes. Lacked adequate instructions for use and lacked a warning statement that would preclude its use in the area of the eye..

MR. ANSELL: And that's a regulatory issue not a safety issue?

MR. ANDERSEN: Yeah. There was no safety --

MR. ANSELL: Well, I take that back but it's --

MR. ANDERSEN: There were no eye problems. The eye problems that were reported were inconclusively linked to the actual product. So, but it's -- this has happened before is the point. And if in the intervening 30 years we haven't heard about much of anything else, that

may speak volumes.

DR. MARKS: I'm sorry we do have the concentration on wave 2. And here, I mean, the November 16th memo from Halyna, I mean, there's one, two, three, four, five, six use test with up to let me see, 12 percent glitter. And they did some pretty detailed examination of the eyes with this by ophthalmologists. So, again, there's nothing that I had that shows that there's a hazard other than a theoretical.

And it's up to 46 percent, I'm sorry. The new table has a concentration of -- any other comments? So, I'll move tomorrow safe that the cosmetic grade is chemically equivalent to the medical grade to that effect and then we'll delete the sulfoisophthalate, the ingredients in this report.

Any other comments? Does industry have any comments? Is there anybody from the glitter industry here? And then Rachel isn't here. It's too bad. I would have been interested if she had any comments.

FDA have any comments?

MR. MILSTEIN: FDA's comments pretty

much have already been expressed by the panel in terms of the cutting and sizing and jagged potential, jagged edge issue.

DR. MARKS: Okay. Talking about phthalates. So, this morning we found this. The guidance for industry limiting the use of certain phthalates as expediencing CDER regulated products. In 2005, the panel decided not to reopen the phthalates particularly at that time we were focused on the possible endocrine disrupter development issues.

We have some new studies. One, an airway study and a couple on diabetes. Alan's summary states the issues well. Is there any reason to reopen?

DR. SLAGA: Do not reopen.

DR. SHANK: Well, those epidemiological studies are not a cause to reopen. I'm not too sure how to handle this. I haven't read it yet. The CDER regulation but if this applies to drugs is it also going to apply to cosmetics eventually.

MR. ANDERSEN: Very specifically not.

DR. SHANK: Okay.

MR. ANDERSEN: Not the medical devices,

not the cosmetics, it's dibutylphthalate, diethylhexophthalate as used as excipients in drugs only.

DR. SHANK: Okay. Thank you.

MR. ANDERSEN: I just didn't want to hide it since it came out last Friday. It seemed timely.

DR. SHANK: Yes. Okay. Then I would say don't reopen.

DR. MARKS: Ron Hill, not reopen? Yeah, okay. Now, in terms of the discussion and the re-review.

DR. SLAGA: Well, we definitely have to discuss the epi studies but as Ron pointed out the early association, there's no way to come up with a concentration to relate to cosmetic. There is concern in my eyes that some of these phthalates may have effect on people who are gamma receptors. Which the gamma ones are the ones that the diabetes drugs, the glitazone class of compounds are effective agonists. And then also the alpha, there's a number of different types of fibrates that interrelate to this too that I just think we just discuss that and that's all we have to do.

MR. ANSELL: Well, this is not a re-review. This was three specific papers which questioned whether this should jump out of cycle.

DR. SLAGA: Yeah.

MR. ANSELL: So, I don't know that, I mean that's of course an issue and we can reopen based on --

DR. SLAGA: No, no. I didn't say reopen. This is in a re-review summary.

MR. ANSELL: But this isn't a re-review, right?

DR. MARKS: It's a thick document for not being a re-review.

MR. ANSELL: I thought this was -- I'm sorry. Maybe I'm out -- I thought this was brought forward specifically to assess three papers that we became aware of.

MR. ANDERSEN: That's correct. It's -- you have the option of reopening based on these new data but the minutes of the meeting could be an adequate summary of the basis --

DR. SLAGA: Right.

MR. ANDERSEN: -- for a decision to not reopen it. Like you did at the last meeting with

respect to parabens. You said, sorry Charlie, there's not enough new information here to support reopening it. And our previous conclusion is still okay. And that's what I would -- if you choose not to reopen, that's what I'd do here.

DR. MARKS: Leave the minutes and let it stand and not actually publish a re-review summary.

MR. ANDERSEN: Yeah, I think if we did otherwise we'd be publishing a re-review every time somebody published something.

DR. MARKS: Right.

MR. ANDERSEN: No, thank you.

MR. ANSELL: It would make the threshold to look at a paper that came through so onerous that we might not want to do that.

MR. ANDERSEN: Right. Giving you the option of saying, fiddlesticks, this is important. We'd better reopen this. That is what --

DR. MARKS: And so, in the minutes we'll capture that you've already said that, Alan, and Ron Shank is --

MR. ANDERSEN: Yeah and we'd make the

note that it specifically excludes any relevance to cosmetics.

DR. MARKS: Okay. So, we'll not reopen phthalates once again and we'll just capture that in the minutes and the biggest three epidemiologic studies don't warrant reopening. Okay.

PEGs cocamine. So, in '99 the CIR expert panel came to an insufficient conclusion. Last year, we looked at some data presented and as a panel decided not to reopen but however, when you look at our team's conclusion with the new data, we thought it was all okay. But somehow we were convinced to not reopen it. So, we're back to do we reopen? Are the structure activity relationships okay? Do we add ingredients?

So, if you look on Alan's memo, the additional data in '99 were the physical chemical properties, the genotox 28 day dermal tox, dermal sensitization. And we have a lot of new information from the American Chemical Council, EPA, et cetera so -- Tom and Rons, what do you think this time around in 2012?

DR. SLAGA: I had reopen and add the

additional compounds but overall I could see --

DR. HILL: I still don't think, you know, if we want to extend into those lower molecular weight ranges, I don't think we have the data for read across. And I think the computational approach is shaky and inconclusive at best in terms of extending down to those low end. If you stick with ones where we know the chain lengths are say six and above then we're probably more than safe.

DR. SLAGA: But we would make that decision the next --

DR. HILL: Yeah, if we were to reopen.

DR. SLAGA: Which ones to eliminate.

DR. HILL: I'm just pointing out if we, in fact, reopen here's how I see it playing out..

DR. MARKS: Yeah, I have -- we have sensitization data that looks good.

DR. HILL: I say as long as we stick to higher polymers --

DR. MARKS: Yeah, that's what it is.

DR. HILL: We'll have no problem.

DR. MARKS: It's on the PEG-15. What on page 17, panel book there it says PEG-2

cocamide actually does not contain PEG functional groups.

DR. SHANK: It's not a PEG.

DR. MARKS: It's not a PEG. So, should that not be in this report?

DR. SHANK: Well, that's one way to go. Is just to eliminate the PEG-2s because they really -- this is a nomenclature problem. Or if we do, I think you could use the tallow ethoxylene in the mean data for read across to take 2 cocamine. I would think that PEG-3 compounds would have PEG-2 compounds in them and if the PEG-3s are safe I think that would cover the PEG-2s.

This can all be handled in the discussion.

MR. ANSELL: And we would very much like to have that discussion.

DR. SHANK: Okay. So, I think yes, reopen. And then whether you include the PEG-2s or not, we'll have to discuss.

DR. MARKS: All the other --

DR. SHANK: My personal preference is to get rid of them because they're not PEGs.

DR. HILL: They are not PEGs. They're

diethanolamines or monoethanolamines is what they really are.

DR. SHANK: The dictionary calls them PEGs but they're not. So, if you have to stick with the dictionary then include them but --

DR. HILL: And from there it jumps up to five and I think, you know, it would be minimal. Well, it would be nice to have data to say there is minimal PEG-2 level compounds in those PEG-5 and above.

DR. SHANK: In the new ones but in the other ones there's PEG-3 if I remember correctly.

DR. HILL: In the add-ons?

DR. SHANK: No, not in the add-ons. In the already reviewed.

MR. ANSELL: Perhaps it's not time to open it but there is data on PEG-2 even if it might not be a good choice for this family. So, I think that's the discussion.

DR. HILL: Okay, well what I wanted to get at, I was very emphatic about it when we discussed this before is because of that nitrogen there. They're not PEGs. PEGylated amine and that's different. And so, when you have PEG-2

what you really have a diethanolamine and if there's impurity in there it's going to be a monoethanolamine. So, then we're in a totally different regime than if we get up to where it's PEG-5. Then there will be minimal quantities of mono or diethanolomines in there.

MR. ANSELL: We're not asking, perhaps, for read across down to two, providing data on two.

DR. HILL: Yeah, okay. Yes. But I would say this --

MR. ANSELL: This is, you know --

DR. HILL: But I'm suggesting that --

MR. ANSELL: We would just like to have this discussion and I don't think that's today.

DR. HILL: No. I was just suggesting, I don't want to see them lumped in personally because I think we're in a very different class of compounds. But that's just my opinion, take it or leave it.

DR. MARKS: Well, I think the other Ron was questioning that, too. And the caveat there was if it's in the dictionary do we have to include it as a PEG since in the dictionary it's a PEG-2

even though chemically it's not truly a PEG. So, we can have that discussion --

DR. HILL: That's fine.

DR. MARKS: -- question of excluding PEG-2, not really a PEG chemically. Let's just go down. So, physical and chemical properties we're all okay? Especially nitrosamines, we can use a nitrosamine boiler plate.

Genotox, we're fine with that?

DR. SLAGA: We are fine.

DR. MARKS: 28 dermal tox using PEG-2. Well, if we eliminate PEG-2 then is it necessary? It is necessary we include PEG-2, Jay are you implying or does the EPA, the structural, the SARs eliminate the need for the 28 day?

It's interesting if we eliminate PEG-2 we get rid of a couple of the insufficiencies like the dermal sensitization we added for PEG-15. We'll have to look at that again. I think that's okay for me to go down to smaller PEGs. I don't know what you feel about that, Ron Hill.

Am I right that only PEG-15 cocamine is the one being used right now?

DR. HILL: It looked that way to me.

DR. MARKS: Yeah. So, it looks like we have all of these met. The insufficiencies particularly if we exclude PEG-2. How about these additional 38 ingredient add-ons at the bottom of Alan's memo there. We didn't talk about that.

So, there are these tallow, the lauaramine, the oleamine, the pomitamine, rapseedamine, soyamine. Do we want to include those 38? Do we feel comfortable? And again, these are supposed to be no-brainers if we're reopening.

DR. SHANK: I would include them except for the PEG- 2.

DR. MARKS: Okay, except PEG-2. Tom?

DR. SLAGA: I agree.

DR. MARKS: No alerts there and, Ron, when you look at those at the bottom, did you look at those?

DR. HILL: You know, since they're named as PEG-2s that's -- I guess I would say misnamed as PEG-2s but they are, maybe they need to be included if we're going to open it.

DR. MARKS: Well, no, I think we can make --

DR. HILL: But I just feel that they're misnamed based on what they really are.

MR. ANDERSEN: Well, I would recommend you do this in two steps so that what Jay is asking in terms of the bully pulpit to discuss them actually happens. I'd just reopen the thing period.

DR. MARKS: Right.

MR. ANDERSEN: You should express the concerns about the PEG-2s. Note that they may or may not even be PEGs and make the point that that's going to be an item for discussion when we next look at this and they may not stay in.

MR. ANSELL: I agree with Alan. I mean, the threshold for the panel is the program serious enough to justify your time. And I think just by virtue of this discussion there's substance enough in here to suggest that if you do reopen it to look at it. And does not preclude any particular decision going down the road.

DR. MARKS: Oh, I agree. I'm just kind of anticipating today, you know, what would we need from the add- on ingredients. Is there some "no-brainers" that we remove right off the bat?

As I said, our team, actually if I'm correct looking at the minutes, we were going to reopen it last year.

MR. ANDERSEN: Yes. That is correct.

DR. MARKS: So, we're back and that's what we said last year. And that's what I'm going to move this year, we reopen. Okay. With the caveat of the PEG-2 and then with the caveat that the additional 38 ingredients listed at the bottom of the memo be included except for possibly PEG-2 additional ingredients.

Okay. Any other comments? Next is alkyl esters. So, in March of this year we opened a re-review of acetyl esters. And then in September we were finding ingredient add-ons. They're on page 39. And so, now I think we're at the point we have in front of us an amended safety assessment of the alkyl esters. Do we move forward with issuing a tentative amended safety report? And are the ingredients now okay? That's in with the table on page 72, 73. So, I guess we should just confirm that indeed what was captured were.

So, if we look at table 1 on panel book

page 72. Does that look okay?

DR. SHANK: Well, this is the same as the list in the conclusion, right?

DR. MARKS: Okay. Do we have any needs? So, I was looking back on page 77. We had the isopropyl lineolate was insufficient because of human irritation and sensitization in genotox. Tom, you thought the genotox was okay? And I wasn't sure. On September 12th we concluded that it was now safe but I didn't see any data to support the irritation sensitivity. Did I overlook that? Monice?

MS. FIUME: Regarding the irritation, the conclusion is going to be stated safe when formulated to be non- irritating.

DR. MARKS: To be non-irritating. Okay. Any other comments?

DR. SLAGA: Great report.

MS. FIUME: Thank you.

DR. MARKS: Yeah. Safe to be non-irritating. Inhalation boiler plate, was that in there?

MS. FIUME: Yes, on the bottom of CIR panel book page 45, report page 7.

DR. MARKS: Okay. Any other comments? So, presumably, I'll be seconding a motion to move forward with a tentative amended safety assessment of the alkyl esters. They're safe as long as formulated to be non-irritating. Tom, Rons, sound good?

DR. SHANK: Yes.

DR. MARKS: Okay. Next is the alkyl ethylhexanoates. So, in September the panel split the alkyl ethylhexanoates from the bigger alkyl esters to focus on the reproductive toxicity of the two ethylhexanoate assimility. This amended report with 15 ingredients that are added. So, are the ingredients okay? That's page 32.

DR. SHANK: The only one that may be a concern as far as I'm concerned is the ethyl hexalt, ethylhexanoate. That's the smallest molecule in the series. We have no information on it. And it might be worth considering to ask for skin penetration data. We don't have any data on ethylhexanol which would be possibly a metabolite.

DR. HILL: We did have data some time

before on ethylhexoalcohol.

DR. SHANK: We did?

DR. HILL: Yeah, we put it in one of the reports.

DR. SHANK: Cause it's not listed on table 2.

DR. HILL: No, I think it might be in the alkyl esters one. I'll check it because even the one we just did; we have ones that ethylhexoalcohol as the alcohol part. It was the one specifically with the acid part that we split out.

DR. SHANK: Okay, then that should be --

DR. HILL: I'll go back and look.

DR. SHANK: That should be added to table 2 on panel book 35.

DR. HILL: I think so, yes. I think so, yes.

MS. FIUME: Ethylhexoalcohol?

DR. HILL: Yes. I know we've looked at that carefully and going back to see if we put it in that one we just looked at and set aside.

DR. SHANK: The alkyl esters?

DR. HILL: Yeah. I thought that's in

there.

DR. SHANK: I don't see it.

DR. HILL: I don't see the alcohol listed separately but I know we've done and I know in one of those reviews, we should probably go back and find it.

DR. MARKS: Which alcohol?

DR. HILL: Ethylhexoalcohol. Data was supplied because of the concern I raised. There was specific data on that alcohol that was supplied in one of the reports. It wasn't listed separately in this but it's one of the ones that cross listed in this one. I just don't remember which one. It wasn't just a trivial submission. There was actually pretty substantial data on that alcohol.

DR. SHANK: And no concerns?

DR. HILL: Nothing that I recall jumping out at me and it was in the context of an ester where that was used at pretty high concentrations.

DR. SHANK: Okay.

DR. HILL: I'm not sure why it shouldn't be because you would think that would be oxidized

up to the acid and if it's a concern with the acid, you would think it would be with the alcohol. Nothing came out if I remember..

DR. MARKS: So, in that --

MR. ANDERSEN: We will find that..

DR. MARKS: -- in that case, Ron, would you --

DR. SHANK: That would have to be added to the report.

DR. MARKS: So, at this point how would you like to deal with the ethylhexal?

DR. HILL: I still agree with him though because --

DR. MARKS: -- ethylhexanoate.

DR. HILL: -- it's the acid component that was the reproductive toxicology concern. And that's the shortest chain one, right? The smallest molecular weight of the group and it's significantly smaller. It's considerably smaller than most of the rest of them.

DR. MARKS: So, since this is an amended safety assessment, should we just eliminate it?

DR. SHANK: I would but if we have the information --

DR. HILL: Is it in use?

DR. SHANK: -- then we should table it until that information can be added.

DR. MARKS: Is it in use? I don't think so. Now, let's see here. Ethylhexal. Yes, it is. 20.

DR. HILL: Yes, it is.

DR. MARKS: It is in use.

DR. HILL: In leave on products up to eight percent according to this. We should leave it and demand the data. Can we have split conclusions where it's sufficient for everybody but this guy?

DR. MARKS: Oh yeah, we've done that.

MR. ANDERSEN: Yes you can but procedurally this was your option to pull the ethylhexanoate compounds out --

DR. HILL: Yes.

MR. ANDERSEN: -- of the previous report --

DR. HILL: Yes.

MR. ANDERSEN: -- and proceed with them separately. So, in fairness to interested parties your first step should probably be to

issue an insufficient data announcement that says we need data for this one.

DR. HILL: And this is really a new report, right? I mean functionally this is a new report since we took it out?

MR. ANDERSEN: Well, we're backing into it but I think it's perfectly appropriate to ask for more data if you think those data are needed.

DR. HILL: It's in use so we should get it.

DR. MARKS: Data for ethylhexanoate and --

MR. ANSELL: So, this was not an add on to a re- review?

MR. ANDERSEN: The ethylhexanaote is an add on to the cetearyl ethylhexanoate. There is no reason that you couldn't just decide not to add it. That's also an option. It's under your control.

DR. MARKS: Exactly. It's a no-brainer. The question is do we want to just eliminate it or do we want to see if there's --

DR. SLAGA: Wouldn't it be easier to eliminate it?

DR. MARKS: Would be easier but if it's in use?

MR. ANDERSEN: My concern is that there's also the logic that if there are uses then maybe somebody actually has those data. If we just ask for it we'll get it.

MR. ANSELL: But that's not where we are in this process. It's cleaner to not add it. If there's a concern about the material, let's prioritize it and move it forward. But to get to this point and then go insufficient because it was a no-brainer just doesn't make any sense to me.

DR. SHANK: Okay, refresh my memory. Originally this was --

MR. ANSELL: This was a re-review.

DR. SHANK: -- had a re-review --

MR. ANSELL: We added a bunch of stuff. You guys decided that a number of them didn't fit in the re-review. You ended up dropping them. We decided to make a re-review B.

DR. SLAGA: Yeah.

MR. ANSELL: And now we're looking at it --

DR. SHANK: So, under the no-brainer

rule it goes. Ethyl esters --

MR. ANSELL: That's fine.

DR. MARKS: Yeah, in '82 the cetearyl ethylhexanoate was safe and then in the re-review '06 it was safe. And now we decide to open it for adding ingredients, just as Jay said, and then split it out so that cetearyl has been -- of the ingredients that's the one that's been reviewed. And then, we have these add ons. And that's exactly right. Procedurally, if it's a no-brainer it should be eliminated.

MR. ANDERSEN: So, if we only add 14 instead of 15 I'm not going to lose any sleep.

DR. SLAGA: Yeah.

DR. MARKS: Well, I'm not so sure it's not a --

MR. ANDERSEN: It's a good expansion.

DR. MARKS: So, when I look at it cetearyl ethylhexanoate has 262 uses under the use table up to a 77 percent concentration. And I didn't see any data to suggest that that was safe to be used at 77 percent.

DR. SHANK: I'd have to go back to the original report on that.

DR. MARKS: Well, there --

DR. SHANK: It was used up to what, 30 percent when we reviewed this --

MS. FIUME: Dr. Shank, cetearyl ethylhexanoate you received wave 2 data saying that that higher use concentration in nail products, that nail product is no longer being produced.

DR. SHANK: Okay.

MS. FIUME: So, cetearyl ethylhexanoate is still being used at the same concentration as before. Cetyl ethylhexanoate is an add on and that is being used at a higher concentration.

DR. HILL: 77 percent specifically.

DR. MARKS: Yes, that's why I -- that's why --

MS. FIUME: It's 52 percent in lipsticks.

DR. SHANK: So, maybe we should scratch that one as well.

DR. MARKS: Yeah, that's --

MR. ANDERSEN: But cetearyl is a mixture of cetyl and something else so --

MR. ANSELL: That's right.

DR. MARKS: So it should be okay is what you're saying, Alan?

MR. ANDERSEN: Yeah.

DR. MARKS: Okay. Fine. So, then we would eliminate just the short chain, shortest chain. Does that sound good?

DR. SHANK: Does to me.

DR. HILL: In terms of read across, yes.

DR. MARKS: That would be the ethylhexanoate. And then we would add the amended safety assessment that this is safe. These ingredients are safe, correct?

DR. SHANK: Yes.

DR. MARKS: So, this would go to an amended tentative safety assessment. Okay.

Any other comments? Anything in the discussion?

MR. ANDERSEN: This goes out for public comment. If industry wants to rescue ethylhexanoate then they can provide data.

DR. HILL: That's good.

DR. MARKS: And in the discussion --

MS. FIUME: I'm going to do background work --

DR. MARKS: In the discussion, then would we repeat as amended, do we repeat the same discussion item about the two ethylhexanoic acid that was in the previous report about liver and developmental toxic and then just basically repeat what was said before?

MR. ANDERSEN: Well, I'd like to find those data anyway. So, yeah, we'll --

DR. MARKS: Okay.

MR. ANDERSEN: -- make the college try to find --

DR. HILL: Well, now, okay. Yeah, what he's asking about is the ethylhexanoic acid.

MR. ANDERSEN: Oh, I'm sorry.

DR. HILL: That's discussed in the alkyl esters report.

DR. MARKS: Correct.

DR. HILL: So, we just rolled it over --

MS. FIUME: And it's one page 4 --

DR. HILL: Its there, right?

MS. FIUME: -- panel book page --

DR. MARKS: So, it's on page 35, yeah. I just --

MS. FIUME: Okay. But on CIR panel book

page 31, in the draft discussion I had brought that language in from the re-review from last time.

DR. MARKS: Okay. Any other comments? So, tomorrow I'll move that we proceed with an amended tentative safety assessment of these alkyl ethylhexanoates, all that are listed with the exception of the smallest compound and that they're safe, okay?

Talc. This is the first time we've seen this. It's a thick report. Thanks, Monice. So, we don't have to worry about a lot of add ons on this one do we? It's talc. So, that makes it simple, although it didn't reduce, yeah. So, Tom, it seems like to me when I read it, there's issues of obviously the cancer and whether there's asbestos or not. And is that the reason, the concern? So, would you comment about that, Tom? How do you want to proceed with this? Supposedly, cosmetic grade is asbestos free.

DR. SLAGA: Well, that is as it states very clearly in here, the cosmetic grade now doesn't have the asbestos. It's asbestos free and does not contain the asbestiform fibers. In the

past you used to get in a lot of trouble but still, there's a number of reports. EPA did inhalation studies which were negative and then NTP, which was also negative. But in different other routes of administration has some limited carcinogenicity but still nothing really, you know, the number of adrenal tumors in female rats and low response.

But in every case it was extensively high saturating amounts of the talc which seem to be the high end of the concentration they use. It had some little problems but a number of people in reviewing those suggested that they really were quite the artifact and that to me, in the other aspect it's related to ovarian cancer which the data's really not -- you can't really -- it's association. There's not really studies to really say it has a relationship, a causative relationship to ovarian cancer.

So, you know, it's really this high levels of this that gets everything into bad perspective. But overall, this has been reviewed, the NTP studies and re-reviewed and re- reviewed. And the majority of them always feel that it's the

high level end that is kind of an artifactual relationship to causing problems. So, I have very little concerns.

DR. SHANK: I agree. If topical application of talc leads to cancer of the ovary, why does it not lead to cancer of the cervix and cancer of the uterus? I think this ovarian cancer situation is not a real problem.

DR. SLAGA: Right.

DR. MARKS: So, my only concern was that if I look at the use, anything else, Tom, Rons, the rest of the tox data? Any concerns from you all?

DR. SHANK: No. No tox concerns.

DR. MARKS: Okay. I look at the use, if I go into page 37, if you look under eye shadow there are over 800 uses with a concentration up to a hundred percent. I don't know whether they're using colored talc or what on their eyelids for that but I didn't see any evidence of no irritation of the eyes in terms of studies in there. Did I miss that? So, I didn't see any eye irritation studies and I guess if you look over -- so, I was a bit concerned that if you're

using a hundred percent talc and it got in your eyes what would it do?

Can you get irritated?

MS. FIUME: On report page 9, panel book page 16, I have summary data from the IUCLID data set. And it's no details but that's what I have. And it's not really applicable to the cosmetic use of talc and therefore it's not in this report so that it doesn't skew things. Is that talc is a filler in drugs and you will see a lot of very adverse effects when people inject drugs like illegal drugs. And that's why it's not in here because that has nothing to do with the cosmetic use. And if it travels intravenously it can actually, there are case studies where it caused blindness but that's a totally different effect.

DR. MARKS: Right.

MS. FIUME: So, but that's the only thing I was really able to find ocular. And that's, like I said, not applicable and not in here. But the only eye irritation studies I found were the no detail provided summary data from the IUCLID data set.

DR. MARKS: And there's no use data. It

would have been nice if we had had cosmetic use data that these preparations had contained eye concentrations. But with that and I -- obviously it's not a (inaudible) so I think that's fine then.

Any other comments?

DR. SHANK: Why is molecular weight of talc given the speed of it in '79 I don't understand what that means. That's a little fascinating, isn't it? I didn't --

DR. HILL: I didn't really note that.

DR. SHANK: Here table 2 is just great. All that detail. We used to get that in the old days. Why did you give it to us this time?

MS. FIUME: Because it was one ingredient and it's not going to happen all the time when there's one ingredient. It's more in case you needed to look at the specific type of uses in combination with the toxicology that's presented. That's why. I'm sorry I can't say you can get used to it.

DR. MARKS: So, tomorrow I'll move, well, actually I will probably second then. I'll move that a draft tentative report be issued with talc

as safe.

MS. FIUME: Can I ask what discussion items you will have?

DR. SHANK: The ovarian cancer issue. I have some notes about that in here.

DR. MARKS: Yeah, that's the big one.

DR. SLAGA: And discussion about the (inaudible) and all of them. It's also stated in here that it's a cocarcinogen with benzopyrine. We should discuss that but that's not relevant. People are not putting benzopyrine on unless no one smokes anymore..

MR. ANSELL: Well, it's benzopyrine not a talc.

DR. MARKS: And so, that's ovarian. There's -- okay.

MS. FIUME: Can I ask, panelists, my computer finally got to where I was trying to get with the ethylhexalcohol.

DR. SHANK: Yes.

MS. FIUME: I have one small paragraph on absorption and distribution. Actually, I'll just let you read it rather than trying to read it at the coffee table. Does that answer his

question?

DR. HILL: Yeah, we had a -- I remember when this came out. We had a -- it was either we got it the day of the meeting or we got in a wave 2 and we had it -- I mean it was like a two or three page summary of ethylhexanol with some --

MS. FIUME: Okay. That's not what I found. I found a brief summary from the dicarboxylic acid report that was our appendix and that is what I have on ethylhexalcohol. I'm sorry to go backwards but if we can avoid that tomorrow.

DR. HILL: No, that's okay. Well, the point is it ought to be in that report.

MS. FIUME: I will pull that in.

DR. HILL: Or did we decide we're taking that one -- let's see. We're taking that one out, right?

DR. MARKS: We're taking the ethylhexanoate --

MS. FIUME: Right because we didn't have the information in the short chain.

DR. HILL: Correct.

MS. FIUME: So, I didn't know if that

ethylhexalcohol helps alleviate the concerns.

DR. HILL: And I think the reason we didn't have this in that big long alkyl esters report is because we were using read across from one of the others that had that there already. It gets complicated when it's this reference is this reference is this because I've had the concern since we've been doing some of that that we lose concentration of use information in that. But in this case I didn't have that concern. It was not just concentration abuse but matter of abuse.

DR. MARKS: Okay.

MS. FIUME: It's a pdf so.

DR. HILL: Where did we go? I think we somehow skipped out of it totally. We have to search again.

DR. SHANK: I'm sorry.

MS. FIUME: Is it all use to find it now?

DR. HILL: We were still reading when it skipped here.

MS. FIUME: Sorry. Didn't mean to slow down the meeting.

DR. MARKS: Shall we deal with the last ingredient while you're finding that and not

reopen?

DR. SLAGA: Agreed. The last ingredient, yeah. Not reopen.

DR. MARKS: Re-review of 2-amino 6-chloro 4- nitrophenol and its hydrochloride salts used in cosmetics. In '97 these ingredients were found to be safe up to concentration of two percent. Is there any reason to reopen?

DR. SLAGA: No.

DR. MARKS: No, okay. Hair dye epidemiology boiler plate and we've already discussed self-testing a number of times today. So, won't reiterate that.

MR. ANDERSEN: Just for us chickens, what did you guys decide? Is there a short answer to that?

DR. SHANK: You mean about the self-testing?

MR. ANDERSEN: For self-testing.

DR. SHANK: That applies to all of the oxidative hair dyes. So, we didn't want to add that to one and be -- that would be a generic issue. And the US law still remains the same so I don't know what we would add to it.

DR. MARKS: Yes, so we basically decided not to --

DR. SHANK: Not to address it..

DR. MARKS: Yes.

MR. ANDERSEN: Okay, good. I mean, arguably you guys are the tail wagging that dog. Let the dog figure it out in this case.

DR. HILL: So, we did have a protracted discussion earlier, however, about the fact that when you have an ingredient and I have less concern about this or the phenylinediamine but just in general, but when you have an ingredient that's used in an oxidative hair dye, under the conditions of use other compounds are formed.

As per Julie Skare's presentation, roughly a couple of years ago and it seems may, besides me, got the impression that the bottom lines of that were that things were formed only transiently and that they ended up in the hair as part of the dye constituents. But that's not what I got out of her presentation. So, we had a discussion about that.

MR. ANDERSEN: So, I will hear about that.

DR. HILL: Yeah.

MR. ANDERSEN: Thank you.

DR. HILL: This is the ethylhexalcohol. It's small, you might need --

MS. FIUME: I'll stay back.

DR. HILL: That's kind of where we got in trouble before.

DR. SHANK: So, there's not teratogenic.

DR. HILL: No --

DR. SHANK: Didn't have a reproductive --

DR. HILL: Yeah. It surprises in a way because -- but I'm guessing it's clear and efficiently and not so much oxidized. So it could easily account for that difference from that to the acid.

DR. SHANK: But there's still all these -- still no reproductive tests.

DR. HILL: Reproductive and developmental tests.

DR. SHANK: It's just developmental.

DR. HILL: Oh, okay. It's not true --

DR. SHANK: No reproductive data.

DR. MARKS: So, we will still delete then, ethylhexanoate?

DR. SHANK: I would, yes.

DR. MARKS: Okay, thanks, Monice for finding that.

DR. HILL: Which report is that in?

DR. MARKS: That's in --

MS. FIUME: Alkyl ethylhexals..

DR. HILL: Okay.

DR. MARKS: Okay? Any other business we need to finish before tomorrow's meeting?

DR. SLAGA: We are not supposed to discuss the baby skin in that? That's only tomorrow, right?

DR. MARKS: Pardon?

MR. ANDERSEN: You can talk about it if you wish.

DR. MARKS: My feeling is I thought Ivan did a great job of setting a base line. And I'd like to hear what's "outside" experts have to say from P&G or J&J, potentially UCSF with Elias and Williams.

DR. SLAGA: Is there much data when the microflora starts appearing on the -- right after

birth?

MR. BOYER: I haven't --

DR. SLAGA: I know that's a big thing with the Federal Government now and trying to characterize all of those both internally and on the skin.

DR. MARKS: We think, Ivan, you're up to the task, since you did such a good job with the inhalation boiler plate that we'll eventually have a baby skin boiler plate. We found the inhalation much more complex as we delved into it than initially or --

Okay.

MR. ANSELL: I am sure payments will be more (inaudible).

DR. MARKS: Yes, right. And less controversial, too.

DR. SLAGA: Well, some of the papers we've got it really shows that they can really excrete those pretty quickly, too. May be more protected than us older guys.

MR. ANSELL: Well, and I think from a risk assessment standpoint that's ultimately what they end up concluding is that these

references are small and we count for a 60 or 70 year exposure. So, you know, it's just such a tiny part that, you know, our conservative assumption over conservative assumption over conservation assumption already baked into the model doesn't require another level of conservative.

DR. SLAGA: Well, and --

MR. ANSELL: But we had some very interesting --

DR. SLAGA: As we get older and our skin gets thinner --

MR. ANSELL: That's right.

DR. SLAGA: -- then there's more of a problem with it, right?

MR. ANSELL: We'll be looking forward to the Counsel taking on 50 year old plus.

DR. MARKS: So, geriatric skin will be the next --

MR. ANSELL: That's right.

DR. MARKS: -- get really lazy.

MR. ANSELL: Maybe that's not so --

DR. MARKS: Well --

MR. ANDERSEN: May you live long enough for geriatric skin to be a problem.

DR. MARKS: And then you've got the feedback on the self-testing. We basically didn't want to pursue that any further. We'll wait and see what comes out with the self- testing initiative in Europe. We acknowledge everything that was presented this morning but and the papers --

MR. ANDERSEN: Well, the program that the industry is going to embark will produce data at some point. We'll see what that looks like.

DR. MARKS: We have a boiler plate on self-testing? Do we or do we not?

MR. ANDERSEN: Yes. Our boiler plate focused on the singular question of when do you read the tests? And at the time when the panel looked at it, industry was advising people to look at 24 hours. And the panel was time out. 24 hours is too soon. You've got to wait 48.

DR. MARKS: Okay.

MR. ANDERSEN: So, you made that pronouncement and I think, obviously I don't buy a lot of hair dye but I assume it would -- stating the obvious. I'm assuming that 48 hours is currently what's recommended. So, the panel's

input into that debate was when do you look at it.

The need for the instruction to self-test is currently mandated if you wish to have the coaltar exemption. If you don't care to have the coaltar exemption, you do whatever you want. I don't think anybody's ever going to do that but it's an option. So, but there's an awful lot of products out there that without that instruction for self- testing I think FDA would take misbranding action against them. Or at least the option would be there.

DR. MARKS: Okay? Any other comments? We're adjourned.

(Whereupon, 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.

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Notary Public in and for the District of Columbia

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