128th COSMETIC INGREDIENT REVIEW EXPERT PANEL

MEETING

BREAKOUT SESSION

Washington, D.C.

Monday, September 9, 2013

PARTICIPANTS:

Voting Members:

DONALD V. BELSITO, M.D.
Clinical Professor, Medicine (Dermatology)
University of Missouri, Kansas City c/o American Dermatology Associates, LLC

DANIEL C. LIEBLER
Director, Jim Ayers Institute for Precancer Detection and Diagnosis
Ingram Professor of Cancer Research
Professor of Biochemistry, Pharmacology and Biomedical Informatics

PAUL W. SNYDER, D.V.M., Ph.D.
School of Veterinary Medicine
Department of Veterinary Pathobiology
Perdue University

Liaison Members:

CAROL EISENMANN, M.D.
CIR Industry Liaison

JAY ANSELL, Ph.D.
LINDA LORETZ, Ph.D., DABT
Personal Care Products Council

KAPAL DEWAN
Food and Drug Administration

Staff Members:

HALYNA P. BRESLAWEC
Deputy Director

LILLIAN C. BECKER
Scientific Analyst

IVAN BOYER, Ph.D.
Senior Toxicologist

PARTICIPANTS (CONT'D):

MONICE FIUME
Senior Scientific Analyst

WILBUR JOHNSON, JR.
Senior Scientific Analyst

CHRISTINA L. BURNETT
Scientific Analyst

LILLIAN J. GILL
Deputy Director

BART HELDRETH, Ph.D.
Chemist

Other Attendees:

BRIAN HUGHES
Dow Chemical Company

DAVID GOLDSTEIN

* * * * *

P R O C E E D I N G S

(8:45 a.m.)

DR. BELSITO: Okay, are we all set? Everybody's computer is up?

DR. LIEBLER: At least you don't have to bother with all that encryption anymore.

DR. BELSITO: Why's that?

DR. LIEBLER: Just lay it out there. It's already out there.

DR. BELSITO: Okay, so I guess we're doing methyl glucose first? Is that correct? So we issued a revised tentative report that the ingredients were safe in the present practice of use and concentration based upon Wave 2 data that we had gotten on a mixture of methyl glucose. Our concern was about oral toxicity, possible repro toxicity, in lipstick products. So we're looking at this to see if with the addition of that material we still agree. I had some minor edits, but don't really have any significant issues with the report. Dan? Paul?

DR. SNYDER: I agree.

DR. LIEBLER: I think it's in very good shape. I made a minor edit to the discussion about the wording of impact of methyl glucose on metabolism. And the proposed revision underlined in the beginning of the discussion, I was okay with that.

DR. BELSITO: That's the suggested revision that the Council had made? Is that what you're talking about?

DR. LIEBLER: Yes.

DR. BELSITO: In the discussion, yeah.

DR. LIEBLER: And it's in the actual discussion text underlined. So I had no problem with that.

DR. BELSITO: Yeah, I agreed. I thought it made the document stronger, particularly now that we have the oral and repro studies on the mixture. Paul?

DR. SNYDER: Yeah, I just had a change here in the revised and in the abstract.

DR. BELSITO: Okay.

DR. SNYDER: We're not really worried

about systemic toxicity. We're worried about systemic exposures. And so the abstract issue was related, too. It says, "No significant skin penetration."

DR. BELSITO: You're at the beginning of the document?

DR. SNYDER: Yeah, and it's linked here, the two issues are linked so to speak. So I revised the middle sentence there where it says --

DR. BELSITO: You're back in the abstract?

DR. SNYDER: In the abstract, yeah. Where it says, "After reviewing the data, including the molecular weights, log Kows and other properties of these ingredients, the Cosmetic Ingredient Review Panel determined that there likely would be no significant" and then instead of "skin penetration of these ingredients," I changed that to "systemic exposures from cosmetic use" because that's really the two things we're trying to bring in there, really systemic exposures and cosmetic use.

DR. LIEBLER: I could live with that. So you would say, "There would likely be no significant systemic exposure from cosmetic use of these ingredients."

DR. SNYDER: Yes.

DR. LIEBLER: That's good. That gets us away from how many molecules are dancing-on-the-head-of-a-pin argument about penetration.

DR. SNYDER: Yeah.

DR. BELSITO: So "no significant systemic exposures."

DR. SNYDER: "No significant systemic exposure from cosmetic use of these ingredients." And then just to make that consistent with that revised in the -- this comes up on several reports where we talk about toxicities, and I'm trying to move it away from the issue of toxicity then to exposure. So then in the discussion on the revised sentence there at the bottom of page --

DR. BELSITO: There are no page numbers, at least not on mine.

DR. SNYDER: Page 36.

DR. BELSITO: Page 35 of the document.

DR. SNYDER: So instead of "would not cause systemic toxicity" to "would not result in significant systemic exposures," or "result in systemic exposures."

DR. BELSITO: And "significant" or just "systemic exposures?"

DR. LIEBLER: You know I don't know that we have to actually make the same point with the exact same wording because this one actually -- this sentence also refers to the toxicity data. So "molecular weights log K and toxicity data."

DR. BELSITO: That's true.

DR. LIEBLER: So I think the conclusion of that sentence probably should focus on toxicity.

The other edit I completely agree with and I think it's fine, the one in the abstract. And you've got in the sentence --

DR. SNYDER: But, again, I'd just exert caution in that we're implying there that toxicity

is an issue, and I don't think we really saw any significant toxicity.

DR. LIEBLER: Right.

DR. BELSITO: But we said that there is none. So Dan has a point because we have some tox endpoints now. So we'll stay with the Council's revision?

DR. SNYDER: Okay.

DR. BELSITO: And then on page 36 of the document -- not the document, page 36 of my.pdf, I don't have any document page numbers -- second line from the top you say, "structure-property relationships." Do you mean "structure activity relationships?"

MR. JOHNSON: Yes.

DR. SNYDER: Yup.

DR. BELSITO: So could we change that?

DR. SNYDER: So this has turned into mostly -- it's inconsistent in how it's written. And so I think we need to talk about that at some point about what we want that statement to say because I think every writer has a different

version that they're using.

DR. BELSITO: So what you want here is that we look at a boilerplate for read-across essentially?

DR. SNYDER: Well, the read-across strategy. And so I said we need consistent wording on read-across strategies.

DR. BELSITO: But are we going to accomplish that at this meeting? I don't think so.

DR. ANSELL: No, the boilerplate --

DR. BELSITO: But I think it should be -- we can bring it up when we do this report or the first report that we do, which will be --

DR. ANSELL: Make a request to staff to come forward with -- as they have with botanicals -- come forward with some draft.

DR. SNYDER: Well, we can talk about it when we get to isethionates.

DR. BELSITO: Isethionates, which would be the first one.

DR. SNYDER: Because I think the

abstract also needs to be brought up, too. The abstracts are written very differently. Some have more data in them. Some have no data in them. Some start off with this is a safety assessment, and they're quite different in how they're constructed. And I thought we'd agreed previously that we were going to have -- what was reviewed, what was found, and what was the conclusion -- a very simple abstract, and we seem to have drifted away from that.

DR. BELSITO: Okay, so when we get to isethionates, we'll discuss abstracts and boilerplate or read-across from boilerplate.

Going along on page 36 of the document -- this is in the second paragraph where we're talking about lipsticks -- it says "the use concentrations reported (up to 1 percent) are considered low to the extent that it is unlikely that systemic toxicity would result from repeated ingestion." That to me sounds a little like we're waffling, but it's unlikely. Do we want to make that statement stronger or is everyone happy with

that? It's sort of like oh, this is safe because it's unlikely.

DR. SNYDER: There's another report that also has a similar issue. Some reports have too many "unlikelys" and too many "maybes" or "possiblys." And so I think we as a Panel need to be a little bit more firm in our --

DR. LIEBLER: Oh, I think we could use much more direct language here in this particular sentence and to simply say "to the extent that systemic toxicity would not result."

DR. BELSITO: Okay.

DR. SNYDER: Where are we?

DR. BELSITO: It's in the second paragraph where we're talking about the use in lipsticks and that we "relied on the isostearic acid esters with methyl alpha-D glucoside to support safety based upon the oral and lack of reproductive effects." And then we go on to say "The use concentrations reported are low to the extent that it is unlikely." But I agree. I like Dan's statement: "To the extent that systemic

toxicity would not result."

DR. LIEBLER: Right.

DR. ANSELL: Probably "such that" instead of "to the extent."

DR. SNYDER: I'd revise that sentence to say "The use in concentration reported (up to 1 percent) are considered low to the extent it is unlikely that significant systemic exposure would result from repeated ingestion."

DR. BELSITO: You could do that, but I said I like what Dan said.

DR. LIEBLER: I think the issue is toxicity, whether there's toxicity or not. I mean exposure isn't necessarily a surrogate for toxicity. This is related to the point we just discussed in the other sentence about couching our conclusion that contact to the exposure versus toxicity or safety basically. So that's why I think I would rather stick to the toxicity language.

DR. SNYDER: So we just change it to "extent --

DR. BELSITO: "To the extent --

DR. LIEBLER: And actually "significant --

DR. SNYDER: "Systemic toxicity."

DR. LIEBLER: Yeah, and Jay just made a suggestion that I like -- "are considered low such that systemic toxicity would not result from repeated ingestion" and that saves a half a sentence.

DR. BELSITO: "Such that systemic toxicity would not result from repeated ingestion."

DR. ANSELL: That may be a double negative.

DR. BELSITO: "Use concentrations reported up to 1 percent are considered low such that systemic toxicity would not result from repeated ingestion."

DR. ANSELL: Right, except right now it's written as "unlikely" that it would.

DR. BELSITO: Right, but we got rid of that.

DR. ANSELL: That's right.

DR. BELSITO: "Such that systemic toxicity."

DR. SNYDER: "Repeated ingestion." We've always got to tie it to cosmetic use. You certainly could ingest enough.

DR. BELSITO: "Would not result from cosmetic use in lipsticks" if we really want to be --

DR. SNYDER: I think we have to.

DR. BELSITO: Okay.

DR. LIEBLER: You couldn't afford to buy enough to make you sick.

DR. BELSITO: So is it expensive?

DR. LIEBLER: I'm assuming.

MR. JOHNSON: Dr. Belsito, so you're replacing "repeated ingestion" with "cosmetic use in lipsticks."

DR. BELSITO: Let me just pop up the thing if I can. Yes, from "cosmetic use in lipsticks."

MR. JOHNSON: Okay, thank you.

DR. BELSITO: And then in the next paragraph, again I think we're sort of very weak in our statement in the third, fourth, fifth line down. It says "Overall, therefore, any impact of dermal application of these ingredients on glucose metabolism would be very unlikely."

DR. SNYDER: So I completely revised that up to the previous sentence. "The potential for complete deesterification of these ingredients to produce methyl glucose was considered insignificant and, therefore, not interfere with glucose metabolism." I think it was just a little --

DR. BELSITO: So get rid of "Overall, therefore, any impact."

DR. SNYDER: Yeah.

DR. BELSITO: Okay. So could you repeat that?

DR. SNYDER: Yes. So after "insignificant and, therefore, not interfere with glucose metabolism."

DR. BELSITO: So rather than going

through this whole convoluted explanation, it's to the point, sweet and to the point. Did you get that, Wilbur?

MR. JOHNSON: Yes, I did.

DR. BELSITO: For the conclusion, Wilbur, you say "The CIR Expert Panel concluded that these cosmetic ingredients." I thought that we should say "The following methyl glucose polyethers and esters" so that it's right up in the sentence what the family name of this grouping is. And then I just had some minor typos. Dan? Paul?

DR. LIEBLER: I have one suggestion, Wilbur, where the -- I think it's on.pdf page 42. It's one of the structures in the table. It's the PEG-120 methyl glucose dioleate. It's a pasted-in structure from another file. You actually indicate it's from the Chemical Abstract Service Registry file. I suggest we just adopt the same representation for all the structures. So this one -- if these others were drawn in, then this one just needs to be drawn in with the same

software so that these structures have a uniform appearance in the document.

MR. JOHNSON: And that's the PEG-120 methyl glucose dioleate?

DR. LIEBLER: Yes, the one that looks different. I'll have the same comment on almost all the reports.

DR. BELSITO: Yeah, there was one where it suddenly went blurry.

DR. LIEBLER: Right. That's all fixable.

DR. BELSITO: Maybe for you, not for me. Paul, anything else?

DR. SNYDER: No, I'm good.

DR. BELSITO: So polyquaternium-22 and -39. This is another one that we went safe in present practice of use and concentration in cosmetics back in June. We talked about the absence of animal and human sensitization data for the -22 that concluded that they're large and they would not likely get past the stratum corneum. We were concerned about contaminants, and we got

information regarding the acrylamide monomer, which is not in -22 and that the -39 contains less than 1 part per million. So that's where we are. We didn't think it would be a problem because of the concentration of use of polyquat-39. So pretty much all the data that we had is here, and the question is are you all satisfied with the discussion and the conclusion as written? I had no significant edits here.

DR. SNYDER: I just had one minor edit in the discussion.

DR. BELSITO: Okay. What page? Give us the page.

DR. SNYDER: It's in the beginning of the discussion.

DR. LIEBLER: It's.pdf page 19.

DR. SNYDER: The sentence in the middle of the second paragraph begins with "However." "However, it was concluded" not agreed "that these polymers are large, highly polar molecules that would not be absorbed and based on oral exposure studies, the systemic toxicity is not likely from

a cosmetic use."

DR. BELSITO: So delete "agreed" and put in "concluded."

DR. SNYDER: It's a little more scientific term.

DR. LIEBLER: So you could also say "However, these polymers are large" and avoid the prepositional phrase altogether.

DR. BELSITO: So you're saying, "However, these polymers are large."

DR. LIEBLER: Yes.

DR. BELSITO: "Highly polar molecules would not be absorbed and based upon acute oral exposure studies" -- so how do we -- "However, these polymers are large, highly polar molecules that would not be absorbed and systemic toxicity is not likely."

DR. SNYDER: "Under cosmetic use."

DR. BELSITO: So we're getting rid of "based upon acute oral exposure studies," and just say "absorbed, and systemic toxicity is not likely."

DR. SNYDER: Well, they're all okay because the oral helps not absorb.

DR. BELSITO: "And, based upon acute oral exposure studies, systemic toxicity."

DR. SNYDER: "Is not likely in cosmetic use."

DR. BELSITO: But, again, that sounded weak. Isn't "is not likely?"

DR. SNYDER: Yeah, I don't like those "not likelys," yeah.

DR. BELSITO: "Systemic toxicity from --

DR. SNYDER: That's why I think there's -- I just like the exposure thing because then there's potential for systemic exposure.

DR. ANSELL: I like the exposure discussion, but in many cases we're not actually talking about systemic exposure. We're actually concluding that there's no structural alerts. There's sufficient data to conclude that the material -- and then the final part is whether you say it's not of concern. I think the FDA often says that. Unlikely is probably more equivocal,

equivocating.

DR. SNYDER: "Systemic toxicity from cosmetic use is not a concern."

DR. BELSITO: "Systemic toxicity from cosmetic use is not a concern."

DR. SNYDER: That's good.

DR. BELSITO: Okay, any other edits?

DR. LIEBLER: The last sentence of the first paragraph of the discussion. It currently reads "Therefore the Expert Panel considered these unreacted monomers to be low and of no toxicological concern given the low use concentrations for these ingredients." So I reworded that to "Therefore the Expert Panel considered these unreacted monomers to be present at levels that would not cause toxicity given the low use concentrations."

DR. BELSITO: So "considered these unreacted monomers to be --

DR. LIEBLER: "Present at levels that would not cause toxicity."

DR. BELSITO: "Given the low use

concentrations."

DR. LIEBLER: Correct.

DR. BELSITO: "To be present at levels that would not cause toxicity."

DR. LIEBLER: Correct.

DR. BELSITO: Any others?

DR. SNYDER: Not from me.

DR. BELSITO: So chamomile, by which we mean matricaria recutita, not the Roman chamomile. I guess the first comment that -- well, just to tell you where we are with this. I can't find it in my report. But basically we looked at this in June and it was lumped with anthemis nobilis, and we said wait a minute. These are two different plants, and we need to separate them out and look at them separately. So that's what we did. For the chamomilla recutita, we asked for sensitization at 10 percent and composition of ingredients other than the oil and sensitization and irritation data at the highest level of use. So we've gotten some new unpublished skin irritation and sensitization data. We've updated

the use concentration data. We also said, wait a minute. This chamomilla recutita has a lot of bisabolol in it, and let's look at our safety report on that. So that's where we are here.

I guess my first comment on this report is first of all, kamillosan is referenced in both this report and in the anthemis nobilis report. In the anthemis nobilis report, it's said to contain 10.5 percent anthemis nobilis. And then it starts showing up in this report. So I don't think it's both. So we need to clarify it. I mean my reading of the anthemis nobilis report suggests that kamillosan is probably anthemis nobilis; however, having said that, my understanding of the alternative medical use for "chamomile," namely chamomile tea and all of these topical and nutritional supplements that are available in Europe, are actually chamomilla recutita; that when people talk about chamomile for botanical drug use, that's the species they're referring to. Having said that, I agree when we're -- if we're going to put data in where we're

not sure, where it just says "an extract of chamomile" or "a chamomile tea was applied to tinctures to the eyes of reproducing conjunctivitis," either it shouldn't go in either report or it may be should go in both reports and say we're just not sure whether this is matricaria or chamomilla recutita or it's anthemis nobilis. But kamillosan definitely has to be one or the other, and we should be able to see that from the manufacturer.

DR. SNYDER: I agree. I had the same issue with regard to the studies in which we don't know which species was used in the testing. So it either has to go in both reports or it has to be deleted from both reports.

DR. BELSITO: Right now it's in both reports pretty much, and that may be okay because by and large they sort of add to support safety of one or the other. But I also think maybe when we're putting them in, somehow there should be a subheading that says "Chamomile Species Unknown" or something so we separate it out and it's a weak

component of that part of the document, if we're going to keep it in.

MR. JOHNSON: Dr. Belsito, what particular study are you referring to with the kamillosan?

DR. BELSITO: Just put "find kamillosan." You'll find it in both the anthemis nobilis documents where at one point -- I mean when we get to the anthemis nobilis, you'll see it, but it says that kamillosan (10.5 percent). I can look it up right now actually. Let me just close out of here and go to anthemis nobilis. Kamillosan is with two "ls," right? So on document 25, not the page number but the document, but 25 of the.pdf, the second paragraph. On anthemis nobilis it says "kamillosan ointment (containing extracts and oil of anthemis nobilis 10.5 percent) to treat cracked nipples." So that's in the anthemis nobilis report. And then in the chamomile report, again you have -- well, I thought I saw kamillosan here.

MR. JOHNSON: Actually it's right before

the use section, the paragraph immediately above that.

DR. BELSITO: Oh, I just misspelled it and that's why I didn't find it. Yeah, so just above it says "kamillosan, an alcoholic extract of chamomile flowers that contains 100 milligrams of chamomilla recutita." I mean maybe it contains both, but I think we need to verify that. It seems to me to be strange that it would be 10.5 percent anthemis nobilis and 150 milligrams of chamomilla recutita. Maybe it is, I don't know, but it was just strange that it appeared in both reports.

And then under Non-Cosmetic Use you talk about "Kamillobad and mouth sprays, Kamillosan M spray, containing chamomile extracts." So I think you need to get the MSDSs or whatever for those products and check them again and make sure that they're in the proper report. It comes up in case reports also in kamillosan.

I think, again, my understanding is that the alternative medical uses for chamomile are all

matricaria or chamomilla recutita, not anthemis nobilis, but I may be wrong.

DR. SNYDER: So going back to chamomilla recutita, we're still insufficient there.

DR. BELSITO: Okay, let me go back through the whole thing. Go ahead, Paul, while I go back through that document.

DR. SNYDER: Well, we had previously gone -- in June we had gone insufficient for skin irritation and sensitization with the flower extract at 10 percent, and we received it at.3 and.2 -- irritation at.3 and sensitization at.2. And then we did get another -- on the second Wave we got an eye lotion at.4 percent with flower extract on 100 individuals. So we're still --

DR. LIEBLER: So my question is was the 10 percent real? That's so high.

MR. JOHNSON: No.

DR. SNYDER: It's at 0.5.

DR. ANSELL: It's been corrected.

DR. LIEBLER: Oh, okay, I didn't see that anywhere.

MR. JOHNSON: Yeah, it's 0.5.

DR. SNYDER: Is the highest use now?

MR. JOHNSON: Yes.

DR. ANSELL: The new maximum is 0.5 flower extract in lipstick.

DR. BELSITO: Well, I thought, though, it was -- well, first of all, again, in the introduction, we need to list what we're reviewing. It says "ingredients as used (German chamomile)," "information relevant to verify 11 chamomile ingredients as used in cosmetics." I think we need to list the ingredients right up front that we're discussing because it's not in the title. And it's like you start the document, you really don't know what the heck you're going to be looking at.

DR. SNYDER: This one has the missing abstract.

DR. BELSITO: Yeah, it's missing an abstract as well, but I mean that's because it's really the first time we're looking at it when an abstract hasn't been generated. But I think as a

matter of just boilerplate, except when it's 5 million products like the PEG-PPG document where you can just reference Table 1 or some table in the document, I think what we're reviewing when it's only five or six or seven ingredients should be listed up front in the discussion -- I mean in the introduction.

I also think that it remains insufficient, but not for sensitization and irritation. I think we have all the information on the flower ingredients, and we have no information on the plant and stem and really whole extract, and they're not really used in cosmetics. If you look at what's used, probably because the plant and the stem of chamomile are not used in cosmetics. It's the flowers that are used. But I don't think that we can rule on the safety of the plant stem because when you look, we have no composition data and there's maybe one or two studies that just say "chamomilla recutita extract," which I would suspect is the flower extract, but we don't know what the heck it's an

extract of.

So I would say that all of the flower ingredients, which are most of them, and I think pretty much all of them that are reported to be in use are safe. But anything from the stem and the leaf is insufficient, at least at this time, for what is the chemical composition of a matricaria recutita stem and leaf.

DR. LIEBLER: So what's really missing is the organics.

DR. BELSITO: Yeah.

DR. LIEBLER: If you look at Table 5, you've got very spotty coverage of the organics. You've got the apigenin under chamomilla recutita flower extract and then nothing until you get to caffeic acid whereas you've got pretty extensive data on the flower oil.

DR. SNYDER: What about the azulene issue also, Don?

DR. BELSITO: I think that is going to be addressed by the botanical boilerplate. And I think, again, it's present in low amounts and the

concentrations used are low. It's.5 maximum leave-on, is that correct?

DR. SNYDER: .4, yeah.

DR. BELSITO: .4.

DR. LIEBLER: So, Don, now that the maximum use concentration is down to a half a percent, you're okay with the irritation and sensitization data that we have in hand? We're not quite that high, but we're close?

DR. BELSITO: Yeah, I mean I think that what you're seeing here are -- it gets very confusing because people -- a lot of the case reports are people who are sensitive to compositae, which chamomilla recutita is a member of that genus of families. So they patch-test positive to compositae mix. Then they bring them back and they are patching them to various species of the compositae plant, and so you're seeing positive reactions there.

Again, in Europe these are used as alternative medicines, if that's the correct word. So you see a lot of products like kamillosan,

which are containing higher levels of this ingredient than you would find in a cosmetic product. And they're being put on damaged skin, which is why people are using them, and then you're seeing some sensitization come out. But I think in the animal studies and the naïve studies, I think we're fine.

DR. LIEBLER: Okay.

DR. BELSITO: Is there one particular study or is it just the bulk of case reports?

DR. LIEBLER: No, no. I wanted to get your impression of this because until just a few minutes ago, I thought well, we're nowhere close to 10 percent. We're still insufficient on irritation and sensitization. Now I think we're close, and I wanted to get your reaction to it.

DR. SNYDER: So where are we on the use concentration because the report now says -- I mean I'm reading here and now it says "any concentrations up to 1.2 percent of the flower." So where are we getting this.5 percent number that was --

DR. ANSELL: From our -- no, it didn't get into the report, but Carol's reporting now the new maximum is 0.5 flower extraction in lipstick products. The report is not correct when it states the maximum use concentration is 1.2 percent of the flower. The 1.2 percent should be 0.5 percent. And in Wave 2 and HRIPT it's.4 percent.

DR. SNYDER: Yeah, that's the one I referred to.

DR. BELSITO: So in the use --

DR. SNYDER: The Cosmetic Use section.

DR. BELSITO: So it's the flower extract -- no, it's the flower or --

DR. SNYDER: This says "the flower."

DR. BELSITO: Right.

DR. SNYDER: In the report.

DR. BELSITO: It says, "Hair Non-Coloring 1.2."

DR. ANSELL: And that should be.5.

DR. BELSITO: And that should be.5. And then lipstick?

DR. ANSELL: Similarly,.5.

DR. BELSITO: For the flower? We don't have a lipstick use.

DR. ANSELL: Flower extract.

DR. BELSITO: Flower extract. Incidental ingestion, that is.5. I think the.4 -- so the highest reported use is going to be.5. There's a.61 for dermal contact for the extract. But, again, the extract has a total of six reported uses. Everything else is flower, flower extract, flower/leaf extract, flower oil, flower water. The flower/leaf extract is probably going to be the biggest issue because there's 349 uses. But, again, we don't know what's in the leaf. If you look, the flower is very well defined. For the chemical composition you've got the extract, flower oil, and flower. And if you scroll down the extract there's not a lot there. Caffeic acid, apigenin, apigenin-7-glucoside --

DR. LIEBLER: Yeah, it's very spotty.

DR. BELSITO: It's extremely spotty. Obviously, there's a lot more in there that we

don't know. So I don't know how we can say because the composition of the flower and the composition of the rest of the plant is more than likely I think very different in this case.

DR. LIEBLER: Well, we just don't know.

DR. BELSITO: Right.

DR. LIEBLER: I mean we just don't know, so I think as part of our due diligence to ask for the data.

DR. BELSITO: So this was the first time we're seeing the report, so I would say the flower ingredients -- the flower oil, the flower extract, everything that is derived from the flower -- is safe as used. And anything derived from the full plant -- the leaf, the stem -- is insufficient at this point for chemical composition.

So, Dan -- in your draft discussion, Wilbur, in the last sentence, I said "The Panel agreed that, given the current use concentrations to the ingredients derived from chamomilla recutita flowers, these components" not "should," but "would be present at levels that are below the

threshold of toxicological concern. The safety of ingredients derived from c-recutita leaf and stem are insufficient for chemical composition." Paul?

DR. SNYDER: So this issue was also brought up by the Council. I think we're using the threshold of toxicological concern a little too loosely. I think that is a very defined threshold. I can of think of many instances -- I understand what we're trying to say, but I think we're using it inappropriately. So I think we have to be cautious about that.

DR. ANSELL: And that is our concern as well, that TTC as it's used, capital T-T-C, is a very defined process. What we really mean in these cases is not the toxicologic concern, but we're not concerned at the levels they're present. And so conceptually what we find, we just don't like that specific terminology. Just turning it to TCT would be okay.

DR. BELSITO: Toxicologic concern threshold?

DR. ANSELL: No, we're just not --

DR. LIEBLER: No, that would be. So I think the suggestion after I read the memo from Council and I basically agree with the point is that by throwing the term "threshold of toxicologic concern," we're using that as a shorthand for a more specific statement about our conclusion. So I agree that in cases where we can say "below the levels likely to cause sensitization," "below the levels likely to cause irritation," et cetera, so that we could be a little bit more specific in our language rather than just laying down the TTC card every time.

DR. BELSITO: So are you making an editorial change someplace, Dan?

DR. LIEBLER: Well, "The Panel concluded that these components are not present at levels of concern." We're saying the same thing. We're just using --

DR. BELSITO: What page are you on?

DR. LIEBLER: Under the draft discussion.

DR. GILL: Let me clarify something. I

think I heard Linda say "below the levels of toxicologic concern." Is that getting back into the language the Council had and the Panel is uncomfortable with, or should we stick to something more along the lines of what Dan just mentioned, the low levels that could cause concern?

DR. LORETZ: I mean our specific concern was that those were --

DR. GILL: So we sort of steer away from "threshold."

DR. LORETZ: Right, right.

DR. GILL: Because I think below the levels of toxicologic concern include --

DR. BELSITO: So just below "any" level of toxicologic concern or "the" levels? I mean what is -- because there are a number of toxicologic endpoints. I guess what conveys best is for each and any toxicologic endpoint that you would be concerned about because in some cases we're talking about genotox and in other cases we're talking about sensitization that are below

--

DR. SNYDER: So "The Panel concluded these components are present at levels that are below --

DR. BELSITO: "Would be present at levels below --

DR. GILL: Or "not present at levels of toxicologic concern."

DR. LIEBLER: I think the problem with this sentence is that this is a draft discussion. These are sort of bullet points that would be included. This isn't the actual, probably the actual language we will have in the discussion when we review the document next time.

So let me just make a point. You've got compounds lumped in here that may produce sensitization, others that have insecticidal activity, and some maybe genotoxic or carcinogenetic. So these are different endpoints. And I think rather than just lump them together and say "below the threshold of toxicological concern," we perhaps deal with each of the

concerns and rephrase as "below the levels likely to produce any risk of genotoxicity," "below the levels likely to produce sensitization," et cetera. So when they develop the discussion, you refer to the compounds of interest with respect to the endpoints that we're concerned about.

So I think the Council's point is in a draft discussion like this and not end up as more final language. But this would be inappropriate to have this whole laundry list of compounds and different effects and then just say "below the levels of toxicological concern" for all of them.

Jay, am I reading your message right?

DR. ANSELL: Well, that's it. It's like the Xerox people. It's okay to make a photocopy, just don't call it a Xerox. The language we agreed to in the last report was not of concern. I think that would work here.

DR. SNYDER: I agree. I don't understand what you're saying, Dan, but I think then it would become a huge discussion that would have to be updated.

DR. LIEBLER: Well, it doesn't have to be.

DR. SNYDER: To go through all the genotox, every little thing. We're just saying that we see the components of these ingredients, and then we just concluded "these components are not at levels of toxicologic concern in cosmetics."

DR. ANSELL: Right. "At these levels they are not of concern."

DR. SNYDER: "In cosmetics." Always "in cosmetics."

DR. BELSITO: Well, I think that as with the issues that we were discussing about having frameworks for abstracts and a boilerplate, we'll get to that when we discuss the botanical ingredients.

DR. ANSELL: We can come back to this.

DR. BELSITO: Unfortunately, I don't think that that is until the end of our session today. So I think we can just highlight the draft discussion and say it will have to be worded

according to whatever boilerplate we come up on.

DR. LIEBLER: Right. I think trying to wordsmith this now at this point is a waste of time.

DR. BELSITO: So we'll go to the boilerplate for botanicals, but do we all agree that the flower ingredients are safe, but anything from the plant -- the stem, the leaf -- is unsafe until we have composition?

DR. SNYDER: I just want to go back to -- Wilbur has separated out very clearly what we had data for and what was used, and I'd like to go back to that because --

DR. BELSITO: You're talking about the little roadmap?

DR. SNYDER: Yeah, this here.

DR. BELSITO: If you look at basically the uses, the only one that has got a large number of uses is flower/stem or leaf, I forget which, and that's Table 6. You've got six reported uses for what's just called the extract and then you have mostly flower. The only other one is what's

listed as a flower/leaf and that's a huge number, 349. I mean I suppose we could finesse that because the highest use is.02, and we know what's in the flower. But if we finesse that, then -- I suppose we could argue that we're not finessing the extract because it's up to.61 on mucous membranes. But I think -- this is really the first time we're seeing the document. I would say the flower ingredients are safe, and for the stem and leaf and the whole extract we need available composition data.

MR. JOHNSON: But Dr. Belsito, this isn't actually the first time because the last time the anthemis nobilis and chamomilla recutita ingredients were in one report. So we separated --

DR. BELSITO: No, I understand, but it's the first time we're seeing the report as chamomilla recutita.

MR. JOHNSON: Yes.

DR. BELSITO: So my understanding is this is almost like it's the first time we're

seeing it. Is that not correct? I mean there was no decision made -- I guess we did issue some insufficiencies last time --

DR. ANSELL: Which were addressed.

DR. BELSITO: Yeah, so I have no clue how you consider this document that we're seeing. But I think if this is going out as -- it will go out as an insufficient whether it's a pink, a green, a final, I don't care.

DR. LIEBLER: So the insufficiency -- if the insufficiencies were for irritation, sensitization, concentration of use, and for composition, we may be okay on irritation, sensitization, and concentration of use. But we're definitely not okay on composition.

DR. BELSITO: Yes.

DR. LIEBLER: So we're still insufficient on that key point.

DR. BELSITO: Yeah, unless you would like something of that.6 for the extract because we have.4 on the lipstick right now.

DR. LIEBLER: Right, and we have -- Jay

just indicated.5, but I don't know what that was for. He said that that was the latest information.

DR. BELSITO: .5 is the Hair Non-Coloring.

DR. LIEBLER: Hair and Non-Coloring, okay.

DR. BELSITO: So it reduced the highest use concentration down to now.61 for the extract and.5 for the flower ingredients.

DR. LIEBLER: So are we still short of sufficient on sensitization?

DR. BELSITO: We have an HRIPT on 104 patients at.4 percent. And I think that, given the fairly widespread use of botanical products particularly in Europe that are actually marketed as over-the-counter drugs, if that word is appropriate to the European market and the limited number of reports that we're seeing and the literature, I think it's okay.

DR. LIEBLER: So you think we're close enough.

DR. BELSITO: Well, if you want to be hardnosed, we could ask for --

DR. LIEBLER: No, no. This is why I asked the question, because I defer to your judgment on this. If you feel that that's close enough and you have a better sense of whether reports are in the literature on adverse reactions to these as used as over-the-counter drugs, that would change my thinking. But if we're not in an area where we really have some concern, then I'm fine with what we have there. So as far as I'm concerned, the insufficiency boils down now to composition.

DR. BELSITO: Right.

DR. ANSELL: So we provided a study on the assessment of plant herbs or extracts and their components.

DR. GILL: This was in Wave 2 data?

DR. ANSELL: Yeah.

DR. BELSITO: Where was this? It was in Wave 2?

DR. SNYDER: In Wave 2 all I had was

irritation and sensitization data.

DR. BELSITO: Yeah, that's all I had, too.

DR. SNYDER: I didn't have any composition data in Wave 2.

DR. BELSITO: The only composition --

MR. JOHNSON: Wave 2 is the --

DR. BELSITO: Was just the bisabolol.

MR. JOHNSON: It's in Data 2.

DR. ANSELL: Where is that in the --

MR. JOHNSON: Data 2, subsequent to the plants and herbs.

DR. ANSELL: How do I relate that to a page number?

DR. BELSITO: We're in Wave 2?

MR. JOHNSON: No, actually it was the.pdf that accompanied the safety assessment.

DR. BELSITO: What page?

MR. JOHNSON: It was identified as Data 2.pdf file.

DR. BELSITO: What page of the entire document?

MR. JOHNSON: It would be on page 69.

DR. GILL: Of the report.

DR. BELSITO: No, we don't have page numbers in the report.

DR. LIEBLER: It's on.pdf page 69.

DR. ANSELL: It's an assessment of plants, herbs, plant/herb extracts and their natural synthetic -- description of the plants, systemics, plant parts and products, ingredients and constituents.

DR. BELSITO: There are some nice pictures.

DR. LIEBLER: I'm not seeing the data.

DR. BELSITO: Yeah, I don't see anything.

DR. LIEBLER: I'm seeing descriptions of the types of compounds that are present, but not amounts. Now, there's a picture on.pdf 74 of the bisabolol family compounds. The closest we have is a description from the essential oil, which is not where our insufficiency lies. And there's four bullet points: Up to 15 percent chamazulene

and precursor matricin and up to 50 percent bisabolols and bisabolol oxides. That's for the oil. So we're still short --

DR. ANSELL: On these --

DR. LIEBLER: Right, for the leaf and flower.

DR. ANSELL: Right, therapeutic relevant compounds like the tributyltins are absent in the root.

DR. LIEBLER: I mean it's a literature review. It doesn't have the information that would go into Table 5, I guess it is. So that's what we need.

DR. BELSITO: Plus on page 72 of the.pdf, it sort of justifies what we're asking for. It says "The roots are used for pharmaceuticals of the anthroposophical therapy. The essential oils differ considerably from the aerial part." So we already have information that things in this plant differ. And we don't have a --

DR. SNYDER: It even goes on further.

DR. BELSITO: Yeah, it's just part of the essential oils. We just don't know the actual percentages.

DR. LIEBLER: So this just doesn't suffice. I mean it's useful appendix material, but it doesn't address our need.

DR. BELSITO: Well, I think it's nice because it hits us with okay, here are the issues, the coumarins, et cetera. And then it goes on to talk about the quality controls for chamomile flowers in preparations, which gets back to my point. I honestly think that this is another case where probably everything in cosmetics more or less is coming from the flower. But when you read the literature and the way people label things, it's the flower and the stem because there are little bits of stem that haven't gotten off of the flower so we label it both ways. But in order to rule -- I mean that's just a guess just like I think the literature is ambiguous on exactly what it is.

DR. LIEBLER: And the question of what's

actually in these? You can imagine a -- remember that "kitchen confidential?" You can imagine a "botanical confidential." Yeah, yeah, we actually grind up stems, and we put them in our cheap botanicals.

DR. BELSITO: Okay, anything else here?

DR. LIEBLER: Yeah, I do have a couple of other issues on this report beyond the composition. So this is actually related to the composition, but on the.pdf --

DR. BELSITO: Can Paul just interrupt?

DR. SNYDER: It looks like it says here "The composition of the essential oil in roots differs from that in flowers."

DR. LIEBLER: Right. It says that right in the.pdf that we were just looking at.

DR. BELSITO: Right, okay. Where are you, Dan?

DR. LIEBLER: .pdf page 28. This is back to the report under Provocative Testing. So there's a series of studies here -- a couple of them are pretty large studies -- and it looks like

the extracts that were used in these studies were specially prepared for these studies by methods that look like they're somewhat different from those described in our report for the commercially available products.

And I'm not saying that there's a problem with this, but I think we need to note it maybe eventually in our discussion. For example, the second paragraph under Provocative Testing starts "The frequency of allergic reactions to a compositae plant mixture." It describes the preparation of ether extracts. Now, up earlier in the document the methods for preparing these -- steam distillation or maceration in oil -- are described and ether extract is different. And if you took a fresh product or a fresh plant and prepared an ether extract, you'll probably get the maximum concentration of any potentially bioactive organics. And this extract could actually have somewhat different properties and perhaps even produce greater responses than you might get from a commercially prepared extract.

So I'm referring to these in my notes as sort of homebrew extracts that were prepared for these studies, and there are a few of them that I've noted. There's one that I noted on.pdf page 28, the study on.pdf page 29, second paragraph under Chamomilla Recutita, the "allergenicity of chamomilla recutita." There's another; this one is "defatted with acetone and macerated in phosphate buffered saline." Then there's another one that was an issue of extract in petrolatum and another one of the extraction solvent. For each, the extract was not stated.

So the problem with these studies is that in some cases they produce what looks like a significant number of positive reactions to the extracts, but you have no way of being able to relate the data back to the type of extract that is commercially provided to producers of cosmetic products.

So I'm not saying that these data aren't useful or can't be evaluated, but we need to have some way to put an asterisk on them that's

basically in the discussion. "The Panel noted that extracts prepared for some of the studies were prepared by methods that appear to be outside the standard procedures for preparing the commercially used ingredients."

DR. BELSITO: Well, I mean the provocative tests are all patch tests, so they're not industry tests. These are dermatologists in Europe patch-testing people with Finn Chambers.

The ether extracts were all probably produced by a guy by the name of Hausen in Germany who's since passed away. He was really interested in botanical dermatology and provided a lot of us, including myself, with these ether extracts of various plants that he had prepared in his lab. And that's probably what they were. The conjunctival testing I don't know about, but I would suspect that all of the other patch-test data that you're seeing from Europe on these patients are probably Hausen's ether extracts.

But I think it's worth making a note, but again this is not like it's big-time safety

testing. This is diagnostic testing to rule out allergic reactions to chamomile in patients suspected of having allergic reactions or in some cases of compositae-sensitive patients to see if they would also react to chamomilla recutita.

So this type of stuff is nice. I think it should be in the report. And if you start seeing thousands of cases of positive patch-tests to an ingredient, as you will see more than likely. We see them coming up -- when we see this huge blip on reactivity, I think it's meaningful. But in this case you're really not seeing this type of overwhelming number of patients coming up positive to chamomile, including some compositae-sensitive patients, which I think is interesting.

DR. LIEBLER: Okay, so anyway I made my point.

DR. BELSITO: I mean we can make the point, "ether extract (which is not a typical cosmetic method of manufacturing this ingredient)" or something.

DR. ANSELL: Well, I think your point is much more interesting as it relates to the whole test. Not only is it a nontypical preparation, it's on nontypical people.

DR. BELSITO: Right.

DR. ANSELL: So perhaps that can be carried into the discussion.

DR. LIEBLER: Right. Well, I'm not saying that we don't use the data. I'm simply saying that we note in the discussion that the types of -- in addition to the variety, plant to plant variety for the botanicals, you have this added variety in some of the test materials that were used in some of the studies that we cited. And that's all, but it needs to be noted.

DR. ANSELL: Well, and the patients, the subjects, may not be typical either.

DR. BELSITO: If you're concerned, I think that any dermatologist reading this when they see provocative testing is going to know that this is a select group of patients. These aren't normal individuals coming in for HRIPTs to assess

whether a specific chemical can induce sensitization at a certain level. I mean if you want -- because otherwise you're going to have to say it every time you talk about the next group of tests. If you want in all documents to create a boilerplate for provocative testing --

DR. LIEBLER: No, no, I'm not going there. This is a case that may occur with other botanicals, but it certainly doesn't apply to all provocative testing. It would not require a boilerplate.

DR. BELSITO: Well, I mean actually it does because you never know whether that material that was used is actually cosmetic-grade material. These can be made up by the investigator. A lot of them are commercially available from companies. Presumably they're buying cosmetic grade. But you're not going to know that, I can guarantee you, from the reports in the literature necessarily unless you go back and they say they purchased it from Chemotechnique in Malmö, Sweden. And you go back to Chemotechnique and you check

their MSDS sheet and you look at -- maybe it'll say cosmetic grade or whatever.

DR. ANSELL: I agree with Dan's point. I think it's a very interesting one. But I also think Dan's reaction to 56 of the patients who tested positive, suggesting a high allergenicity potential, is perhaps not the right conclusion either. So I just wanted to add that not only is the test material atypical, but the subjects themselves. Maybe we need something about provocative testing.

DR. BELSITO: That's what I was saying. I mean if you're concerned that this could be misinterpreted, the issue came up when we were looking at -- I don't remember if it was gallites or what -- in a lipstick and they took patients who had cheilitis. So this is a patient population where you're looking for something in a lipstick and they saw a very high percentage of patients patch-testing positive to whatever ingredient we were looking at. That's the same thing here.

So if you want to create some type of boilerplate to alert people that when we're talking about provocative tests, "provocative tests refer to patch-tests and other testing techniques that are done in patients suspected of having an allergic reaction to this ingredient or potentially allergic reactions to this ingredient and are not representative of the sensitization capacity of these ingredients in the normal population; furthermore, it's not clear that the ingredient used for patch-testing is the same as commercial-grade cosmetic material." And just create that as a boilerplate before all provocative testing.

DR. LIEBLER: So I don't think we need to make the boilerplate queue any longer. We have more boilerplate candidate language than what the staff will ever get around to drafting for us. And this is probably -- this could be addressed in the discussion because we're going to have to have a paragraph in the discussion that acknowledges the variety of the range of ingredient

compositions that we're dealing with here -- between the oil and the flower and the stem leaf. And once we do have data to discuss that, we'll say the Panel had to consider that. We also had to consider that the preparation methods differed between industry, and in addition some of the preparations used and some of the testing described in the literature also may further differ from those for commercial products. And we don't need to say anything more, just simply that we were aware of that, that we took that into consideration.

Then there's the whole other issue of whether people in provocative testing are atypical. It sounds like that's well-known to people who are familiar with that sort of literature and doesn't need to be beaten to death. So I think that sort of takes care of itself.

I actually have a couple of other issues I wanted to get on to, if I may. These are the sections on the anticarcinogenicity. I'm not really sure that -- so this is on.pdf page 35.

I'm not really sure that these sections are relevant. The toxicity to the cell lines associated with cancer -- so basically this isn't in vivo studies where they were able to inhibit skin carcinogenicity like we'll see with the rosemary. But instead these are atoxicity to tumor cell lines. And you can beat tumor cell lines to death with chemicals in vitro. That doesn't mean that's a true anticancer effect or an anticarcinogenicity effect. So I don't think this is, based on the data we're showing here, it's not necessarily cancer specific or really relevant to in vivo activities.

DR. BELSITO: So would you get rid of the entire anticarcinogenicity section?

DR. LIEBLER: Yes.

DR. SNYDER: We had this discussion last time, and the other team -- we had a lot more in there, remember? We had a lot more other data on those types of issues. And they relinquished, I think, all but this data. They were kind of adamant that this data had some biological --

DR. LIEBLER: So we could have -- we could consider the in vivo model, which is in the third paragraph, to remain. But the first two are basically cell line studies; that you're killing tumor cell lines with these compounds. I don't think that has any particular in vivo relevance. So the first two paragraphs of that anticarcinogenicity section could go.

DR. BELSITO: So you would continue -- you would keep the cytotoxic activity?

DR. LIEBLER: Yeah, you could keep that because at least it's an in vivo model.

DR. BELSITO: Well, if we do keep the first two paragraphs, tomorrow I think that it's sort of redundant going in the first paragraph to say "against the following human cancer cell lines, human prostate cancer cells." Just say "against the following human prostate cancer cells derived from," but I will --

DR. LIEBLER: Another thing you could do if the other team really wants to keep that in is that you could decrease it substantially because

it's much ado about probably nothing.

MR. JOHNSON: So, that study on the flower oil, would that be deleted as well?

DR. BELSITO: The first two paragraphs, Wilbur, is what Dan's suggesting.

MR. JOHNSON: Yeah, I'm talking about -- yes.

DR. BELSITO: The cytotoxic activity? Is that what you're asking about?

DR. LIEBLER: The third paragraph?

MR. JOHNSON: Under the oil subheading, there's another anticancer activity study. Since we were dealing with that section, I didn't know whether or not you were also referring to the data on the oil in terms of deleting it.

DR. LIEBLER: Yeah, right, the flower oil. I mean it's the same issue.

MR. JOHNSON: Okay.

DR. LIEBLER: It's basically these cells being beaten with these compounds.

So I also had some more concerns under Biological Activity,.pdf page 36, the paragraph

under Anti- Inflammatory Activity, chamomilla recutita, the effect of chamomilla --

DR. SNYDER: That's another one they wanted to keep.

DR. LIEBLER: Well, I think there's poor justification for it. I remember reading in the transcript of our discussion, they were interested in maintaining the stuff on wound healing, and I don't think it's necessary.

DR. SNYDER: And, Dan, and the anti-inflammatory.

DR. LIEBLER: So I think this is of dubious relevance, basically its effects on neutrophils in vitro, and concentrations are much higher than would be in vivo biologically relevant.

DR. BELSITO: So delete it or shorten it.

DR. LIEBLER: Right. And I had the same on.pdf under Pharmacologic Activity, the GABA-like activities.

I think that's also irrelevant, as is

the Antioxidant Activity. The Antioxidant Activity paragraph right under it is about the reaction with DPPH, which is -- you can buy this radical in a jar from Sigma. It's the most stable radical in the world, and you can buy it in a jar and lots of things react with it and it doesn't make anything biological. So that paragraph can go. So, again, this is the middle of 37.

DR. BELSITO: So both paragraphs deleted or shortened. We'll see if the other team is okay.

DR. LIEBLER: Okay, that's it.

DR. BELSITO: Paul?

DR. SNYDER: So I want to go back and ask Dan -- so in looking at the boilerplate for the botanicals I think there's lots of issues to discuss, but what it came down to me was the real issue is the same issue that we're presented with here. What is the composition of the starting material and what were the extraction methods or methods used to derive the ingredients that are used in cosmetics? And so if you go to the

Methods of Manufacture section in this document, we don't say anything about --

DR. BELSITO: Page?

DR. SNYDER: I have a Word document, so I --

MR. JOHNSON: Page 20.

DR. SNYDER: So I think in these botanicals what we're obligated to do is talk about really the materials and methods, what are the components and the composition of those components, and then what are the methods used to make the extractions or derive the ingredients that are used then in cosmetics?

And so I think we need to have those expanded upon in a little bit more detail because throughout this report -- I just went through it while you guys were having that discussion and highlighted -- we have aqueous solvent, ether solvent. We have extraction. We have I think four or five different extraction methods used. And so I see now that in the animal studies, we're doing an aqueous extract as opposed to a solvent

extract that was used for the cosmetic --

DR. LIEBLER: So there are two issues, Paul. These are good points you bring up. There are two issues, though, that we tend to confuse. One is how the commercially supplied ingredient is extracted from the plants.

DR. SNYDER: Right.

DR. LIEBLER: And that's provided briefly under Method of Manufacture. And if we had any more complete information that would be welcome, but at least we do have information here.

And then there's the issue of how that ingredient that was originally extracted by steam distillation, let's say, how that was then presented to the test system or the people or the patch or the animals. Was that put in petrolatum? Was that put in an aqueous suspension? Was that put in whatever? And that's going to be study-to-study specific whereas the method by which the extract was produced in the first place is a separate issue.

DR. SNYDER: Okay.

DR. LIEBLER: So it's two different things.

DR. SNYDER: Thanks for covering it. So the animal testing that was done was an extract in an aqueous solution.

DR. LIEBLER: Right.

DR. SNYDER: Would that be significantly different from one that was in a solvent or in a different -- do you know what I'm saying? Because that could change the exposure.

DR. LIEBLER: Only to the extent that if the aqueous mixture didn't fully dissolve all its stuff. It might have been that that's the form that the product was available to them in. A lot of times these decisions are sort of practical decisions based on how you receive the product.

DR. SNYDER: So I guess the point I was trying to make was should we have some language in our report that says exactly what you said, that the issue of the extraction method is irrelevant to exposures or irrelevant to toxicity?

DR. LIEBLER: Oh, it's not irrelevant

because it determines what the mixture contains after it's taken out of the plant. Then the next step is the presentation of that mixture, depending on the vehicle used in a particular study or the composition of the product. And in both steps there's a lot of variation, I guess. That's the problem. And I think we need to capture that in our discussion and ultimately in our boilerplate.

DR. BELSITO: Anything else, Paul?

DR. SNYDER: No, I'm fine.

MR. JOHNSON: Dr. Belsito, just one comment. In Wave 2, some of the structural components of chamomilla recutita were provided. And I would just like to know whether or not those structures should be included in the report because at the last meeting you had mentioned including some of the structural components, the structures for those in the report. They're in Wave 2.

DR. LIEBLER: I saw them. I think they're fine to put into the report.

MR. JOHNSON: Okay.

DR. LIEBLER: Because you're basically showing some of the major organic components.

DR. BELSITO: Anything more on chamomilla recutita?

Now we move on to the other chamomile, anthemis nobilis. So, again, same thing basically. We split these into two and asked for additional data on the composition of the nobilis ingredients except the flower oil, skin irritation and sensitization data on the ingredients except the flower oil at use concentration of 10 percent. And we, again, have this issue of deciding what kamillosan is, so that will be an issue for this report. And also when we're talking about just chamomile without the species defined, we need to be very specific in those sections that we're not sure whether this is anthemis nobilis or chamomilla recutita.

So what we got was composition data, updated use concentration data, HRIPT, a leave-on skin lotion containing 3 percent, and that was in

Wave 2. So the question is where are we with this? I thought that we still don't have the sensitization and irritation data -- well, no, I'm sorry. They were safe as used and, again, in the introduction we need to name the ingredients that we're looking at.

DR. LIEBLER: So we still don't have the composition on the flower extract, right? The chemical composition?

DR. SNYDER: All we have is on the flower oil.

DR. LIEBLER: Yeah, and that's got seven uses and the flower extract's got 423 uses.

DR. BELSITO: I guess my thinking here -- and I reviewed this a while ago -- was when we look at the -- we have stuff on the flower. What we sort of missing is -- I mean if you look at the two columns, we have flower oil and we have flower. I think what we're missing from the flower are basically the oil components, which in the whole flower are going to be less. So my thinking was if you put the two together, you know

what the heck is in the flower, and, in fact, the composition of the oils in the flower as it is are going to be lower than what you're seeing in the more concentrated oil. So I didn't have an issue with that.

DR. LIEBLER: Well, if we take that view here, then I think we need to take that view with chamomilla recutita.

DR. BELSITO: We are. We're saying the flower is fine, but we have no data on the stem and leaf.

DR. LIEBLER: Oh, stem and leaf, I see.

DR. SNYDER: Anything that's added to the flower.

DR. LIEBLER: Okay, flower, flower oil, right. So there's no stem/leaf.

DR. BELSITO: For recutita.

DR. LIEBLER: For nobilis. Well, I agree. The thing that I think was sort of insufficient here or that are lacking information was on the organics. And, of course, the organics would be present in the oil because the flower had

these ppms on inorganics primarily in things like fat and fiber and so forth, which wasn't terribly helpful. Okay, so I think I agree. We're no longer insufficient on composition. I think it's a reasonable assumption on the oil-to-flower comparison.

DR. BELSITO: And all we have here are flower- derived materials.

DR. LIEBLER: Yeah, that's the key.

DR. BELSITO: And then, again, we need to clarify that kamillosan, and in the introduction we need to list the ingredients we're reviewing. And then I just had some minor typographical --

DR. LIEBLER: Same here.

DR. GILL: So let me ask for clarification again. We do have the data, all of the composition data. We're satisfied with the composition data we've received.

DR. BELSITO: Yes.

DR. GILL: For flower and --

DR. LIEBLER: Or inferring the flower

from the oil. So that's the cache that we're doing it.

DR. SNYDER: So I think it's important in the introduction to state that "all of the ingredients used in cosmetics are derived from the flower component of the plant; and, therefore, this material related to the" dah, dah, dah, dah can be used to support all of those.

DR. LIEBLER: The composition data from the oil.

DR. SNYDER: Yeah. So I think you need to just capture that clearly in the introduction. That just sets the tone for the rest of the report.

DR. LIEBLER: Yeah.

DR. SNYDER: As opposed to the other report, we did the opposite. We say that "the ingredients used in cosmetics are derived from all components of the plant and only composition data is available for the flower."

So what is the highest concentration of use of this again? This is now 10 percent back

down to --

DR. BELSITO: No, this is --

DR. SNYDER: So the 10 percent were the carryover --

DR. ANSELL: The maximum use of the flower extract in a leave-on is 0.05. There is one reported use at 10 percent, but that's not supported.

DR. LORETZ: It's flower water.

DR. SNYDER: So they're at 10 percent with flower water.

MR. JOHNSON: Jay, what do you mean by that as unsupported?

DR. ANSELL: That it was a single reported use of the flower water used at 10 percent.

DR. BELSITO: But it's also in a rinse-off.

DR. GILL: And that is specifically what the Panel asked for, the concentration at 10 percent of irritation and sensitization.

DR. ANSELL: Right. And if there's a

concern, you're prepared to support 0.05 percent?

DR. GILL: Uh-huh, so at the highest.

DR. ANSELL: It's really not the highest. It's a single report. And we confirmed that is the right number, but there's only one use at that level. And if the Panel is concerned with a use at that level, we'd be willing to accept a lower threshold.

DR. BELSITO: On the Leave-On section -- you know, the 10 percent is in a rinse-off, so I'm not getting excited about that. I guess I'm more interested in what's in a leave-on, and you have 4 percent for the flower water. But I don't see where that's coming from. You have dermal contact 1 to 10, and you have a bunch of others that are not reported. So where is that 4 for leave-on coming from because I just see --

DR. SNYDER: There is a deodorant, a dermal contact deodorant underarm at 1 to 10 percent, so it's more than rinse-off.

DR. BELSITO: Okay, so --

DR. SNYDER: For the flower water.

DR. BELSITO: But then it says rinse-off is 2 to and the dermal underarm deodorant --

DR. SNYDER: So that's wrong. That should be 1 to 10.

DR. BELSITO: It's dermal contact. For the dermal underarm deodorant there's no concentration reported. Either my.pdf or your Word is dermal underarm, nothing -- there's one ingredient for flower extract, but the concentration is --

DR. SNYDER: Well, what's the dermal contact 1 to 10? That includes the rinse-off.

DR. BELSITO: The 10 is rinse-off.

DR. SNYDER: Gotcha.

DR. BELSITO: But I don't know where the 4 is coming from.

MR. JOHNSON: There's a 4 percent of anthemis nobilis flower water used in foundations at 4 percent.

DR. SNYDER: So that's not in Table 5, so where did you get it? That's raw data that you have from the --

MR. JOHNSON: Yes, from the Council.
DR. SNYDER: So Table 5 needs to be updated?
MR. JOHNSON: Yes.
DR. GILL: There is a leave-on at 1 to 4 percent in Table 5.
MR. JOHNSON: Yeah, and that's at 4 percent.
DR. BELSITO: Yeah, but it's not clear where that is coming from. So what we're saying is it's a foundation.
MR. JOHNSON: A foundation, yes.
DR. BELSITO: And that is for the flower water?
MR. JOHNSON: The flower water, yes.
DR. ANSELL: Isn't it.4?
MR. JOHNSON: No, it's 4. That's on page 8 of the use concentration data received from the Council.
DR. BELSITO: What page of the.pdf?
MR. JOHNSON: 46.
DR. BELSITO: 4 percent, yeah,

foundation. Got it. Okay, so let's just -- we have sensitization for the anthemis flower oil at 4 percent. And then we have flower oil 4 percent for petrolatum. I mean I think that the water extract is going to be much less sensitizing than the flower oil. We have 4 percent. I mean, again, I think we're fine, particularly since the 10 percent is in a rinse-off. I'm not going to argue with that. We have 4 percent oil, so I think these are safe as used. We'll have to attach whatever we agree on for the botanical boilerplate.

Ingredients of concern here for the discussion obviously are going to be the usual heavy metals, pesticides, whatever botanical combination boilerplate we come up with. In looking at what's in here, I didn't really flag anything for this one unless I'm missing something. I mean we're -- pretty much what's in this isn't really anything of significance in terms of allergens that I've heard coming out of the oil industry. So I mean I don't really even

think there's anything to flag in terms of ingredients of concern.

DR. LIEBLER: Safe as used.

DR. BELSITO: Okay. Paul?

DR. SNYDER: Yup.

DR. BELSITO: Okay. The next one is formic acid. So in June we reopened the safety of formic acid, a pH adjustment to evaluate it for its new reported function as a preservative and then to add the salt, sodium formate. We asked for use concentration data. We have a whole bunch of new data: Toxicokinetic, irritation, sensitization for formic acid and the formate. And before we had restricted to 64 ppm of the free acid because of irritation, but since that time we've taken up the caveat of formulating to be nonirritating. So the question is are we okay going safe as used here?

DR. LIEBLER: I think so.

DR. BELSITO: Yeah, I did, too. I had a comment here in the draft discussion that we should also point out that the concentrations used

-- the highest dermal contact being.02 percent and the highest questionable leave-on in a non-coloring hair product was.2 percent -- are very low. So I'm assuming -- and this was another question that I wanted to bring up. When you say that the highest dermal contact is.02 but it's in a non-coloring hair product, do you presume that non-coloring hair products don't contact the scalp because the scalp is certainly skin?

DR. GILL: I thought there was some discussion a couple of meetings ago where the assumption was that it does contact the skin, the hair coloring product.

DR. BELSITO: Yeah. Well, this was a non-coloring hair product. But still, I mean, you apply anything to your hair, at least when I do it, it's all over my scalp, my neck, my forehead, and everyplace else. So the highest dermal contact if it's in a non-coloring hair product should be.2 percent. In fact, the table needs to be corrected. But I still would point out the low use level of.2 percent as part of the discussion.

Paul? Dan?

DR. LIEBLER: Yeah, I have a lot of small comments. I'll just mention a couple. On Composition and Impurities, you list technical grade formic and then commercial grade and then pharmaceutical grade. The pharmaceutical grade specifications --

DR. BELSITO: What page are you on?

DR. LIEBLER: Oh, this is on.pdf 15 under Composition and Impurities. There must be an error here because the pharmaceutical grade specifications look way worse than the technical grade specifications. And I'm not sure what's relevant to say the technical grade. I mean we usually think of that as the lowest grade stuff. I'm not sure what is used in cosmetic ingredients, but probably is relevant to correct the pharmaceutical grade and to determine if that's what's actually used so that you're only reporting what's relevant.

Under UV, that discussion is unnecessarily long and detailed, and I'd recommend

shortening it.

Photodecomposition section --

DR. BELSITO: Hold on, hold on, where are you now?

DR. LIEBLER: Still on.pdf 15, UV Absorption. That can be shortened. I provided a shortened description.

Photodecomposition section is not relevant. It's a specialized circumstance and really not relevant to cosmetic use. It's photooxidation of formic acid in the presence of hydrogen peroxide with a low-pressure mercury vapor lamp. That can go.

DR. BELSITO: So you're suggesting deleting the entire Photodecomposition section?

DR. LIEBLER: Yes. And then, let's see, then the -- on.pdf page 20 under Sodium Formate, there's a lengthy discussion of free radical generation in Fischer male rats was studied. This could be simply shortened to say "a spin trapping (electron spin resonance study) was used to detect free radical formation in Fischer rats." Provide

the reference and leave it at that.

DR. BELSITO: Did you make those corrections in the document?

DR. LIEBLER: Yes, these are all -- I'm just going through things just to let you know what I flagged.

And let's see, I've got another -- on.pdf page 21 under Cytotoxicity, I thought -- again, this is another cell line study where you're dumping formic acid on cell lines. And these data mainly compare obscure differences in the responses of these two cell lines. I don't think that's of any importance for our report, and I suggested that that be deleted.

DR. BELSITO: The entire first paragraph?

DR. LIEBLER: Yeah. Actually both -- I had the issue really for that whole Cytotoxicity section: Formic Acid, Sodium Formate, and Formic Acid and Sodium Formate. So these are all about these studies with these retinal pigment epithelium cell lines. They're not epidermal cell

lines. I think that the choice of cell lines is somewhat obscure and of dubious relevance to the types of cells that would come into contact with these ingredients, retinal pigment epithelium not being particularly relevant. And then this cell model is not a model for anything.

DR. BELSITO: So you're deleting the entire --

DR. LIEBLER: I'd delete that entire Cytotoxicity section.

DR. SNYDER: Based on questionable relevance to cosmetic use?

DR. LIEBLER: Yup, exactly. And that's it. And for the things that I've mentioned, other than the deletions, I've specified some revised language for Wilbur.

DR. BELSITO: Paul?

DR. SNYDER: I had the same, just minor bits.

DR. BELSITO: Okay, so we're going with a safe as used, and we'll bring up Dan's recommendations for deletions tomorrow.

DR. SNYDER: When --

DR. BELSITO: Yeah, that's what the conclusion is.

DR. LIEBLER: Can we take a quick break?

DR. BELSITO: Yeah. So 10:34. Can we be back at 10:45, in 11 minutes?

(Recess)

DR. BELSITO: Okay, all set. So iodopropynyl butylcarbomate. This is a re-review. In '98 we went with safe at concentrations less than or equal to 0.1 percent and not for use in aerosolized products. It was largely based on the lack of inhalation, toxicity, and since then we've created a boilerplate to deal with those issues.

Currently, the uses have increased significantly, probably because some other preservatives have been limited and/or banned in the EU. It's used in 942 products, concentrations of 0.05 percent in leave-in and rinse-off products. In the EU, there is new regulation that limits it to 0.02 percent in rinse-off products and also restricts it not to be used in products

for children less than three years of age.

I took the opportunity when I was in meetings in Europe to ask my European colleagues about this in dermatology, and they really didn't have a sense as to why, based upon sensitization, that the EU was limiting it to 0.02 percent. So I think based upon the materials that we received, I suspect that it has to do with the issue of this having an iodine molecule and potential effects on thyroid. But we have a 104-week chronic oral effect with no -- in rodents with 104-week chronic oral with no effect or at least no reported effect on the thyroid. So endocrinology is not my strongpoint. What I can tell you is at least patch testing-wise I see a lot of irritant reactions with this patch testing. I don't see a lot of truly allergic reactions coming up with it and our data before supported the safety at 0.1 percent.

So I'm leaving it up to other people on my team and we'll hear what the other team has to say, if they're concerned about the absorption of

iodine from this molecule and effect on the thyroid because that's the only reason I can come up with for these EU restrictions in terms of 0.02 percent and not to be used on children less than three.

DR. LIEBLER: So I read through the EU document that's part of the wave two data which provides a summary of some of the literature data. And it includes data on the liberation of iodine from organics by deiodination or dehalogenization enzymes. And since I read this on the plane on the way up, I didn't have time to really go to the literature and look at any of the papers myself but it looks to me like the iodinases and perhaps the dehalogenases act on aromatic iodocompounds and phenolic iodocompounds. And these activities are necessary to control the synthesis of thyroid hormone -- T3 and T4 and so forth.

This is an alkyl iodine compound and I'm -- actually, it's a really unusual alkyl. It's an alkynol iodocompound. I don't know if there's actually any enzyme activity in mammalian systems

that would liberate or at least even moderately efficiently liberate iodines from these compounds.

For this to be much of an issue you would have to have pretty high usage and you'd have to have pretty effective removal of iodine from this so that it could be absorbed as iodine as opposed to this alkynol iodocompound. So I actually found the argument that this would be a source of iodine and lead to iodine overdose to be, I think, not a very compelling argument.

DR. BELSITO: Paul.

DR. SNYDER: Well, I had queried the basis for the EU decision. I read through the materials that were provided in the second wave, and I think with the new information that Dan has talked about between the aromatic form and the alkyl form, I don't think there's any reason to reopen it.

DR. BELSITO: Okay. I guess then if we're not going to reopen, which I'm fine with, we do have to address in the wave two data that -- I guess part of what was driving it is the results

when they fed the compound and in six days of a fixed diet at 0.01 percent to the free IPBC in two volunteers they saw no increase in iodide urinary extraction, and at 0.02 percent they did. And I think that's why they were setting those new limits or putting the limit at what, was it 0.02 for rinse-offs and 0.01 for leave-ons?

So I guess how do we explain that bit of data? I mean, is this just, okay, yeah, you feed it, it gets broken down but on the skin it doesn't?

And then that raises the next point for me in the frequency and concentration of use Table 1, it says "incidental ingestion not reported. Mucous membrane 102 uses."

So I'm having problems coming up with 110 uses that wouldn't involve at least some lipstick use for mucosa. Is this in 102 vaginal products? Or 102 anal products? Or 102 mascara? I don't know. Do you think of mascara as a mucus? And when I think of mucous membrane exposure I'm thinking primarily of lipsticks or vaginal

products.

MR. JOHNSON: It's not used in lipsticks at all.

DR. BELSITO: Fine, but what are the 102 mucosal uses?

Yes. For the record, just identify yourself.

MR. STEINBERG: David Steinberg. A couple comments, and I think that might explain the mucosal use.

IPBC is probably the best antifungal preservative that I've ever come across. It's been used industrially since the '50s. We started looking at it and in terms of refined it to a cosmetic quality in the late '80s, early '90s. Its maximum effectiveness as a preservative is at its maximum solubility in water, which has been reported to anywhere from 150 to 175 ppm. So putting over, let's say, 200 ppm to make it easy, gives you no preservative increase. It does give you more irritations as you go higher and higher. It is used in water-based products. It is not

used in anhydrous products. It doesn't work in anhydrous products. If you're putting it in, you're just wasting money.

The other factor which needs to be incorporated is that the iodine molecule will break off from the parent under basic conditions. The higher the pH, the longer exposure to warmer the temperatures, the more you're going to break the iodine off and it is not especially been measured except you see discoloration in the cream or lotion where it's being used because iodine has that classical color. So it's obvious that something has happened. Furthermore, when you break the iodine molecule off the parent, it is far more irritating than the molecule with the iodine.

So it's used principally below a pH 7 at a use level of between around 150 to maybe 200 ppm max. And the reason that you find it in mucosa types of contact is because it's such a good antifungal agent. There are a group of products which are used in that lower quadrant of the body

which come in contact with mucosa membranes in which antifungal properties are very important, such as douches and things like this. It's not used as an active ingredient; it's used as a preservative.

DR. BELSITO: So is that where those 102 come from? Vaginal douches?

MR. STEINBERG: I would be very suspect. They might even be included in things like mascaras where it is commonly used and considering that an indication.

DR. BELSITO: Where do we get this number? Who supplies the number of mucous membrane? I thought that we looked at the types of products it was used in and came up with a total number. I'm just, you know, incidental ingestion not being reported, mucous membrane 102, I mean, we're not talking about a discrepancy of one or two here. There are 102 products that you're saying are coming into contact with a mucous membrane with concentrations of up to 0.05. And if it's in contact with a mucous membrane, it

can much more easily get absorbed.

MR. STEINBERG: And 0.05 you're wasting -- you're at two and a half times at the level in which it works. You've exceeded what its functionality is.

DR. BELSITO: I mean, we have five mascaras. We have seven other eye makeup preparations. We have 14 eye lotions, 10 eyeliners, one eye shadow.

MR. STEINBERG: One of the reasons why you see use at 500 ppm is one of the first commercial cocktails. At a ratio in which you added it at the percent suggested, you've got 500 ppm.

DR. BELSITO: I mean, I think there's, I mean, at least based upon the list that I saw, I mean, do we normally consider a mascara mucous membrane exposure?

MR. BOYER: I think we have been because of exposure to the conjunctiva.

DR. BELSITO: So any eye makeup would be consider mucous membrane exposure?

MR. BOYER: I would assume that's what they did.

DR. BELSITO: But then the number is still wrong.

MR. JOHNSON: I'll just check that.

MS. GILL: Yeah, I think it's clear that we need to go back and check that number to make sure that's accurate.

DR. BELSITO: Okay. So what we just heard is that -- and David, correct me if I'm wrong -- that using more than 0.02 percent of this would be overkill, yet we're faced with the fact that if that, in fact, is the case, there is overkill here. We have it up to 0.5 percent. And then we have what Europe is doing, which seems to be driven by a thyroid issue. You know, if, in fact, this is not used in any lipsticks or oral products that would be ingested, what we're hearing from Dan is that this breakdown to formulate absorbable free iodine when put on the skin is not a very likely scenario and the restrictions in Europe are based upon that, this

again in the clinics is more of a problem with irritation. And at that point we're testing with -- and there was -- I don't remember if it was in wave two or in the report, Axel Schnukus talked about what is the right concentration to test this on? And the Germans I think are now using 0.3. The North American group looked at 0.1, 0.5. Even at 0.1 we see a lot of irritation but not really a lot of sensitization. So, I mean, I don't think we need to reopen this but we need, if we don't, a very firm discussion as to why we've chosen not to reopen it.

Dan and Paul, I mean --

DR. LIEBLER: Well, I agree with you. The problem is a firm discussion can't be crafted here because we have too many unknowns.

DR. BELSITO: Well, we know that it's not used in a lipstick.

DR. LIEBLER: Okay.

DR. BELSITO: It would appear that the number of mucous membrane exposures at 102 is not correct. And the only thing that comes close to

it in the list that we have at the end of the document would be eye cosmetics. I think the only thing in my mind that we would have to craft in the discussion, again, my sense is the restrictions that are being applied in Europe in terms of the 0.02 in rinse-offs and 0.01 in leave-ons and not to be used in kids is based upon this dosing effect that they saw when they gave 0.01 percent free IPBC to two volunteers and the urinary iodine excretion was, I guess, a baseline. And then when they gave 0.02 percent they saw almost a doubling in that iodine excretion suggesting that when you feed this, you release free iodine and they're concerned.

But, on the other hand, they did no thyroid testing to show that that amount of iodine had an effect. They were basing it off of the recommended iodine dietary concentrations.

DR. SNYDER: What are the differences between these two? Because only one patient stayed. The other one it actually lowered.

DR. BELSITO: Yeah.

DR. LIEBLER: See, it doesn't -- this table doesn't make any sense. The positive control should be the 100 microgram iodine oral dosing, and that hardly made a dent in their excretion of urinary iodide. And I think the amount of iodine, the total -- I haven't been able to do the calculation but it looks to me like the moles of iodine applied in the IPBC couldn't possibly account for the bump that they're reporting in iodide excretion in these patients. And it makes me wonder whether these -- yeah, it makes me wonder how these measurements are really done. Are these data any good?

MR. ANSELL: Well, it's important to remember that whereas we share common data, it's possible that there were other elements that went into the conclusion. For example, European iodine levels in the diet. It's possible that no one supported it. You know, that the restrictions were of current use concentrations and so no one challenged the data. It's hard to kind of piece a data point and draw a direct line to any

particular conclusion absent a reading that the whole SECS opinion as to why they did what it is they did.

So I think you guys can look at the data and draw your own conclusions and not try to piece together why a different expert group ended up coming up with the conclusion because there are a lot of elements that would go into it.

DR. BELSITO: Right.

MR. JOHNSON: Dr. Belsito, I'd like to point out that the EU restriction on the use in deodorants and antiperspirants is even lower --

DR. SNYDER: 0.0075.

MR. JOHNSON: -- at 0.0075 percent.

DR. BELSITO: Right.

DR. SNYDER: Why would you use it in a deodorant or antiperspirant? It's antifungal. Logically, it makes no sense to use it for that purpose.

DR. BELSITO: Okay. So yeah, so what Christina is saying is the 102 comes from a combination of other cleanliness products, bubble

baths, and bath soaps.

Thank you, Christina. So that would be rinse-off. Okay. So, I mean, from a skin standpoint I don't think we need to reopen it. I guess what I'm hearing from Dan and Paul, please comment if you like, but we're not seeing a reason to reopen this report at this point; right?

DR. LIEBLER: Right.

DR. BELSITO: And then in the discussion you just need to address that we don't think that the release of free iodide from commercial preparations would result in any significant thyroid toxicity. Is that the right word?

DR. LIEBLER: Yeah. And I don't think we directly need to respond to this table of these two volunteers, do we?

DR. BELSITO: No, I mean, we don't need to directly respond to anything other than to, you know, I think we need to note --

DR. SNYDER: We were aware of it.

DR. BELSITO: -- that at least part of the issue of the SECS was potential thyroid

effects because they're doing, you know, it's reported to be used in 14 baby products. We don't know the concentration of use, and they're saying it shouldn't be used in children less than three years of age for any product intended for use on an infant population. So, I mean, I do think we need to at least when we say we're not reopening say, okay, we're aware that Europe has restricted this to 0.02 percent in rinse- offs, 0.01 in leave-ons except underarm deodorants where it's 0.0075 and that it shouldn't be used infants less than three years of age. However, in reviewing the data, you know, we don't feel that release of free iodine and thyroid toxicity will be an issue and this ingredient is used in cosmetics and we see no irritation or sensitization data that would suggest that the current levels are unsafe and we elected not to reopen it.

DR. SNYDER: The basis of the 0.01 previously was comedogenicity.

DR. BELSITO: Well, that was the highest level. How was it used? Because it's -- back in

the old report we just had ranges. So, in fact, in this report we didn't even have ranges at that point. We just had total number of formulations. So that was back when we were stuck not even knowing how it was used. So here, I mean, where we know that it's not even used up to 0.01, I mean, the highest we have is 0.05.

Now, I mean, do you -- I still don't think that that's a reason to reopen it. We had here for sensitization in the old report --

DR. SNYDER: (Inaudible) as a basis for the limit?

DR. BELSITO: You know, it was a very difficult time in the life of the panel when we're trying to rule on safety of ingredients and we had no idea of concentration ranges and we were setting limits based upon what was the weakest link in the chain and what level did we have there. So I think we had this comedogenicity study and 0.01 percent and we said, okay, well, we'll limit it there. You know, we had some sensitization data and irritation data at higher

levels that were okay and were looking for a level to set it at.

DR. SNYDER: Well, that's my only issue is, is it still valid to have that 0.01 percent limit if it's safe as used and it's not been used above that?

DR. BELSITO: 0.05? Well, I mean, I don't know the dynamics of how we would -- I mean, we'd say we're not reopening, unless you wanted to reopen to reduce the concentration that we say is safe from 0.01 to less than 0.05. But again, I don't think we have data to tell us that that we can say that 0.01 is not safe. So I just don't think we need to reopen it and what we really need to address is, you know, our understanding -- that we're aware that Europe has restricted it, changed concentrations. We don't think thyroid toxicity endpoint is an issue and we see no sensitization and irritation data that would suggest that the current use levels are creating issues in that arena as well. Period and amen.

MR. ANSELL: Yeah. This came up because

of a 15- year cycle. If we had some alternative approach as we have discussed previously, would this have made the cut? I mean, there's no other information.

DR. SNYDER: Yeah, I agree. But I think studying back, if we reviewed this today we would be safe as used.

DR. BELSITO: Right. I agree.

DR. SNYDER: And so I'm just having somewhat of an unjustified limit based upon old data and old procedures that drove them to basically set an artificial -- somewhat artificial limit based upon comedogenicity.

DR. LIEBLER: Well, if we had unlimited time or resources we could go back and do it "right" and work around to the past but it's just not worth the time and effort. We're not going to really change anything because the old limit is equivalent to what's being used.

MS. GILL: Yeah. I would recommend not opening it and leaving it at the limit.

DR. BELSITO: Okay. So we're not going

to reopen.

DR. SNYDER: But there'd have to be much more lengthy discussion about -- in the re-review document regarding why the limit was set and why the iodine issue is not an issue.

MR. JOHNSON: Why --

MR. ANSELL: Well, was it predicated on --

DR. SNYDER: A previous limit.

MR. ANSELL: Because the previous limit already considered the EU limitations. I think the issue, at least in my mind, is that nothing has changed in the last 15 years that would justify reopening it, not resurfacing all of the discussions from '95 unless you feel that something you did back then was wrong. So I think the discussion is that little had changed in the last 15 years which would justify reassessment.

MS. GILL: But I think there should be some mention in the discussion that talks about the EU because they have changed. And I think for the panel to acknowledge that in the discussion

and then say why it's not pertinent here.

DR. BELSITO: Yeah, I agree.

DR. SNYDER: I had a question mark as to when they made that. Do we know when it was?

DR. BELSITO: Just recently, I think.

MS. BURNETT: 2004?

MR. STEINBERG: No, I think the major change was I think 10 years ago.

DR. BELSITO: Ten years ago?

MR. STEINBERG: Yeah. I can get you the exact dates but it was about 10 years ago was when they came out with this.

MR. ANSELL: Yeah, but then it's clearly appropriate.

DR. BELSITO: Okay. Well, I mean, in the old report we had an HRIPT on 95 patients at 0.125 percent that was negative, and although we talk about the comedogenicity in the discussion, I think that also was supporting our job.

Okay. So we're not going to reopen. We'll take a look at the discussion, and basically the two discussion points would be that we don't

think the release of free iodine is an issue. So we're not concerned about thyroid toxicity and the 0.05 percent doesn't seem to be a sensitizer and we didn't see the need to change our prior conclusion.

Okay. Re-review summaries. That's in the administrative book past all the minutes here.

Okay. So that's going to be on 18 of the PDF. I don't think I had any comments. I thought they were fine.

DR. LIEBLER: Same here.

DR. SNYDER: I just had one to the retinyl palmitate --

DR. BELSITO: Okay.

DR. SNYDER: -- discussion. Instead of "recognize the public media visibility (inaudible) new study," I just said for retinyl palmitate, "The panel thoroughly reviewed a 2012 NTP photocarcinogenicity study completed by the NTP." And just leave it at that. I don't think we need -- and then talk about -- I don't think we need to put in there the public media visibility concern,

the new studies, and all that. We reviewed it. We found flaws in it. I don't think that it matters much.

DR. BELSITO: So you're suggesting that it be changed that the panel reviewed the photocarcinogenicity study completed?

DR. SNYDER: Yeah.

DR. BELSITO: Dan, are you okay with that?

DR. LIEBLER: Which paragraph are you changing? Under the discussion?

DR. BELSITO: Discussion, the first sentence. Instead of saying we recognized all the public hype about these, simply say for retinyl and retinyl palmitate the panel reviewed the photocarcinogenicity study completed by NTP.

DR. LIEBLER: Okay. Fine.

DR. BELSITO: Anything else? Okay, well that was good. Okay. So now we're going to isethionate. So we got updated use concentration that the isethionate was not used in a powder but a wipe and that it was 2.5 percent and not 3

percent in that wipe. That was, I think, the only wave two data that we got. And okay, so based upon that, on page 20 of the PDF it says, "The panel discussed the issue of incidental inhalation exposure from suntan preparations and baby care products." I'm assuming that we can delete baby care products. That was the wipe. And then also "and up to 3 percent in other products that may become airborne." That can be deleted. It's not used as a powder.

Do you see where I'm at?

MS. BURNETT: Mm-hmm.

DR. BELSITO: At the end of that paragraph, just before the conclusion, a detailed discussion summary of the panel's approach, I thought that that came out -- we talk about inhalation and then we talk about other things and then we come back to this, that that last sentence should be moved up to after the inhalation. So local respiratory systemic side effects, period. A detailed discussion and summary of the panel's approach, yada, yada, yada. And then the next

sentence, "The panel considered other data available to characterize the potential advice of binate salts." I thought that should be a separate paragraph. You know, keep all of the inhalation stuff together.

DR. SNYDER: Yeah, so along the same lines of discussing inhalation. So on that paragraph that starts the last paragraph before the conclusion section, "The panel discussed the issue of incidental inhalation exposure," and then the second sentence says, "There were no inhalation toxicity data available." And then in the next sentence we say "in the inhalation studies." We've got to be careful there that we can't just plug a boilerplate in. We've got to verify that we had data because we plugged in that boilerplate statement. You know, high doses of respirable particles in inhalation studies do not indicate risk, but there were no inhalation studies. So we've got to be careful about that.

DR. BELSITO: So we need to get rid of that sentence?

DR. SNYDER: Yes.

DR. BELSITO: Anything else?

DR. SNYDER: This is the one we were going to talk about the abstract and the boilerplate.

DR. BELSITO: Yeah.

DR. SNYDER: And this is actually a good one because the abstract actually incorporates that statement about data gaps.

DR. LIEBLER: So I had a comment about that. The term "bio handling" is basically slang, and we kind of understand on this panel because Ron uses it, Ron Hill uses the term and I know what he means, but I don't think a reader would necessarily understand it. So I'm proposing we replace bio handling with similarities and physical and biological properties or physiochemical properties. So in the abstract, for example, instead of "and the expected bio handling enabled grouping," you would say, "and the expected similarities in physiochemical properties enable grouping."

MS. BURNETT: Can you repeat that one more time, please?

DR. BELSITO: Physio or physico?

DR. SNYDER: Physico.

DR. BELSITO: Okay.

DR. SNYDER: Physico chemical? Okay.

DR. LIEBLER: Physico, physio?

DR. BELSITO: Well, physic to me is more structural; physio is more biologic.

DR. LIEBLER: Okay. Anyway, either of those would be fine. Physico is fine.

Similarities in physic chemical properties. I'm changing it on my copy here.

DR. BELSITO: Okay.

DR. LIEBLER: So this would also come up in the discussion so that the language in the abstract though would change that sentence. The phrase that's relevant here is "and the expected bio handling" would be changed to "and the expected physicochemical properties enable grouping."

DR. BELSITO: Well, not the expected.

The physical chemical properties.

DR. LIEBLER: Well, in some cases they're known, and then the gaps that you're reading across are the expected. So that's why I left expected in.

DR. BELSITO: Okay. So what line are you on?

DR. SNYDER: Or predicted?

DR. LIEBLER: The third line of the abstract.

DR. SNYDER: Would predicted be better than expected?

DR. LIEBLER: Yeah.

DR. BELSITO: And the predicted?

DR. LIEBLER: Predicted is fine. I like that.

DR. BELSITO: Okay.

DR. SNYDER: So going back to the abstract, so this is a good one for Christina to capture the three things that we said the abstract has to have -- what we've reviewed, what we found, and then what was our conclusion. And so we

reviewed -- and I think we can make it even better, "the product formulation and safety data of 12- iseothionate salts." So I added in the product formulation and safety data because we always do updated product formulation as a part of our review, not just safety data.

DR. BELSITO: Product formulation and --

DR. LIEBLER: And safety data of 12-iseothionate salts. And then I had the same issue with the expected bio handling that we've already resolved. And then our conclusion. So I think that's -- you should do that on all of those -- on all the (inaudible) use that system. And all of these have these data gaps but they may have issues that came up on how we resolved those issues.

DR. SNYDER: So, Paul, you're proposing substituting product formulation and safety data for toxicological data?

DR. BELSITO: No. The Cosmetic Ingredient Review Expert Panel reviewed the product formulation and safety data of

12-iseothionate salts.

DR. SNYDER: Okay, good. That's good.

MR. ANSELL: And we'll swing back to this in the retanical template but --

DR. SNYDER: Well, then it's a slippery slope.

MR. ANSELL: Well, I think one of our comments is just that the structure of the abstract should include the review of what's found and the conclusion. So we like that part of the proposal.

DR. BELSITO: Anything else? Okay.

DR. SNYDER: I have a question for Dan. (Inaudible) chemistry here, so bear with me.

DR. LIEBLER: Which page?

DR. SNYDER: Under chemistry definition of structure.

DR. LIEBLER: What PDF page are you on?

DR. SNYDER: I have a Word document.

MS. BURNETT: Fourteen.

DR. SNYDER: So the second sentence says

"the ingredients in the report are related by." Should it be more perfect to say "they share a common 2-hydroxy" instead of related by?

And then further down, "these chemicals have the classical structural components," or should it be "typical structural components of surfactants"?

I just -- it kind of stuck out to me as a chemist.

DR. LIEBLER: I like both of your -- I like both of your edits and they're not really about chemistry, so, but I like them.

DR. SNYDER: I just didn't, you know, they're not really related. They may share a common core or something but --

DR. LIEBLER: Actually, I corrected sort of an incorrect statement here that is chemistry.

DR. BELSITO: So share a common core?

DR. SNYDER: No, just share a common and then it gives a structured name there.

DR. BELSITO: Common 2-hydroxyethanesulfonic acid?

DR. SNYDER: Yeah.

DR. BELSITO: Okay. And then what was your next comment?

DR. SNYDER: The last sentence right before the structure. Instead of classical you just say a typical structural component of surfactant.

DR. LIEBLER: So I did correct one thing because the sentence contains the word simple alkyl esters or mixtures of simple alkyl esters of 2-hydroxyethanesulfonic acid, that implies that the esterification is on the ethanesulfonic acid part and it's actually not. So I just reworded it to --

DR. BELSITO: Where are you, Dan? I'm sorry.

DR. LIEBLER: Under chemistry, same paragraph where Paul just made his two little changes.

DR. BELSITO: Right.

DR. LIEBLER: The second to last sentence. "While the rest of the ingredients in

this report are simple," and I just changed simple alkyl esters for mixtures of simple alkyl esters or -- I changed that phrase to fatty acyl esters formed with 2-hydroxyethanesufonic acid. So it's clear from, at least chemically correct, to characterize these as esterified between the fatty acyl ester -- so basically, the fatty acyl esters for the hydroxyethanesulfonic acid provides the alcohol piece. That's all. Because the way it was written it meant the complete opposite.

DR. BELSITO: So could you read that again for me, please?

DR. LIEBLER: Sure.

DR. BELSITO: While the rest of the ingredients in this report are --

DR. LIEBLER: Are fatty acyl esters formed with 2- hydroxyethenesulfonic acid.

DR. BELSITO: Fatty acyl A-C-Y-L?

DR. LIEBLER: Right. Esters formed with 2- hydroxyethanesulfonic acid.

So the previous language implied the wrong structure.

DR. BELSITO: Formed with 2-hydroxyethanesulfonic acid. Anything else?

Okay. So alkyl amides. This is Christina also. So in June, we determined that the available safety data were insufficient. We are evaluating these. We requested additional irritation sensitization data for lauroyl lysine at the highest use concentration, 45 percent, and lauroyl glutamate at the highest use concentration, 40 percent. We discussed differences in the absorption of disodium malatine finite compared to other ingredients, but decided the toxicological consequences would be minimal. We got HRIPT data on sodium lauroyl glutamate on concentrations of 22 and 30 percent in the report. And the question is are we okay with what we have now? We did not -- and then we got wave two data, sorry, on skin irritation for lauroyl lysine at 5 and 20 percent in olive oil. Maximization tests for lauroyl lysine at 50 percent in olive oil. Repeated (inaudible) testing 8.36 percent of lauroyl lysine, 600 panel-predicted patch testing,

12.5 percent lauroyl lysine. And then for the glutamate we got some irritation data -- 5 percent distilled water and the maximization test induced at 5 and challenged at 2.5. And use concentration on this --

DR. LIEBLER: Of the glutamates. I thought we were still short.

DR. BELSITO: I thought that it was okay for leave-ons and 4 percent rinse-offs to 40 percent. The uses that we have here now are -- I thought were in line with that.

So for --

DR. LIEBLER: So the high concentrations for the glutamates look like they're rinse-offs.

DR. BELSITO: Right.

DR. LIEBLER: And is that -- is that the reason you're okay with the sensitization data at the lower concentrations?

DR. BELSITO: Yes.

DR. LIEBLER: Okay. Then I'm fine with it, too.

MS. BURNETT: I'm sorry, Dr. Belsito.

Can you repeat what your finding is?

DR. BELSITO: I thought that they were safe as used when formulated to be nonirritating. And I actually -- the highest tested 5 percent was a mild irritant. It's used in leave-ons at 4 percent and rinse-offs at 40 percent, so my only concern was a possible irritation at 4 percent.

DR. SNYDER: What was the highest use?

DR. BELSITO: Highest use in leave-ons that I saw was 0.4 percent. This is one where I printed out -- well, I printed out these tables I told you, Paul, for all of them but I didn't bring the copies so it makes it hard. There were so many ingredients. But that's what I wrote in my notes here.

Yeah, the highest is sodium lauroyl glutamate, 4 percent in the leave-on and 40 percent in a rinse-off. That's page 57 of the PDF. And we have for the sodium lauroyl glutamate, mild irritant when tested up to 50 percent distilled water and a sensitization guinea pig -- modified maximization testing in guinea

pigs induction at 5 percent and challenged at 2.5 percent was negative.

DR. SNYDER: We have a 45 percent use in lipstick?

DR. BELSITO: I didn't see that.

MS. BURNETT: That's for lauroyl lysine.

DR. SNYDER: Oh, lauroyl lysine. Okay.

DR. BELSITO: Right. And we have a negative 50 percent in olive oil for that one.

DR. SNYDER: That was the only one I had liked because it was so high.

DR. BELSITO: So I basically said safe as used when formulated to be nonirritating just to cover the fact that we don't have an irritation threshold. We know that 5 percent is mildly irritating and 4 percent is the highest use for the glutamate.

And if you're comfortable with that then in the discussion due we need to say something about TEA amine impurities and nitrosation? Because TEA is --

DR. SNYDER: I had that where we tagged

that any available on disodium malyl tyrosinate (inaudible) kind of left hanging out there.

DR. LIEBLER: It didn't come from me. I have no concerns about that one. I mean, it's just a little different derivative than many of the others but it's nothing that would cause me any concern. We've already included it.

But Don, back to your question about nitrosation, where are you in the document? Are you in the discussion?

DR. BELSITO: Well, one of the ingredients that we're looking at is sodium TEA lauroyl collagen amino acids, TEA lauroyl keratin amino acids, TEA cocoyl alaninate. There's a lot of triethanolamine containing compounds here. So, you know, my question in the discussion is do we need to say anything about these TEA containing compounds, about potential amine impurities and nitrosation in our discussion?

DR. LIEBLER: I guess in principle there's a chance of trace amount of a second amine might be present in these but we have some

essentially boilerplate language that we use for that, don't we?

DR. BELSITO: Yeah.

DR. LIEBLER: More than one sentence?

DR. BELSITO: Okay. So we need to add to the discussion the amine impurities nitrosation boilerplate?

DR. LIEBLER: That's fine. I have a proposal to free up some space.

DR. BELSITO: Okay, hold on.

MS. GILL: We can go to that (inaudible).

DR. BELSITO: Pardon, Lillian?

MS. GILL: I was saying we can go to that report and pull out the boilerplate language we used for TEA.

DR. BELSITO: Okay. So my proposal before we get into any other is that we change the draft conclusion to "the CIR Expert Panel concluded that the available data are sufficient to make a determination that the amino acid alkyl amines listed are safe under the intended

concentrations of use when formulated to be nonirritating." And then a list of the ingredients.

Okay, Dan, I'm sorry.

DR. LIEBLER: Yeah. My comment is on the discussion, so PDF page 29. It's the second to last paragraph.

"The panel noted the uncertainty regarding the method of manufacturing," and it's the issue of enzymatic hydrolysis versus acid or base hydrolysis. And although in principle it's true that enzymatic hydrolysis could yield residual peptides that might have some adverse effects, I think that it's probably not -- this language probably is not very applicable or at least could be shortened a lot in this section because you're basically making these amino acids and then azolating the amino groups on these. And doing enzymatic hydrolysis to make these seems like it would be so expensive and inefficient, which I suspect is probably not even done. So I would say that we could shorten that paragraph.

Instead of going into the detail about what kinds of residual peptides would be made we would simply say that the panel suggests that cautions be taken to avoid contamination of the products with partially -- with peptides with peptide contaminants and not waste this much discussion talking about the methods. Because this is a different situation from like wheat hydrolyzed protein kinds of ingredients where then we have the issue of, well, they could have done it a couple of different ways. Here, I think it's unlikely that enzymatic hydrolysis is used to make the amino acid precursors in the first place.

DR. BELSITO: Okay. So simply say, "The panel noted the uncertainty regarding method of manufacturing. The panel stated that industry should manufacture amino acid alkyl amides in a way that ensures that no residual peptides remain."

DR. LIEBLER: Correct.

DR. SNYDER: Or the hydrolysis procedures.

DR. LIEBLER: Just keep it as short as possible.

DR. BELSITO: Short and sweet.

DR. LIEBLER: Right.

DR. BELSITO: So in the absence of further clarification, "The panel stated that industry should manufacture." That's much more to the point. You can't miss it.

Thanks, Dan. Anything else?

DR. LIEBLER: My next question would be can you ensure that no residual peptides remain (inaudible) the last part of that. Can you ensure that no peptides remain or should it be minimized or something? I mean, does it (inaudible) expectation to say no?

DR. BELSITO: Little or no. Is that fine?

DR. LIEBLER: Well, in a way to minimize residual peptide content.

DR. BELSITO: Minimizes residual?

MR. ANSELL: Yeah, in a way that minimizes residual peptide content.

DR. BELSITO: Okay. So that -- what now becomes the last paragraph in the discussion, since we got rid of the requested data, "The panel noted the uncertainty regarding method of manufacturing. In the absence of (inaudible) clarification, the panel stated that industry should manufacture amino acid alkyl amides in a way that minimizes -- that minimizes residual peptides." Right?

DR. SNYDER: Peptide contaminations, something like that.

DR. BELSITO: No, just residual peptides. Do you want to say contamination?

DR. SNYDER: Right.

DR. BELSITO: I don't like contamination when it comes to cosmetics. Contaminants almost seems like you're putting something in there.

DR. LIEBLER: That's adulteration.

DR. BELSITO: Yeah. Speak for yourself.

DR. LIEBLER: Adulteration is with intent. Contamination is by accident.

DR. BELSITO: Okay. Rick?

MR. ANSELL: I would say so.

DR. LIEBLER: Do we need to ask the Aggies and the Jesuits for clarification?

DR. BELSITO: Yes. Okay. Anything else here?

DR. SNYDER: I had a question for Christina. We had an issue about the search drive you use.

Do you do search only (inaudible) because you've got no (inaudible)?

MS. BURNETT: No, I searched for (inaudible). It's how I worded it in the profile. I think I corrected that.

DR. SNYDER: Okay. Thank you.

MS. BURNETT: I just focused -- there's always a carcinogenicity search. It's just to throw out oral because it's amino acid. You're going to get all sorts of hits and so (inaudible).

DR. SNYDER: So then I have a further question to Lillian in regards to the -- we don't really capture in the documents anywhere the search strategy used. It's in the --

MS. GILL: At the very beginning at the strategy. Yes.

DR. SNYDER: Yeah, it's in the strategy part but we never really capture that in the document and I'm a little concerned that sometimes when we say that we use kind of a global term that no studies were discovered or something. To me I would like to be more specific. I would like to say no studies were identified by a literature search and what we searched, or submitted. And so it's really two issues. Sometimes we use discovery to encompass both. We didn't identify any of our search strategy and we didn't (inaudible). Yeah, so I think it's in our best interest to imply more specifically what we did. We did a thorough literature search, didn't find anything, didn't identify any studies, and then also none were submitted.

MS. GILL: I think we need to be consistent because sometimes we do say "and none were submitted." So it would be more consistent with that.

DR. BELSITO: Okay. Anything else? Okay. So the next one is alkyl betaines. It's one that --

MS. BURNETT: According to Wikipedia it's beta because it's derived from beets so it's supposed to be pronounced beet.

DR. BELSITO: Okay. Wikipedia is always right.

MS. BURNETT: Yes.

MR. ANSELL: Yeah, we love Wikipedia.

DR. BELSITO: Wikipedia is even better. Okay. So, you know, God bless you, Christina, for having to go through these ECHA documents because, boy, they are hard to review. You click and then you have to click again and then you have to click again and then you have to read and you scroll down.

MS. BURNETT: Ask my officemates how much of a headache it was for me.

DR. BELSITO: Oh, no. I mean --

MS. BURNETT: There was language you did not want to hear from me.

DR. BELSITO: I did my own, too. I mean, this was -- I sort of thought that you bombed on this great summary. I wish you had sent this out before I blinded my eyes.

MS. BURNETT: I finished it Friday. I only did the analogs. I didn't get to the actual betaines itself because I needed to do cross because I already had data (inaudible).

DR. BELSITO: Well, I did the betaines, too, but not as well as you did the C12-15 or C12-14. You know, I think when you add all this data in we're going to find it's sufficient. The question is do we want to table it? And if so, we can do that and go to lunch. Or do we want to look at what Christina has summarized and say it's sufficient, in which case I don't think we can do that in 10 minutes, but maybe we can.

Did anyone, other than myself, try and get through all of that ECHA data?

DR. SNYDER: I scanned it.

DR. BELSITO: I thought by the time you finish it all it's pretty sufficient to say that

these are safe.

DR. LIEBLER: I got this this morning.

MR. ANSELL: Well, I think that's definitive.

(Recess)

DR. BELSITO: Okay. So when we left with the fire alarm we were just discussing -- and I just spoke with Pope Francis. He's agreed to start beatification for Christina for going through the ECHA documents.

DR. LIEBLER: It's a long process so don't get excited.

DR. BELSITO: But I mean, I guess I scanned them. We could go safe as used but it sounds like Dan hasn't.

DR. LIEBLER: I just read them during the lunch break.

DR. BELSITO: Okay. And then there's a whole other series of betaines, as well.

MS. BURNETT: Correct, but a lot of that data is already incorporated.

DR. BELSITO: Right.

MS. BURNETT: So I don't think there's a whole lot to add.

DR. BELSITO: Right. I mean, I'm fine safe as used or we could table to await formal incorporation of the ECHA into the documents. I'm comfortable either way. I mean, I'm comfortable going safe as used.

DR. SNYDER: The only thing is we have no impurity data.

DR. BELSITO: Okay. We have method of manufacture though, don't we?

MS. BURNETT: No.

DR. SNYDER: Nothing.

DR. LIEBLER: Can we table it to incorporate these data even though we think they'll probably be sufficient and to get impurities data or method of manufacture? Do you anticipate that those data would be gettable?

DR. BELSITO: I have got impurities, method of manufacture. We also have no UV but there are no ring structures so I didn't think we needed that. We need the aerosol boilerplate.

And it looked like there was barrier disruption caused by some of these, so I suspect that we may want to put the usual --

DR. SNYDER: Irritation?

DR. BELSITO: Yeah, well, I think it would go when formulated to be nonirritating but I guess if there's no irritation you won't see barrier disruption, so then penetration wouldn't be an issue. That's a good point.

Yeah, I mean, impurities and method of manufacture.

MS. BURNETT: Or you could -- however you go, I can get -- since this is already in table form it's going to exist in table form in the report, so it's just a matter of carrying over. I can get (inaudible) put it in pretty fast, so you can just issue an insufficient data announcement now and not table it, and then by the time you see it again it will be complete.

MR. ANSELL: We continue to have a problem with concluding it's insufficient when the original review just doesn't have stuff that you'd

like but were never asked for. So at this point, you know, we feel that if the first review is somehow deficient --

MS. BURNETT: This is the first review.

MR. ANSELL: Right. At had the first review it would be sent back to staff to search for things and ask for things that you think should be there. And not conclude that it's insufficient because the staff did or didn't conclude --

MS. BURNETT: We weren't saying concluded. Just issue an announcement asking for --

DR. BELSITO: Right. Because the data are currently insufficient.

MS. BURNETT: So that we have --

DR. BELSITO: I mean, it's not a final.

MR. ANSELL: No. It just suggests that it was deficient, and we fully support the idea that the staff should be able to go through the data and conclude what they think is important and not important. But in the first review, to

conclude that it's insufficient somehow puts the onus on industry to come up with this data when, in fact, it may be there. It could have just been that the staff chose not to include it because --

DR. BELSITO: We're not saying -- I mean, it's not a formal. I mean, just currently the data are not sufficient to allow for assessment of safety and what the panel is asking for, and we've always used the term insufficient, and these are our data means.

MS. GILL: And the data was requested and what came in was insufficient to make a safety decision, so the data is insufficient to draw a conclusion.

DR. BELSITO: You know, and it may actually be there in the ECHA documents. I mean, there were some tabs that I didn't bother opening. There were tabs that said impurities, I remember, and there were tabs that said method of manufacturing. And quite honestly, I didn't bother to open them. I looked more at the dermal irritation sensitization and chronic toxicity. So

it may be in those documents.

MS. BURNETT: I have this website up right now.

MS. GILL: If it's -- I think if it's there and it has not had an opportunity to be included then that's different than we did not have the data and it was not submitted.

So Christina, are you checking to see?

MR. ANSELL: I would prefer that in these circumstances, on the first go-through, that it be tabled to determine whether the material is available as opposed to a conclusion that the data is insufficient. It's just a recommendation.

DR. BELSITO: I mean, we're going to have to re- read the entire document anyway with the inclusion of all the material because it's going to be a huge amount of material that will have been included from the ECHA documents. So I don't have a problem with tabling it for inclusion in the ECHA documents. And when you go through them again, Christina, just check all the tabs for impurities and method of manufacturing.

MS. BURNETT: Looking at it right now I'm crying.

DR. BELSITO: Is it there?

MS. BURNETT: If it is, it's not easily accessible. I will (inaudible) and I think my concern is going backwards. What I understand is the procedures were rewritten to cut out a step. It says when you table it you go back and see whether or not it is there when you've clearly asked for it before.

In this case, if it was there and the site -- we weren't able to get it or now that we can summarize the data, it may be linked to this particular ingredient (inaudible).

MS. GILL: And I think my concern (inaudible).

DR. LIEBLER: So between the Council and the CIR, maybe you all could work out what you'd like to call this situation because we basically are saying we can't go forward until the information is in hand. And it doesn't matter to us that much whether it's referred to as tabling

the document or saying that it's insufficient. Insufficient without pejorative intent.

DR. BELSITO: Right. I think we should -- I'd like to move ahead. You know, Christina is looking at it right now. Under manufacturing, what they're doing is they're labeling for REACH and they're doing tonnage and how it's used. And also when you look at the safety tabs, what they're talking about is more like occupational exposure. You know, rinse the eyes, wash the skin with water. So I know those tabs aren't going to help us because I opened them and they're basically like a material safety data sheet.

MS. BURNETT: It's referring to some kind of -- I'm looking at manufacture for betaines. And it says process category. And there is a bunch of codes.

DR. BELSITO: Yeah.

MS. BURNETT: (Inaudible) use enclosed process. No likelihood of exposure. And it gives a couple more (inaudible). It doesn't tell you the actual chemical process, however they make it.

So in this case the ECHA site is not helpful.

(Discussion off the record)

MS. BURNETT: So we're going to have to have outside help finding this because it's not -- I mean, I've looked --

DR. BELSITO: Okay.

MS. BURNETT: -- my searches have already covered everything else.

DR. BELSITO: So --

DR. LIEBLER: So the information --

DR. BELSITO: -- impurities, method of manufacturing, we need to insert the aerosol boilerplate into the cosmetic use and we have to mention that there was no photo data but we're not concerned because there are no ring structures that would likely absorb.

DR. LIEBLER: No chromophors.

DR. BELSITO: No chromophors. Just chromophobes.

MS. BURNETT: Is that with a P-H?

DR. LIEBLER: Yeah, P-H. Chromophors.

MS. BURNETT: I figured it was.

DR. LIEBLER: So I expect that method of manufacture and impurities, once they are in-hand, will be unremarkable. The issue isn't that we have any suspected concern; it's we just don't have anything yet. If we do have them, I don't anticipate it to alter our course of action at all.

DR. BELSITO: Okay.

DR. SNYDER: Wheat?

DR. BELSITO: Do you want to take this now --

MS. BURNETT: Sure.

DR. BELSITO: -- because my corrections are in here.

MS. BURNETT: I'll give it a good look over and then you can help me with your handwriting.

DR. BELSITO: Yeah. No, it's mainly just misspellings.

MS. BURNETT: Okay.

DR. BELSITO: It's nothing major. Okay. So that's the alkyl betaines. Hydrolyzed wheat

protein. Okay. That's another one I did on paper. Is this yours, too, Christina?

MS. BURNETT: Yes.

DR. BELSITO: Okay. So you know, I looked at this and I think that really all the issues that we're going to have with these hydrolyzed proteins can be resolved if we say that they have to be less than 30 kilodaltons or less than or equal to 30 amino acids long because at that level they don't seem to bind IgE, which is the major issue and the thing that was the issue in Japan. And then I guess the next issue is should these -- even without restrictions, should they be put on damaged skin where they could get absorbed and would they theoretically sensitize to wheat or gluten? And there was some data in here and it was in rodents where they were actually able to sensitize individuals to wheat. Or was it the Japanese human studies? I can't remember.

MS. BURNETT: There was a sensitization study 24 (inaudible).

DR. BELSITO: Yeah. The dermal --

MR. BOYER: What they are observing in human subjects in both Japan and Europe, but particularly in Japan there's people who are exposed to hydrolyzed wheat protein ingredients through the conjunctiva and through the sinuses and so forth. They apparently can develop sensitization to hydrolyzed wheat protein.

DR. BELSITO: Yeah. And that was the eye drop challenge of one patient that we had. But yeah, this was a dermal, nonhuman sensitization in tape-stripped mice where they were able to sensitize the hydrolyzed wheat protein. Now, we don't know the molecular weight so, I mean, it's not clear that these were less than 30 kilodaltons or less than 30 amino acids, but I thought, you know, as we originally did, I believe with parabens about not to be used on damaged skin, that that might be a caveat. The other question would be inhalation because here you would not only worry that it would get down to the alveoli; the real inhalation problem would be in the nasopharyngeal area. I thought that we

could go safe, not to be used on damaged skin, not to be used in products that could be inhaled, limit to less than 30 kilodaltons, and something the Council raised that I would agree with, a bold label on packaging of any of these hydrolyzed proteins indicating warning, this product contains wheat, gluten, whatever. But that was my thoughts anyway.

DR. LIEBLER: So I basically agree with that. And the only modification I'd make, Don, is about the exclusion of peptides of greater than 30 amino acids. Practically speaking, it's going to be nearly impossible for them to totally exclude that or to know whether they have. So I would change that to say that the mixture should be prepared to minimize components of greater than 30 amino acids in length. It's just like minimizing any other contaminant.

DR. BELSITO: So you're going to say minimize --

DR. LIEBLER: Minimize --

DR. BELSITO: -- peptides greater than

30 amino acids?

DR. LIEBLER: Right.

DR. BELSITO: What about weight? Nothing about weight? Just the amino acid?

DR. LIEBLER: You could say either. Thirty amino acids is a ballpark number that relates in the way you just mentioned to IgE activation. So you could either say 30 amino acids or 30 times 150 to give you whatever kilodaltons that is. But it's easier just to say 30 amino acids or approximately 30 amino acids.

You know, the other point I had, and this is more speculation, but since these issues with the soap in Japan continue to hydrolyze wheat protein involved a soap, it's possible that the issue wasn't necessarily that it had some bad wheat hydrolysate in it, but it might have been the way it was formulated with the other ingredients of soap that made an otherwise relatively innocuous -- a preparation that would have been innocuous in another type of product cause a problem in this product. So perhaps a

caution to formulate these to be nonsensitizing or maybe you're coming at the same issue with not to be used in damaged skin.

DR. SNYDER: But I do have a statement that says, "Surfactants in soap facilitate the dermal penetration."

DR. LIEBLER: Yeah. That's what I was thinking. That's what made me think about it. It might have been the way that the wheat proteins were formulated into a product that contains some other things that would have increased the likelihood that they would cause a problem.

DR. BELSITO: But the greatest use of these are in shampoos which are going to have surfactants.

DR. LIEBLER: Right. Yeah.

DR. BELSITO: So if we say not to be used in surfactants, we're going to eliminate their use essentially.

DR. LIEBLER: No, no, I'm not saying that but maybe to be formulated to be nonsensitizing.

DR. BELSITO: Yeah, that's I think too vague. I mean, I think we have data that shows if there's less than 30 amino acids --

DR. LIEBLER: Sure.

DR. BELSITO: -- these aren't an issue and it's a better way of going about it. And then if we say not to be used in products, you know, not intended for use in damaged skin, products that could be inhaled, I think we eliminate, and I guess what Ivan was saying is probably products that would be applied to the eye.

MR. BOYER: Actually, there is facial soap in which apparently people wash their eyelids and so forth with and that contact with the conjunctiva --

DR. SNYDER: (Inaudible) body moisturizer.

MR. BOYER: It seems surface (inaudible) to some extent why some people are getting sensitized.

DR. BELSITO: So not on damaged skin or products intended for application to the eye?

MR. BOYER: That could work.

MR. ANSELL: It would have to be eye area.

DR. BELSITO: Yes.

MR. ANSELL: Cosmetics would not.

DR. BELSITO: Eyelid, eye area.

DR. SNYDER: But then does your size restriction eliminate?

MR. ANSELL: Well, that's kind of, you know, we have good data on the molecular weight. I also know from our PEG experience that the damaged skin can be very confusing to the community because it doesn't really go to the extent of damage. Does that mean sunburn, abraded, atopic? I'm not sure that the molecular weight distinction -- I mean, how damaged is damaged skin that we'd be worried about main materials which qualified based on the molecular weight?

DR. BELSITO: Well, the studies in the animals were 10 tape strippings. And if I recollect correctly, from the presentation that we

had when we did damaged skin, the tape strippings is about what atopic skin is like; was that right? Because they showed that the parabens weren't an issue on 10 tape-stripped skin and that's why they were when they were put on third degree burns. But here, 10 tape strippings did allow sensitization of those animals. So basically, damaged skin here is impairment of the stratum corneum because that's all you did with tape stripping. You really don't take much of the living epidermis away. So I think that, yeah, I guess damage is subject to interpretation. You can say, oh, that's a third degree transdermal burn. I don't know how better to say it, you know. Areas deficient in the stratum corneum? That takes care of all the mucous membranes, right? We don't have to specify eye areas. But that doesn't help the consuming public. Not to be used on eczematous skin? You know --

DR. SNYDER: Where the stratum corneum is not intact or something. They wouldn't know that. I mean, you have to give them some

reference of some clinical entity; right? Is that what you're trying to do? Come up with some --

DR. BELSITO: Well, I mean, I guess these aren't guidelines for the public; they're guidelines to industry. So not to be used in products intended for application to areas deficient in the stratum corneum.

DR. LIEBLER: I think damaged skin is okay to use. I mean, I think we're going to really tie ourselves in knots trying to come up with some language that encompasses more specifically the various possibilities for what could constitute damaged skin.

MR. ANSELL: Perhaps in the discussion if we were clear as to the underlying data which resulted in that recommendation.

DR. LIEBLER: Exactly, because we could point to the fact that this study with tape-stripped skin showed sensitization.

DR. BELSITO: Well, I'm just now looking as we're having this discussion. You know, really, it's mucosal applications as well. So is

this used in any --

DR. SNYDER: Here.

DR. BELSITO: I'm getting there.

DR. SNYDER: Fifteen mucous membrane products, hydrolyzed wheat gluten and hydrolyzed wheat protein 113 up to 0.1 percent.

DR. BELSITO: Mucous membrane?

DR. SNYDER: Yeah.

DR. BELSITO: It's huge, 118 products total.

MS. BURNETT: That's most personal cleanliness products. Bubble bath.

DR. SNYDER: Well, I think if we frame it correctly and the main issue is sensitization, basically peptide contaminants and that they should limit the amount of peptide contamination of (inaudible).

DR. BELSITO: Yeah, but what we know is that less than 30 amino acids won't trigger IgE release. It won't bind to mast cell receptors to trigger IgE release. We don't know whether -- we don't know what the hydrolyzed wheat protein that

sensitized these mice -- what the composition of that is. So it's entirely possible that a 20 amino acid hydrolyzed product could cause sensitization to the whole molecule. We simply don't have that information. What we know is that if you're sensitized -- even if you're sensitized, less than 30 isn't going to trigger IgE. The converse, whether less than 30 triggers sensitization we don't know.

I think based upon what we have, I think we have to say it should not be used on damaged skin and in products that may contact mucous membranes. And if industry is concerned, if the manufacturers of those 118 products, you know, want to show us some data at a certain level or whatever there's no sensitization occurring with mucous membrane exposure, you know, we'll consider that. But at this point, I mean, the data clearly shows that you can get ocular sensitization and with tape stripping you can get sensitization.

Okay. So to recapitulate where we are, safe, minimize peptides greater than 30 amino

acids in length, not on damaged skin or products intended or products intended for application to mucous membranes. Mascaras aren't intended to be applied there. Or products that may contact mucous membranes? Is that a good way of saying it? Not in products that could be inhaled. And then the question is do products that are going to contain these hydrolyzed proteins need a clear warning on them stating like foods do this contains gluten or this contains peanuts or this contains soy?

MR. ANSELL: I would recommend that the panel stay away from labeling. Labels and labeling really cross into a whole regulatory regime that would have to be considered within the context of existing FDA regulation. And --

DR. BELSITO: I thought that was an industry comment that you wanted that kind of label. Did I misread that?

MS. GILL: I thought that was, too.

MR. ANSELL: I can't find that comment.

MR. BOYER: It's wave two and it was

from a member.

DR. LIEBLER: Oh, that was the hodge-podge of comments on hydrolyzed proteins.

DR. BELSITO: Right. Yeah.

DR. LIEBLER: Yeah, so I actually am cautious about that for an additional reason. In addition to the point Jay made, which I think are perfectly valid, but I think the additional reason is that once you've digested these down, they're not really gluten or wheat anymore. They're short sequences that have sequence identity to wheat proteins but they're derived from wheat proteins, but it's not like saying it contains wheat or it contains gluten anymore because it really doesn't. These things are no longer really wheat. They're no longer really gluten.

DR. BELSITO: I will tell you that as a chronic label reader by virtue of what I do, I increasingly see products, for instance, shea butter, you know, sort of surprised me, should not be used by people with tree nut allergy. Or things that have peanut oil should not be used by

individuals with known sensitivity to peanuts. You're seeing that on cosmetic labels already. I'm fine not going the labeling route and let manufactures do what they want to do, but actually, it was an industry point that was brought up about labeling.

MR. ANSELL: Yeah, did it come from us or was it a company?

DR. BELSITO: Yes. It's here. "Please see below for some comments to feedback to the CIR regarding the draft assessment and the use of animal- and plant-derived amino acids." Point 4.

MR. ANSELL: Yeah, from a member company.

MS. BURNETT: Yeah, it wasn't you. It was another company that passed along (inaudible).

MR. BOYER: The other thing to consider, too, is when you're breaking down and when you're preparing hydrolyzed wheat protein, what you may be left with are peptides that are long enough to still represent epitopes. In fact, the research seems to indicate that the epitopes in those

hydrozolates are very similar. They react in a very similar manner to the epitopes that you find in intact proteins and intact gluten and so forth. And in fact, when you break up proteins, you can end up with a mixture. You can end up with a mixture of fairly large polypeptides that can then intermingle. They can basically aggregate and so forth so you end up with epitopes.

DR. LIEBLER: So my interpretation of this, because I did note those same concerns, my interpretation of those studies is that they're all done with hydrolyzed products. Right?

MR. BOYER: I think so.

DR. LIEBLER: They're all done with hydrolyzed products. So the thing that you can't know in that case is whether or not there is residual unhydrolyzed material that produced the observed effect as opposed to attributing it to the hydrolyzed material. And the only way to do that experiment right would be to actually synthesize the shorter pieces and determine with purified synthetic shorter pieces whether or not

they produced these effects or not. That would be the right experiment to do. And I don't think that was done. I think it was these hydrolysates that were incompletely characterized in the conclusions. And if I got that as a paper to review that is what I would say as a reviewer. They cannot conclude that these shorter products actually have the biological activities that they attribute to it because they cannot exclude the residual presence of longer products.

MR. BOYER: That's very true. In fact, all of these are brought up from a point of view of a hypothesis.

DR. LIEBLER: Right.

DR. BELSITO: Okay. And the only other comment that I had, Christina, is on page 24 of the PDF. It says a 25 percent aqueous solution. Now, we were told in the beginning that that's how these are supplied, as a 25 percent aqueous solution. So is this 25 percent of 25 percent? Or is this the actual product that is provided to companies to blend into their products?

MS. BURNETT: It would probably be seen as 25 percent solution.

DR. BELSITO: So it's what's actually supplied by the manufactures to companies to then blend in. So it's actually 25 percent, not one-fourth of 25 percent?

MS. BURNETT: Right. I believe so.

DR. BELSITO: Okay.

MS. BURNETT: Without having the data. Yep.

DR. BELSITO: Okay.

DR. SNYDER: So --

DR. BELSITO: So I just put a note to check that. Otherwise, I really didn't have anything. Yeah. No, I think that they're probably what is actually supplied by the manufacturers of hydrolyzed wheat protein because it says someplace in the document that it's -- the final product under method of manufacturing. The final product is a 25 percent water solution of hydrolyzed wheat protein and then when you look at here they all say 25 percent aqueous solution.

DR. SNYDER: So (inaudible) it's well below the molecular rate we're saying; right?

DR. BELSITO: Well, it's about where we're setting it, yeah, because 350 kilodaltons was said to be equivalent to approximately 30 amino acids. So that's (inaudible) good too in a sense that it looks like where we want them to be.

DR. SNYDER: And that didn't list it anywhere (inaudible).

DR. BELSITO: Right.

DR. SNYDER: So that's more data to support that that is a good cutoff.

DR. LIEBLER: Wait a second. Thirty amino acids times an average of 150 molecular weight is 4,500. So 4.5 kilodaltons would be your 30 amino acid average cutoff.

DR. SNYDER: (Inaudible) study data that said the polypeptides less than 30 kD could not (inaudible).

DR. BELSITO: Right.

DR. LIEBLER: So I think we should --

DR. SNYDER: Thirty amino acids or 30 --

DR. LIEBLER: Thirty kDs.

DR. BELSITO: They said 30 kD and then they also said less than or equal to 30 amino acids.

DR. LIEBLER: Well, those are very different numbers.

DR. BELSITO: Okay.

DR. LIEBLER: These are very different size molecules you're talking about. Thirty kD, you know, is 30,000.

DR. SNYDER: Right.

DR. LIEBLER: Divided by 150.

DR. SNYDER: Is 20.

DR. LIEBLER: Equals 200 amino acids. Thirty thousand molecular weight divided by 150 is 200.

DR. BELSITO: So that's why amino acids is probably a better number to go with.

DR. LIEBLER: Yeah. That's why I was saying -- and the other thing about that, 30 amino acids is 30 amino acids. If you guess a kilodalton weight, then it depends on what number

you assume for the average amino acid weight and so on. If we decide to use 30 amino acids, we can just use that. If we decide to use a kilodalton equivalent of 30 amino acids it would be 30 times 150, which would be 4.5 kilodaltons.

DR. BELSITO: I like 30 amino acids.

DR. LIEBLER: Yeah.

DR. SNYDER: But it still appeared to me that the ingredient they're using in formulation is well below that.

DR. BELSITO: Well, it's about -- yeah, it's slightly less than 30 amino acids.

DR. LIEBLER: Yeah, that's true. The range is about 5 to about 30 amino acids for these.

DR. SNYDER: So maybe we need to expand the discussion about the manufacturer or the user.

DR. BELSITO: Well, we just point to those studies where at a molecular weight of 350 there were no issues supporting our view that these products should be minimized amino acids greater than -- or peptides greater than 30 amino

acids.

DR. LIEBLER: Right. This is actually -- I put a note in my copy here to Christina -- is to suggest that you actually start the discussion with the nature of -- describing the nature of the ingredients that compared to amino acids that these are mixtures of polypeptides ranging from about 4 amino acids to about 30 amino acids in length. Or I'm sorry, about 4 amino acids to up to 200 amino acids in length with a median size of X. And that's the only thing that --

DR. SNYDER: We have that in here.

DR. LIEBLER: That's the Table 2?

DR. SNYDER: No, this is under the chemistry with the average micro weight of amino acids 135 daltons and they range from 4 to 220 amino acids in length.

MS. BURNETT: You're saying put that in the discussion?

DR. LIEBLER: Yeah, I'd say explain that up front so that the reader understands that these are mixtures of peptides of varying lengths but

the range is predominately X to Y and the median is approximately Z. And go on to explain that peptides at more than 30 amino acids can participate in type 1 hypersensitivity reactions by cross linking IgEs. Then you can go right into the stuff that you have as the opening text which is the safety of amino acids.

At the end of the current discussion there is the additional data needs on method and manufacturing data and composition and characteristics. I felt that even though what we got was not extensive, the material in table 2 pretty much answers the question for me. So the hydrolyzed wheat proteins are produced by both enzymatic and acid or base hydrolysis. The composition is documented even though it is not for a lot of batches or products. So I would say that my concerns about the lack of information on those two points have been satisfied.

DR. BELSITO: Well, we're specifying now. We don't care how it's manufactured, whether you hydrolyze it or do it enzymatically or however

you want it. It should be done to minimize amino acids (inaudible) peptide not integrated in 30 amino acids.

DR. LIEBLER: No, I agree with that. It's just that we didn't have enough information to have an adequate method of manufacture section before and now we do.

MS. GILL: So, Dan, you're suggesting that that last paragraph before the conclusion can come out?

DR. LIEBLER: Yes.

DR. BELSITO: Well, we're deleting -- yeah, the panel requested additional data.

DR. LIEBLER: Right.

DR. BELSITO: We're deleting all of that?

DR. LIEBLER: Correct. Because of size restriction.

DR. SNYDER: Take all that out.

DR. BELSITO: Okay. Well, in the section above where we talk about type 1 and median hypersensitivity can possibly occur

following exposure to protein-derived ingredients on tape -- I think we need to add on tape-stripped skin and mucous membranes. And something -- therefore, the panel felt that these products should not -- that hydrolyzed wheat protein and hydrolyzed gluten should not be used in products that may be inhaled or incidentally contact mucous membranes.

DR. SNYDER: So where are we going with this? Are we backing ourselves into a hole here with regards to -- if we had data that says the starting point for the ingredient used in products is below the sensitization level, and we clearly understand what that level is, I'm not certain -- we're on a slippery slope here because can't we get to -- can they get to a level where they're going to be safely used if they don't do that?

DR. BELSITO: Well --

DR. SNYDER: These are going to be safe as long as the hydrolysis is complete enough to minimize the composition of longer than 30 amino acids.

DR. BELSITO: What they would need to do though, you know, quite honestly, to show us that that, in fact, is the case is repeat the mouse tape-stripped studies with the products that --

DR. SNYDER: The 30 molecular weight? 350 molecular weight?

DR. BELSITO: Was clipped, abraded, and occluded. That was irritation. Nonirritating human irritation patch test, ocular. But they didn't look at sensitization. When they looked at sensitization in the next study they tape stripped, so it wasn't irritant on abraded skin but they didn't look long term. So that doesn't really help us. And it doesn't say in this mouse study with tape stripping what they actually used. It just says hydrolyzed wheat protein.

DR. SNYDER: Can we get more information on that? What was specifically used?

MS. BURNETT: I can pull up the study.

DR. BELSITO: I mean, and then you go on and they do this study -- protein hydrolysates in hair care products, three groups of patients. And

you look, boom -- 11 hair dressers with hand dermatitis and you get --

DR. SNYDER: Then we go into hydrolyzed collagen and hydrolyzed milk. No reaction to the hydrolyzed wheat hydrolysates were observed.

DR. BELSITO: But you don't know what those individuals were exposed to. They may simply not have been exposed to hydrolyzed wheat. And you don't know why you picked them out. I mean, because hydrolyzed milk protein is used in a lot of hair care products as well.

MS. BURNETT: Mean (inaudible) was 40 or 50 kilodaltons.

DR. SNYDER: Yeah, so it's above.

DR. BELSITO: What?

DR. SNYDER: It was above the sensitized --

MS. BURNETT: Forty to 50 kilodaltons in the mouse study.

DR. BELSITO: So it's above the level we're imposing but we don't know whether below that level would have been negative. So I mean, I

think that we can reach a conclusion. And then if industry is concerned they can repeat the mouse study with what we're recommending. A 350 kilodalton product and do it on mucous membranes and tape- stripped skin and show us it doesn't sensitize.

DR. SNYDER: Right. And that's where we're stuck. We know that less than 30 can't trigger the type 1 reaction but we don't know whether --

DR. BELSITO: Yeah, but you could figure that out in the study. You could try and sensitize the --

DR. SNYDER: Yeah, but we don't have the data now.

DR. BELSITO: Right. We don't have the data that tells us.

DR. SNYDER: Right.

DR. BELSITO: Right, but you could easily do the study. I don't know how much money it's going to cost, number one. Number two, the issue is in Europe now you can't market a product

as a cosmetic product that's been tested on animals. And I don't know that there's any other use for hydrolyzed proteins other than in cosmetics. If there is you can get away with it. If there isn't, you can't. You're stuck.

DR. SNYDER: And if we had the data then all the other things would go away because we wouldn't have to worry about mucous membrane.

DR. BELSITO: Right. Exactly. If you give me data on tape-stripped skin I'd get rid of the mucous membrane. I'd get rid of the aerosol. And go back to the prior thing that people with known sensitivity shouldn't use it but --

DR. SNYDER: I like that better than where we were going.

DR. BELSITO: Well, but I don't think we have a choice; do you? I mean, how can we say? We have data that shows that you can sensitize. Granted, it's with a 45, 40 kilodalton product. But we don't know that less than or equal or 30 amino acids won't do the same thing. We don't have that data.

MR. ANSELL: So the issue is not elicitation but rather whether it can be induced?

DR. BELSITO: Right.

MR. ANSELL: So don't (inaudible) studies ask for addressing the question of adoption?

DR. BELSITO: I understand, but you're certainly not going to try to induce humans. I mean, human repeated insult patch testing is not for determination of a hazard. It's to confirm safety. And Europe already has a problem with human testing to begin with. I'm not quite sure -- in silico is where they're heading but I think we're stuck with it.

MR. BOYER: It's possible, too, the industry could use some simple in vitro biochemical studies, IgE and so forth, isolated to see whether or not or to determine some cutoffs as to where you're likely to get a sensitization response.

DR. BELSITO: I mean, maybe there is data out in the literature that you can sensitize

with a protein of a certain -- smaller than a certain peptide. That certainly would also be a way of answering a question if the data is out there already. We haven't searched for it.

MR. ANSELL: And I guess that's my point is that it would be desirable for the panel to iterate a specific question as opposed to also defining what the answer is or how the answer would be determined.

DR. BELSITO: So peptides of bigger or smaller amino acids do not induce type 1 hypersensitivity?

MR. ANSELL: So it's insufficient for protein size that induces sensitization?

DR. BELSITO: Yes.

DR. SNYDER: That's probably the first step we should go to rather than all that other stuff about --

MS. GILL: Or is it safe with a limitation?

DR. BELSITO: What?

DR. SNYDER: We don't know that

limitation. That's a whole other step. We know the limitations for elicitation but we know the limitation for sensitization.

DR. BELSITO: Okay, so basically where we're at is safe if the hydrolyzed, rehydrolyzed gluten peptides are manufactured in a way to minimize amino acid chain lengths greater than 30. At this point pending data that shows that peptide lengths less than or equal to 30 can or cannot induce sensitization, our recommendation would be not on damaged skin or products that may contact mucous membranes. And not on products that could be inhaled.

DR. LIEBLER: Fine.

DR. SNYDER: We can't do the safe thing yet. We don't know what the size limit is for sensitization, right?

DR. BELSITO: But if we say not to be used on damaged skin, contact mucous membranes or inhaled then we're not worried about that. The sensitization occurred on tape stripped skin and

on mucous membranes. So basically, you know, proteins get across in tox stratum corneum. So I'm not so concerned about normal skin.

DR. SNYDER: But in this human study, this hair dresser, hair care, what was that? Those were not damaged skin were they?

DR. BELSITO: Well, if you're a hair dresser you de facto have damaged skin unless you're very elite individual because they're shampooing and hair and cutting wet hair eight hours a day. Plus they had active dermatitis. They have hand dermatitis so they were clearly --

MS. LORETZ: But the damaged skin, going back to the PEG's report when we did the study to look at that and we ended up putting a qualifier on it just because our concern at the start was damaged skin could mean dry skin versus third degree burns. Is there a thought of further defining that or is that later down the road?

DR. BELSITO: Well, in this case, you know, what we got for the PEG's report was simply that when they taped stripped skin it wasn't an

issue in terms of absorption that those clinical case studies were due to the fact that it was third degree burns. And essentially you were just -- you might as well be giving the stuff intravenously.

In this case it's ten tape stripped skins which from the presentation that we were given is about the equivalent of patients with atopic dermatitis. And so, I think just saying damaged skin here, I mean I agree with Dan. You know or you could say skin lacking stratum, an intact stratum corneum barrier including mucous membranes. I don't care how you want to phrase it.

MR. ANSELL: I thought we had discussed that perhaps a more robust discussion in the discussion might be the way to resolve that. That the damaged skin caution arose from data on tape stripped.

DR. LIEBLER: Right. So a little more detailed but not an awful lot.

DR. BELSITO: Right.

DR. LIEBLER: Fair enough?

MR. ANSELL: Sounds great.

DR. LIEBLER: Good.

DR. BELSITO: We'll see what the other group says here.

DR. LIEBLER: All right.

DR. BELSITO: Okeydokey. I think we've chomped that to death. Okay, so where are we next? PEG/PPG Ethers.

DR. LIEBLER: Oh, we've got a long ways to go here.

DR. SNYDER: I know, let's pick it up.

DR. BELSITO: Oh, well. Come on, would you -- good job where we're accounted for. So, okay, June meeting 131 Alkyl PEG/PPG Ethers that are appropriate for inclusion in the report, ingredients were safe. Present practice of use when formulated to be non-irritating, discussion about potential penetration to the stratum corneum, we're comfortable with that. The data graph and gaps read across, we incorporated a lot of summaries from the PPG and PEG's report.

I thought Monice did a great job here and I think that I didn't have safe as used if the team is okay with the included ingredients in Table 1 and I had a few edits.

DR. LIEBLER: I'm in the same place and I also had a few edits and a suggestion that we draw the structures using the structure drawing software and have a uniform representation of the structures in the table. Pain in the neck but worthwhile. And I did have one specific suggestion in the document on pdf page 33 where you're referring to the CIR Safety Assessment on PPGs.

I think the discussion to excerpt from that would be on the PPG derivatives as opposed to propylene glycol itself which is really not very relevant to this particular report. So we could thin out any mention on propylene glycol and focus on the polypropylene glycols instead.

DR. BELSITO: So just propylene glycol connect as a penetration enhancer, is that the one you're talking about?

DR. LIEBLER: No, I'm on right --

DR. BELSITO: Where are you?

DR. LIEBLER: -- before penetration enhancement from the CIR Safety Assessment of PPGs and then in the italics there you've got two paragraphs.

DR. BELSITO: Right.

DR. LIEBLER: The first paragraph is -- the first two sentences is about propylene glycol.

DR. BELSITO: So you could get rid of those?

DR. LIEBLER: I think we could get rid of that because that's not particularly relevant to this particular report.

DR. SNYDER: But all the italicized stuff is going to go away?

DR. BELSITO: No, it's not.

DR. SNYDER: I thought we couldn't republish data we've already published.

DR. BELSITO: You can summarize it.

MS. GILL: -- we summarize it.

DR. BELSITO: Okay.

DR. LIEBLER: So you can start with animal studies using PPGs.

DR. BELSITO: Okay.

DR. LIEBLER: That's the relevant content.

DR. SNYDER: What about the idea that we're posing 105 of the 131 ingredients have no reported use?

DR. BELSITO: Oh, well, we've done that before.

DR. SNYDER: I mean it's, you know, if we feel that we can extrapolate the safety, you know, on the other hand we have critics out there saying that there are 6,000 chemicals used in cosmetics and we don't have safety data for X number of them. I mean, this is what we're trying to do is to show that --

DR. BELSITO: But I mean, so we're pretty comfortable with the read across is fairly robust for --

MR. ANSELL: I think that's really the question is not the number, it's the rigorous in

which the family has been formed.

DR. BELSITO: Right.

MR. ANSELL: If that's a good family then the number's not really relevant. So that's the question, I think is it's not --

DR. BELSITO: That's what I understand. If we're comfortable with being able to read across everything that's in Table 1 then I'm fine with it.

DR. LIEBLER: Yes, I don't have a problem with it.

DR. BELSITO: Okay. Any other comments? Great job, Monice.

MS. FIUME: Thank you.

DR. BELSITO: Okay. Alkyl sulfosuccinate salts. Okay this is under sulfosuccinates, right?

DR. LIEBLER: Yes.

DR. BELSITO: So at the June meeting we reopened the now diethylhexyl sodium sulfosuccinate to add seven dialkyl sulfosuccinate salts. And issued a tentative safety assessment

with the conclusion safe as used in the present practices when formulated to be non-irritating and fine and I had no substantive comments on this one.

DR. LIEBLER: Same here.

DR. SNYDER: Still waiting for mine to open. But I didn't have any on my notes so I don't think there's anything.

DR. BELSITO: Okay. Parsley, sage, rosemary and thyme, sorry, Monice but this is another one I did on paper so hopefully --

MS. FIUME: That's fine.

DR. BELSITO: I thought that first of all, there were several ingredients that functioned only as fragrance ingredients. The flower wax and all of the water extracts were listed as fragrance ingredients and should we be reviewing those ingredients or should we be cutting them out?

DR. LIEBLER: So I read this and then I read the, I guess it was the wave 2 suggest or maybe the memo at the end. It was either a memo

at the end or the wave 2 that suggested that we table this report and consider the possibility of issuing a report on the constituent ingredients. Right? That was a suggestion that was made?

MS. FIUME: It was. It was, it came in the main package.

DR. LIEBLER: Okay, so I encountered it. It was at the end I think. It was in the memo at the end.

MS. FIUME: Yes.

DR. LIEBLER: So that's why I encountered that after I considered the report. So I guess my question in response to that suggestion is whether or not the individual ingredients have significant uses and use concentration data to allow us to bracket our needs for data and to consider these in an actual report.

In other words, I understand the logic of focusing on some of the main potentially bioactive constituents but then is there enough actual use and data to help us figure out what

data we would need to evaluate those individual ingredients?

MS. FIUME: There are data out there on some of the individual constituents, however, as we encounter more and more botanicals as a writer, if we start reviewing all the documents we start with Dr. Duke's. We find other documents that have what main constituents are and what the percentages are. But as the writer, it becomes a question of what is a main constituent? What level of those constituents are a concern? Which ones are in cosmetic use? And what is the chemical characterization of the actual cosmetic ingredient versus, like if it's the extract, versus what is out there?

DR. LIEBLER: Like carnosols, for example.

MS. FIUME: Right. And there is some information out, there is information out there. I forget. I know I looked at it but I can't remember from the BCRP how many uses it would have. As we're going through and I struggled with

this and the writers have talked to it. It does become at what point is it a report of the constituents versus a report on the ingredient that's being used. So I understand what you're saying but I guess my answer is it's a confusing situation for us as well.

DR. LIEBLER: 'Cause I think of an evaluation of carnosol, if it were to be different then the evaluation of a botanical that contains carnosol's a major ingredient, then if it were to be different then we would need to know something about what kinds of products carnosol was used in and concentrations and use context to know if that was anything different than the occurrence just in botanicals. And I think this would generally apply to these other individual chemical constituents.

So although I see a potential logic of reviewing the individuals, 'cause that way we can refer to our previous reviews when we do some of the botanicals, we just might not have enough context for the use of the individual ingredients

for that strategy to actually work for us. And that's what I'm concerned about. But I don't know enough about the uses and concentrations just for some of the major ones in rosemary to know if that's an issue for us to consider here and now.

MS. FIUME: So, for example, carnosic acid is listed in the database and is just listed as an antioxidant is what its use is listed as.

DR. BELSITO: But I thought that whole point was just should we be reviewing rosmarinic acid with the botanical? I didn't take it to mean we should be evaluating botanicals solely based upon their constituents. You know what I mean? So I mean, quite honestly that's what I thought and I didn't have a problem putting rosmarinic acid in here since it's a major component, number one. Number two, we had some safety data on rosmarinic acid itself and number three, it's apparently listed in the cosmetic ingredient dictionary.

So I thought it was fine to keep it in. But --

MR. ANSELL: Well, that was our comment.

DR. BELSITO: Right.

MR. ANSELL: Although this discussion might be well worth having.

DR. BELSITO: But I don't think you can go, I mean, unless you get something like peppermint where carbone is the overwhelming, you know, principle ingredient that you can really base your safety evaluation trying to put together all the individual ingredients in these botanicals. I think that's going down a slippery slope.

On the other hand if a botanical has a major ingredient like rosmarinic acid and there's also data, safety data, on that ingredient and that ingredient as a purified ingredient is used a fragrance ingredient, I think it could be thrown in with the botanical.

MS. GILL: And I think that's the approach the writers are taking, Don.

DR. BELSITO: Right.

MS. GILL: The question, I think, from

our perspective as we discussed is what's major and as we look, go down the list of components, where do we draw the line on what's major? Which is I think the comment from the council as well.

DR. BELSITO: Okay.

MS. GILL: Why rosmarinic acid and none of the others. So the discussion that Dan was having is important but I -- what you just described is how we've approached this before.

DR. LIEBLER: So, if there, for example, perhaps a good rule of thumb to deal with this is if you have a specific chemical component that is significant component of a botanical and is relatively unique to that botanical, like the rosmarinic acid for example, then we can consider it along with the botanical. But if we have something like caffeic acid or luteolin or ursolic acid, these are things that are in lots and lots of different botanicals, you know, we could keep rosemary on the back burner for ages while we do all of those.

And then that would be a clever way of

avoiding ever doing botanicals, actually. We could just put them behind all the individual chemicals but that's just not going to be workable for us.

DR. BELSITO: So I guess what we're saying as a boiler plate, if it a major's constituent you need to have botanical, it's a cosmetic ingredient and there's some safety data, we'll include it. If it's not unique to that botanical, then we won't include it.

DR. LIEBLER: Right. And I'm fine with that. I was really trying to respond to the comment here in this memo 'cause I thought it was worth discussing.

DR. BELSITO: But I think that brings us back to Table 1. Again, my question where we have rosemary flower leaf stem water function fragrance ingredient, rosemary flower wax function fragrance ingredient, leaf water fragrance ingredient, water fragrance ingredient.

I thought it was not the purview of this panel to look at safety of the fragrance

ingredients, so should those be in here to begin with? I can see when it, you know, benzyl alcohol is both a fragrance and something else that's a cosmetic function.

MR. ANSELL: Well, the CIR procedures address that don't they?

MS. GILL: Yes.

MR. ANSELL: And they --

MS. GILL: It is covered if it is a fragrance. I think part of the question was whether or not its whole purpose was a fragrance and we have made a connection if we're going to ask that question.

MR. ANSELL: Right. Mixed use ones are more confusing but if it were solely a fragrance it would be outside the purview of the panel.

DR. BELSITO: Okay. I mean I don't have a problem leaving them in. I mean, you know --

DR. LIEBLER: So I was going to suggest dumping the wax simply because of chemical dissimilarity from the other things. The wax is probably going to contain long chain lipids that

-- it's waxy because it contains a lot of highly hydrophobic materials that -- and that the whole product will behave differently, the whole mixture will behave differently than the others.

So I just thought the wax could go. It just doesn't fit literally whereas the others could stay there and then we could still dump in the we consider them as only fragrances.

DR. BELSITO: Okay, so we're going to delete the wax because of its chemically dissimilar. They have questions regarding --

DR. SNYDER: Wouldn't we hold that same caveat then for any of these derived ingredients that have functions only related to fragrance?

DR. BELSITO: Well, that's what we're trying to figure out.

MR. ANSELL: Well, it's already the CIR procedures already state that, that materials which are exclusively fragrances are outside the scope of the panel. The place where it becomes confusing, as Lillian pointed out, is there are ingredients which may be mixed use.

DR. BELSITO: Right.

MR. ANSELL: And they may bring other functions than simply fragrance.

DR. BELSITO: Right, so we're going to --

MR. ANSELL: In which case they would be here and then CIR is supposed to coordinate with the RIFM panel to make sure that the relevant data is --

DR. BELSITO: So we're going to check with regarding the water extracts. Once we get rid of the wax which is also reported just as a fragrance, we're going to check whether the water extracts are solely fragrance ingredients or if they have mixed uses. If they're fragrance ingredients we'll delete them from our consideration, although I would say that we could still if there's data on their safety, use that data. It just wouldn't be part of the ingredients that we review.

MS. FIUME: Dr. Belsito, that is the protocol we are trying to follow now with these

botanicals. If something is listed as just a fragrance ingredient, confirm with RIFM that that is its only use and see if they have a data profile or anything, a monograph on those ingredients that we can incorporate for that use.

DR. BELSITO: Okay.

MS. FIUME: For information in our report.

DR. BELSITO: Okay, and then I have a note here that I thought really do we have enough information on the constitution of the flower? Again, when you look at it it's totally empty. You know, what we have is the whole plant. Is that sufficient?

So we have great data on the plant. We just don't have any data on the flower. And what we have are we have the rosemary extract, we have a flower extract, we have a flower leaf stem extract and we have leaf, which we have at least a little more data on.

So do we have enough on the flower constitution? And really do we have enough on the

leaf; it can be leaf extract is used at 10 percent which I thought were insufficient for sensitization at 10 percent of the leaf extract.

DR. LIEBLER: So the plant's mostly leaves. So I would argue that the plant data which are pretty extensive could probably cover us at least for the leaves, leave and shoots. I don't know about the flower. This is a little better situation than we had with one of the chamomiles where we had, I think it was just the flower oil, right?

And we, it was hard to interpolate that to the other plant constituents but here we have the whole plant data. I would argue that we're probably okay with that, without having extensive data on the flower. Do we have a lot of uses on the flower?

DR. BELSITO: Quite honestly, I never knew that rosemary had a flower.

DR. LIEBLER: Oh, they're really tiny.

MS. FIUME: It does. Actually when it flowers then the spice gets bitter. You don't

want it to flower if you're using it as an herb is what I've been told.

DR. LIEBLER: And they are covered with bees. We used to have rosemary out in front of our house in Tucson and they'd be flowering right when I had to put the Christmas lights out.

DR. BELSITO: Okay, so rosemary flower extract we have a total of 36 uses. Flower stem we have a concentration but no reported uses and a rinse off and that's it. So not a lot of uses probably because there aren't a lot of flowers.

DR. LIEBLER: Hard to get, yes.

DR. BELSITO: Yes.

DR. LIEBLER: But really the action is rosemary extract, rosemary leaf extract and leaf boil. That's where almost all the uses are.

DR. BELSITO: So the plant data covered the composition that we need.

DR. LIEBLER: I think plant data covers that, yes.

DR. BELSITO: Okay. So then in the discussion we need the pesticide heavy metal

boilerplate and we need the inhalation boilerplate. And then I guess the ingredients of concern here are caffeic acid, thujone and methyl eugenol? So when we develop the botanical boilerplate those are the things we need to address.

So the leaf extract is used up to 10 percent but we don't have sensitization which I think is an insufficiency. Or would you disagree?

DR. SNYDER: Agreed. I mean sensitization and (inaudible).

DR. BELSITO: Right, for the leaf extract. There were reproductive effects on male and females as and antiestrogenic effect but the doses were super high so that needs to go in the discussion.

DR. LIEBLER: And I think the in vitro studies described on page 16, non-human, the effect of methanol extract leaves on NaBPH, depend on microsome metabolism of estradiol and estrone in liver microsomes. I don't think that's relevant. Essentially the effect of these

compounds on microsome metabolism doesn't really serve as a model for interaction with estrogen receptors or really for modulating estrogen receptor signaling.

DR. BELSITO: So where are you, Dan?

DR. LIEBLER: I'm on pdf page 16; let's see about halfway down where it says effects on estrogenic activity. In that first section, the first one, two, three paragraphs are all about microsomal dependent oxidation of estradiol or glucoronidation and all those I think are irrelevant and can go.

And then I'm okay with the CD1 mice in vivo studies but the extract --

DR. BELSITO: So you're deleting the first three paragraphs?

DR. LIEBLER: Correct. The first three paragraphs. But the fourth paragraph you can keep.

DR. BELSITO: So the group of seven or eight six week old, that's okay?

DR. LIEBLER: Yes.

DR. BELSITO: I'm going to assume that corrects the only typo I had (inaudible) fennel. You did a great job there. So you're not going to get the paper document.

MS. FIUME: Darn. I like this paper document.

DR. BELSITO: I know you were looking forward to my handwriting.

DR. LIEBLER: She'll tear the office apart looking for it. I know he had one. He always has one.

MS. FIUME: But at least it says AU so I always knew if I needed to figure it out it was marked.

DR. BELSITO: Okay so that's my list of things that I had to bring up. Oh, penetration enhancement before do we need to discuss that at all? It was really not that great. I'm just raising it. I'm not saying we need to say it shouldn't be used with things that we said didn't penetrate. I don't even know what page that's on. Penetration. Penetration enhancement, it's 14 of

the pdf on aminophylline. "Did enhance the penetration of, however the increase in permeation was less than that observed with 50 percent ethanol." Okay, so no mention about penetration enhancement, okay.

DR. SNYDER: So I have a question in the summary, this third sentence that says "rosmarinic acid is a constituent of the plant as well as a cosmetic ingredient." So we talked about that but what was the final resolution. It was we're not implying that this is a safety assessment of rosmarinic acid?

DR. LIEBLER: No, we are.

DR. SNYDER: We are? So then we should state that then.

DR. LIEBLER: That's the one individual chemical that's included with this.

DR. SNYDER: Okay, so then we need to make sure that we state that. So we should say because rosmarinic acid is a major constituent of the plant as well as an individual cosmetic ingredient, for safety assessment it includes or

something along those lines, right?

MS. FIUME: So, Dr. Belsito, just to make sure I have everything correct, so it's going to go IDA for an HR IPT on the leaf extract at 10 percent which is the concentration of use? Since it's going out as IDA I wasn't sure, are you requesting chemical characterization on the flower ingredients then or on the flower?

DR. BELSITO: I mean, we could if it's available but Dan said he's comfortable with the total composition of the plant particularly given the small use of the flower.

MS. FIUME: Okay, so don't put it out at all or as if available.

DR. BELSITO: If available, yes.

MS. FIUME: If available? Okay.

DR. LIEBLER: That's fine.

MS. FIUME: And then the wax will be deleted?

DR. BELSITO: Yes.

MS. FIUME: And we're double-checking on those that are just fragrance ingredients?

DR. BELSITO: Right.

MR. ANSELL: So just so I'm clear there were a series of acids that we suggested including and did we get to them?

DR. LIEBLER: Yes, we talked about that. This is in the memo at the end?

MR. ANSELL: Yes.

DR. LIEBLER: Yes. You also suggested including carnosic acid or basically raised the question why rosmarinic acid but not carnosic acid, oleanolic acid or solic acid, et cetera, et cetera, et cetera. And then perhaps you should a discussion including the plant components or reports concerning plant extracts or perhaps the CIR may want to consider having a report on diterpenes before a report on rosemary derived ingredients is completed. And I thought we talked about that and decided not to do that.

MR. ANSELL: To include the ingredients but not to include the discussion, I mean the discussion would have -- I tracked that. That was the inclusion of ursolic and carnosic.

DR. BELSITO: Well, it's not clear to me that those are unique to rosemary.

DR. BRESLAWEC: No, but they're present in higher concentrations than we first though, than the rosmarinic acid.

DR. BELSITO: Well, what we had said before you came in, Halyna, was that we would add a component if it was unique to that botanical and didn't cross over to other botanical products and also was listed as an ingredient in the cosmetic dictionary.

DR. LIEBLER: I mean I raised the question in response to the memo, Halyna, about whether -- if we were going to pursue that strategy of actually doing a report on some of these terpines, then I raised initially the question of do we have data on uses and use concentrations of these that would allow us to actually do a report and not get stuck at square one. And I don't think we have the answer to that and I think there's a lot of headshaking going on. So we kind of defaulted back to okay, let's do the

botanical with the or let's do this ingredient with the highly characteristic/almost unique compound rosmarinic acid and that might be a rule of thumb to use in future such situations where we have a botanical ingredient and a characteristic ingredient that can be evaluated alongside it where there's some data for it. Otherwise, we're stuck.

DR. BRESLAWEC: Okay, I just -- I'm sorry coming in late to the discussion but did you include your discussion the consideration that these particular ingredients and the amount of certain components is, what's the term that you used, Carol, is standardized?

MS. EISENMANN: Right. These ingredients are normalized to carnosic and carnosol which that's probably the question to begin with because well, why, is that's (inaudible) about carnosic acid. They're very similar to rosmarinic and I'm not sure rosmarinic is really unique to rosemary. I think it's also found in sage and some other related ingredients.

DR. LIEBLER: So would we review these in sage or would we --

MS. EISENMANN: Right, right.

DR. LIEBLER: -- review in the first plant that comes --

MS. EISENMANN: And I just don't -- what's the rationale for putting rosmarinic in this report and not carnosic acid when that's the one that being -- it's 25, 17 or 25 percent. They're normalizing their extracts to carnosic and carnosol. This is in the food chemical codex.

DR. BELSITO: Well, actually, Paul just brought up a very good point. There are no reported uses or use concentrations from rosmarinic acid which is going to make this very difficult to say safe as used if we're looking at an individual ingredient based upon the safety data. Then we're back to the pre, that limited period of time where we had no use concentration data and we're setting artificial limits based upon however the wind was blowing over our finger that day. So maybe we should just drop it from

this report and say --

DR. BRESLAWEC: Yes.

DR. LIEBLER: Okay, I like that better.

DR. BELSITO: I do, too.

DR. LIEBLER: Depending on how the way the suggestion was worded, what I was getting at is please consider adding all these other compounds. And what you really meant was please consider not including rosmarinic acid.

MS. EISENMANN: Well, yes.

DR. BRESLAWEC: I think actually the request was please discuss this.

MS. EISENMANN: Right. Right, I mean because this will come up for other reports.

DR. LIEBLER: But if we ran this --

MS. EISENMANN: Should you review a component with the plants when you didn't do it for licorice. You did them separate.

DR. LIEBLER: Okay. I guess I was after licorice but anyway.

DR. SNYDER: You'll have to drink some Jagermeister.

DR. BRESLAWEC: We can give you a copy of the report to read.

MS. EISENMANN: There's two reports actually.

DR. LIEBLER: Yes, send me the gift box.

DR. BELSITO: Okay, so --

DR. LIEBLER: Without the rosmarinic acid.

DR. BELSITO: We're going to delete the wax because it's chemically dissimilar. We're delete the rosmarinic acid because there are no use concentrations and we've just made a decision we're not going to review individual ingredients with a whole plant. We're going to check whether the water extracts are solely fragrance ingredients and if they are they'll be dropped from the report in terms of what we're reviewing. However, the safety data, if any, will not be dropped.

We're going to ask -- we're going to use the pesticide heavy metal inhalation, boilerplates in the discussion. Our botanical boilerplate our

concerns are caffeic acid, thujone and methyl eugenol. We're going to point out that there were repro effects but at very high doses and we're going to go for insufficient for sensitization the leaf extract at 10 percent.

Anything else? Okay. Phylmethamine. Okay, the June meeting we requested data on irritation and sensitization for the three ingredients at four percent and purities data submitted felt that our needs were met. There was no indication that primary amines are converted to secondary amines and because primary and non-nitrosating, the language of the discussion we said could be changed and we need to finalize the report. But regarding the amines I had some issues as it's currently written.

It says under impurities, secondary amines anhydrous were present at a maximum of zero point five percent weight. Nitrosamine at 50 parts per billion. So that sort of contradicts what we were told, is that correct? This is page 16. So do we still need the nitrosating language

in the discussion?

MR. HUGHES: Just --

DR. BELSITO: Yes, identify yourself, please.

MR. HUGHES: My name is Brian Hughes, I'm with Dow Chemical Company. The idea of 55 per billion of the nitrosamines was put in there because the EU cosmetic directive which required that the 50 part per billion is actually the limited detection for nitrosamines in our tests and we have never found it at that level. So that's how that crept into the language.

DR. LIEBLER: So it should be nitrosamines at less than 50 ppb.

MR. HUGHES: Should be.

DR. BELSITO: Now, since I'm not a chemist, secondary amines are the ones that can be nitrosated, is that correct?

DR. LIEBLER: Correct.

DR. BELSITO: So this statement then says, secondary amines were present at a maximum of zero point five percent weight. So that would

mean we do need the nitrosating language unless this information is incorrect.

DR. LIEBLER: So, yes, this information is useful because it says that in the starting materials the product contains secondary amines at maximum point five percent and nitrosamines were not detectable or detectable below that limit at 50 ppb. But still, we should specify that products using these should be formulated in a way to minimize or to prevent the formation of vancosamines. So we can still say that, right?

MR. HUGHES: Even though this is more of a specification than it is actual detection.

DR. LIEBLER: Yes, I mean, right. What we're saying is a specification for how the product should be provided which your information you're providing is apparently information on a typical representative batch or batches.

MR. HUGHES: Yes.

DR. LIEBLER: And the application of a particular method of detection and the bottom was 50 and we didn't see any.

MR. HUGHES: Correct.

DR. LIEBLER: So those aren't inconsistent. You're doing your job and we're doing our job.

DR. BELSITO: So how are we handling this, Dan?

DR. LIEBLER: So we can include the nitrosamine boilerplate.

DR. BELSITO: Okay. We need to include that. Okay.

DR. LIEBLER: Thanks.

DR. BELSITO: So we'll say secondary amines anhydrous were present at a maximum of zero point five percent weight, nitrosamines less than -- that needs to change, right? So less than 50 --

DR. SNYDER: Less than 50 parts per billion and in parentheses, below the level of detection. It should say less than 50 parts per billion and in parentheses, below the level of detection.

DR. LIEBLER: Limit of detection.

DR. SNYDER: Limit of detection, right.

DR. BELSITO: Okay. So then in the discussion we need to re-add the nitrosating boilerplate.

DR. SNYDER: In the intro, in the summary and discussion and everything it's more than just a -- it has emulsifier function in addition to a pH adjuster capture, correct? Under the introduction you said, its primary use in cosmetic is an emulsifying agent and then it also functions as a pH adjuster. But we only refer back to its pH content never as an emulsifier. We need to include that throughout the function.

MS. BECKER: In the table here the pH adjuster fragrance -- emulsifier.

DR. SNYDER: Under the introduction, you said tromethane is used in cosmetics primarily as an emulsifying agent, ANPD, AEPD, function as pH adjusters in cosmetics.

DR. LIEBLER: Is that correct?

MS. BECKER: Checking. Fragrance ingredient and pH adjuster, no emulsifier. I

don't know where that came from. I apologize.

DR. BELSITO: Okay, anything else?

DR. LIEBLER: No.

DR. BELSITO: If not, safe as used?

DR. LIEBLER: Yes.

DR. BELSITO: Okay. So alumina, the June meeting we said they were alumina, aluminum hydroxide insoluble not likely to cross the skin, didn't need sensitization, ingestion from lipsticks possible but the amount not a toxicologic concern. Need to point out that the cosmetic ingredient was not aluminum but make a little statement that we're aware of concerns regarding aluminum and Alzheimer's disease as well as some other tox endpoints which I think the writer did a good job on.

And so, we're here to decide whether that's it. It looks like I had some typos. I don't know if anything is really substantive. Okay in the abstract, the next to the last sentence it says, the safety assessment does not address aluminum as a cosmetic ingredient. Do we

want to say that?

MR. ANSELL: Well, we have a real problem with the amount of aluminum included throughout the entire report. We open with this is about alumina hydroxide not aluminum and yet we have massive sections in the toxicology about aluminum. We have the DARPA papers brought up about breast cancer and aluminum. We got aluminum reports and its use in drug applications. We have its use in antiperspirants. Its use in --

DR. BELSITO: But that's aluminum chloride and aluminum hydroxide which we're looking at.

MR. ANSELL: It's --

DR. BELSITO: The breast cancer is aluminum but we said we wanted to put a little bit in the Alzheimer's but we said we wanted to put a little bit in there to show that we're aware of it.

MR. ANSELL: Right, and we think that --

DR. BELSITO: You think there's too much?

MR. ANSELL: Way too much.

MR. BOYER: Well, there's a whole section now on aluminum toxicology and that's towards the end of the document.

DR. BELSITO: Right.

MR. BOYER: And I think that the panel at the last meeting requested that kind of a write-up to begin with.

DR. BELSITO: We did.

MR. BOYER: And that's, I mean, that's why that's in there at the present time. But I believe the panel's intention was to determine whether or not first of all that met the need, second to what extent it might be reduced and where it might be placed as well. And I think one of the council's comments was that a lot of this could be condensed or that particular section could be condensed and incorporated into the introductory section. And dealt with right up front.

DR. BRESLAWEC: We don't have any issues with discussing the toxicity information but it

has to be placed in context and the relevance of the data that are presented here. It needs to be identified, highlighted. The panel is well aware of the differences between the different ingredients. The panel is well aware of the nuances but somebody reading this report who's not aware of it, really it's very difficult to follow in that sense. This is a very important ingredient for the cosmetic industry and there are issues surrounding similar sounding ingredients. So the report has to be tight. It has to be robust and it has to be credible because the industry and the others will be using this report.

So our request is to table the report so that we, at least, have another chance to take a look at how it's rewritten so that the relevance of the various toxicity sections which are well written and we don't have a problem including them, but so the relevance of those toxicity sections on the ingredients that they're tested is clear, vis-à-vis the ingredients that are under review. We don't think the current report clearly

does that. There are a lot of phrases throughout the report that when taken out of context, just taken even in context don't make a lot of sense.

DR. LIEBLER: So, you know, as I read this and I hear this discussion I think that this might be an example of something that we might be able to address effectively with some of the improvements in electronic publishing. And a lot of papers that we write now, we have a section of data or something like this where it needs to be mentioned and there's a lot that we've done that we've put in supplemental data. See supplemental results. See supplemental discussion, see supplemental this or that and then the journal will have that supplemental stuff. It's just a hyperlink away for the reader.

But this could be dealt with in the introduction that this report is on alumina which it's chemically defined as such and such and not on aluminum or aluminum compounds which nevertheless have attracted tremendous interest because of other toxicities and health concerns.

The panel considered this literature and see supplemental discussion. And it could be dealt very effectively with that if the journal uses that format or presentation and that way and we could use this is a way to streamline our reports in certain cases by parking the relevant stuff out of the logic flow of our main document but still making it clear that the panel actually reviewed the literature and considered it and was able to explain why it's distinct from the ingredients that are being reviewed in this particular report.

And if we did that and also combed through for what you're concerned about which would be inappropriate mentions, you know, little small editorial things, I think it's problem solved. And the only question I have is will the International Journal of Toxicology, does it utilize supplemental information?

MS. GILL: I don't know if it does or not.

DR. SNYDER: I think we've broached that one time before about having supplemental and they

currently don't.

DR. LIEBLER: And we should check because that's something that is, if they do electronic publishing they probably do now. And we should check because that's the way to do this, the 21st century.

DR. BELSITO: Well, I guess the question is this was a final report. You're not asking us to change our conclusion. You're simply, what you're suggesting is that there be editorial changes made to the body of the document not to the conclusion, is that correct? You don't want us to say these are unsafe?

DR. BRESLAWEC: No, absolutely not.

DR. BELSITO: Right, and we've already said they're safe.

DR. BRESLAWEC: But I think we would like an opportunity for review. I mean it has statements in there saying alumina and aluminum hydroxide as used in cosmetics are not approved active ingredients in antiperspirant products. Well, neither has it killed yet. I mean --

DR. BELSITO: But I guess my point is do we need to table this or can we just finalize it and allow you to make cosmetic changes before it goes to print?

DR. BRESLAWEC: This is a really important ingredient for the industry. It has to be a cohesive report that we can use and it's a report that's written in sections that isn't tied together. And that's where my concern is.

DR. BELSITO: I understand. But does that require that we table this or can we not say our final conclusion these are safe as used and then let you people do whatever editorial tightening up you want to do?

DR. BRESLAWEC: Well, if you say safe as used and don't table it, we don't get an opportunity to comment on it.

DR. BELSITO: Well, that's what I'm asking.

DR. BRESLAWEC: Now, we would like an opportunity to comment.

DR. BELSITO: That would be the case.

But you had days, 60 days.

DR. BRESLAWEC: And we made comments and these are comments on the report that has incorporated our comments.

MS. GILL: I think this is -- some of the comments we got quite late. I think we got those Thursday, Wednesday or Thursday about tabling the report. So the report as written doesn't incorporate that request to tighten it up and to make sure that the use of aluminum and where it's confusing isn't there. So.

DR. BELSITO: If our regulations require that if we go final you don't the opportunity to make your editorial changes then I don't have a problem with tabling it. I was just asking the question couldn't we go final and let you make your editorial changes? And what I'm hearing is no. Once we finalize it that this has been encrypted and chiseled in stone and no changes can be made. Fine, table it. Are we all okay with that?

DR. LIEBLER: Yes, International Journal

of Toxicology does include supplemental information.

MS. GILL: It does?

DR. LIEBLER: I just looked on their current online table of contents, yes. There's an article with supplemental information as a separate hyperlink. So it's a vehicle that you can use to do reports.

DR. BELSITO: Okay.

MS. GILL: But I'm not sure in this case it would address the council. So I think you can --

MR. ANSELL: The movement to respond to the panel's desire would be satisfied by moving it into supplemental information. And I think the suggested text that we understand that there's confusion between aluminum, aluminum salts, aluminum hydroxide in the text and then referring people to if you're interested in aluminum, here's where to look, would be entirely consistent.

MS. GILL: So, Jay, would it need to be tabled if that section were supplemental

information and then the words Dan suggested at the beginning. Some language in the introduction about that information as found there and so did the use and the terminology, the corrections made about what's a --

MR. ANSELL: I think the amount of editorial work within the body really we want another shot to look at it. And if that requires tabling within the process then yes we would want to table it. And then idea that you can move all the data that's been pulled out into supplemental is fine but it's really the report as stands that we want to have a --

DR. BELSITO: We table it. Okay. Achillea, so in June we got new sensitization data at point oh four percent, seems to satisfy the safety. The highest use concentrations concluded they were safe as used. We discussed the LLNA and expressed concerns about using LLNA for mixtures. Council has made some changes in the conclusion and abstract formulated to be non-sensitizing. And so now we're being asked to look at this

document and see is everything intact the way we want it.

I guess first and foremost just as a matter of corrections, I mean the genous should always be capitalized. So Achillea should be capitalized throughout. I had on page 26 of the pdf document going on to page 27 we mention at the bottom in our summary about constituents of concern. I think we should include pesticides and heavy metals as well as the sensitizers.

Then on page 27 of the pdf on the panel, the incidental inhalation, we have one, two, three, four, five, six, seven, eight, nine lines down, it says, respiratory tract present no toxicological concerns based upon the chemical and biological properties. It should be, "of these ingredients." And I think that was all I had. Otherwise, I thought it looked good. Paul?

DR. SNYDER: Yes, I just had a few editorial things.

DR. LIEBLER: Minor edits, nothing else to add.

MR. ANSELL: We would like to raise a comment concerning the conclusion that since the material contains non-sensitizers that the formulated to be non-sensitizing phrase be added.

DR. BELSITO: So in present practice of use in concentrations in cosmetics when formulated to be non-irritating?

MR. ANSELL: Non-sensitizing.

DR. BELSITO: Non-sensitizing rather.

DR. SNYDER: If we had HRIPT of the use concentrations that were negative.

MS. LORETZ: That's because it's a botanical and known sensitizers in it so it's -- it would only be that circumstance.

DR. BELSITO: Well, I guess looking at what you have the highest thing that would bother me so far is linalool at 4,000 parts per million. So that's what, point oh four percent of a plant? And then the concentration of use is I thought very low.

MS. BECKER: Zero point zero four percent.

DR. BELSITO: Zero point zero four?

MS. BECKER: Percent is the highest --

DR. BELSITO: Highest concentration and the concentration of linalool is point --

MS. BECKER: In the plant before processing at max 4,000 ppm.

DR. BELSITO: Right. So 4,000 ppm is point oh four percent, correct? One, two, three, four, five, six, point four percent. So point four percent and the highest concentration of use is?

MS. BECKER: Zero point zero four.

DR. BELSITO: Point oh four percent. So you got point zero zero one six. Pretty low percentage of a sensitizer to be concerned about plus as Paul said we have HRIPT data.

MR. ANSELL: I guess the consensus was that the inclusion of the phrase would highlight or underline the presence of the material and make sure manufacturers were aware.

DR. BELSITO: Well, I mean I'm more concerned that we get the boilerplate in there,

that it not be combined with other things that contain linalool that then create a concentration of linalool in the finished product that are issues which, you know, is my concern. So my concern isn't with this as used if it's the only linalool containing ingredient in the finished product I'm not concerned. I mean, if you want to say and that's going to be an issue for all the botanicals is when you're adding botanicals that you could get to levels of an ingredient that could then sensitize.

If you want to put when formulated to be non- sensitizing, I'm very happy to do that. And then that would reinforce the boilerplate that we'll be raising when we see other botanicals that have sensitizers which is going to be pretty much true for all the botanicals we look at.

DR. LIEBLER: I mean if you do it for this one, why not do it for all botanicals? Because they'll all essentially have sensitizers in them.

DR. SNYDER: And we addressed it pretty

good in the summer. I mean we say that we acknowledge they're in there. So we say that there are levels below.

DR. BELSITO: Right and then we need to discuss the boilerplate about stacking them on top of each other. I mean, I'm fine putting it --

MS. EISENMANN: I thought it might be useful for all the botanicals that are asteraceae family because they have a known issue of being sensitizers themselves.

DR. BELSITO: Right.

MS. EISENMANN: Not necessarily other plants but that one family.

DR. BELSITO: Right.

MS. EISENMANN: It doesn't include what these other that you reviewed, too.

DR. BELSITO: Right. I'm fine with putting that in.

DR. LIEBLER: Okay, but that's a different kettle of fish because the way it was pitched to us just now is that they have sensitizers in them. Well, so do all the

botanicals. So.

MS. EISENMANN: But I mean that family in particular has issues.

DR. LIEBLER: Right, that makes more sense to me.

DR. BELSITO: And I'm fine since we're going to be creating a boilerplate. I think whenever we have a boilerplate that we'll say you need to use caution when combining this with other botanicals that might contain linalool or cinnamal or whatever the ingredient sensitizer of concern is. That we then put in the conclusion when formulated to be non-sensitizing, I'm very happy with that. I think it really reinforces what do they mean not sensitizing and when they read the discussion they'll clearly see, you know, particularly the ingredients we're concerned about. I'm fine. Dan? Paul?

DR. LIEBLER: If we do that we just need to add a sentence to the discussion.

DR. BELSITO: Yes, for the others.

DR. LIEBLER: To explain that we were --

that that family --

DR. BELSITO: Well, there will be a sentence in this discussion because we're going to have the botanical boilerplate coming up in a few more so that's something that needs to be added to the discussion.

DR. LIEBLER: But do we have any language in here, Carol, that already refers to the family that you're referring to? Or is this going to hit people kind of out of left field if we mention it in the discussion?

DR. SNYDER: I think we can add that right at that last sentence here.

MS. EISENMANN: I think it was a description of the plant in the beginning I think that puts it in that family with the historical name of the compositae.

DR. LIEBLER: I'm not seeing it.

DR. BELSITO: Summary of the original.

DR. LIEBLER: It's only mentioned in passing in provocative testing. This is on pdf page 22 under the summary, the original safety

assessment second paragraph. In provocative testing a number of patients reacted to a compositae mix that contained yarrow. Is that what you're referring to compositae?

MS. EISENMANN: It's also earlier I think there's a little description of the plant right here in the front. It's like in the chemistry section.

DR. BELSITO: I'm looking. I don't see it.

DR. LIEBLER: I don't see it.

MS. BECKER: It might be in the original safety assessment not this one.

DR. BELSITO: No, I don't see it, Carol.

MS. EISENMANN: Okay. It must have been in one of the other plant reports.

MS. BECKER: I think it is in the original.

DR. LIEBLER: So if you -- so the suggestion to add the non-sensitizing now makes more sense in light of what you just said as opposed to the logic of well, these contain

sensitizers because almost all botanicals do. So but we need to have enough of a description so that we can mention it first in the chemistry section and then mention it in the discussion that botanicals of that family have been associated with sensitization and provide a reference.

So then do we say even though we have an HRIPT at highest use that was negative we still raise the concern?

DR. BELSITO: Yes, because the formulation needs to ensure that this product when combined with potentially other botanicals or other sources of linalool or whatever happens to be the allergen of concern will be non-sensitizing.

MR. ANSELL: Right, it can be used safely.

DR. LIEBLER: Okay.

MS. EISENMANN: Well and then also the variability within one.

DR. BELSITO: I understand, right.

MS. EISENMANN: And the extracts, too.

DR. BELSITO: So we need to put somewhere I don't know that we need to introduce, we can just put it in the discussion that, you know, the panel is aware that as a member of the compositae family this contains sesquiterpene lactones that have been shown to be sensitizing. You know, at the levels of reported use of Achillea millefolium this should not be an issue, however, when blended with other botanicals, you know, whatever the boiler plate we decide and then that would be the way we'd introduce it.

DR. SNYDER: I think we have the place to do it right here already in the discussion because we talk about the idea that the cosmetic formulation can contain multiple botanicals.

DR. BELSITO: Right.

DR. SNYDER: I think we need to and this is what I was thinking about in the (inaudible). I mean we can make it specific to this, whatever family the constituents in and this case is a good example because here we can say, we should identify the constituent concerns. We identify

them in the report and then the use of other botanical ingredients to make it plain these constituents or concern in combination with milleforme could result.

DR. BELSITO: Well, we have it in the next paragraph. The panel noted that among the constituents are these botanical ingredients, were linalool, thujone, quercetin and hydroquinone.

MS. EISENMANN: One comment. Instead of ingredients it's components of the plant.

DR. BELSITO: Components, right.

MS. EISENMANN: Because there was some analytical data that showed thujone was not present in at least one of the ingredients at a level of 300 ppm.

DR. BELSITO: Right.

MS. EISENMANN: So the components there are what's in the plant rather than ingredients. We don't know for sure. I mean they may or may not be in the ingredients.

DR. BELSITO: Right, I understand but I mean my thinking was this whole section starting

on 26 of the pdf with the cosmetic formulation may contain multiple botanicals, through the first full paragraph on page 27 is going to need to be readjusted depending upon how we agree on the boilerplate. So I wouldn't waste time with this. At this point we've agreed when formulated to be non- sensitizing and then the conclusion we'll worry about wordsmithing the discussion once we get to the botanical boilerplate. Does that make sense? Okay, should we take like a five minute break?

DR. LIEBLER: Sure.

DR. BELSITO: So it's 3:10. Be back at 3:15. Stretch your legs.

(Recess)

DR. BELSITO: Okay, are we all set to regroup here, folks? Okay, so we're on our one hair dye ingredient for this meeting which is hydrocypropyl Bis (N-hydroxyethyl-p-phenlyenediamine) and last time we looked and we -- no concerns regarding this specific hair dye. A major question was our

recommendations regarding self- testing and the Europeans' concern that this could induce sensitization in the population and we've now dealt with that in our discussion.

And so, we're going to safe as used with this. And I had some comments here. In the abstract it says that the language is somewhat convoluted. It says safe as a cosmetic ingredient in the practice of use and concentration of this safety assessment in cosmetics which is not -- so I deleted all that. Was safe in the present practices of use and concentration in cosmetics as described in the safety assessment which I believe is our boilerplate.

Some typos. On page 20 of the pdf where is says the panel noted that the use of oxidative hair dye formulations involves exposure to precursors and coupling agents as well as to their reactor molecules. And then you go on to talk about reaction intermediates and human exposure and is to the coupling agent, a reaction products not to a reaction intermediates.

It's my understanding that at least for p-phenylenediamine Bandrowski's base, which is a reactive intermediate, is one of the potential sensitizers. So I don't think that that's a true statement. And I'm not sure that we should be saying that. I think reaction intermediates can be sensitizers.

MR. ANSELL: Let me get our hair dye. Here she is.

MS. LORETZ: I'm sorry.

DR. BELSITO: Well, on page 20 of this document, of the pdf, the first paragraph it says, while reaction intermediates may be formed, human exposure is to the precursors and coupling agents and to reaction products not to reaction intermediates. Well, that's not true because reaction intermediates occur on the human to begin with. So there is exposure to the intermediates, no?

MS. LORETZ: It has to do with the level of exposure and how.

DR. BELSITO: Okay, but has it not been

shown that in some individuals allergic to p-phenylenediamine Bandrowski's base is one of the potential allergens and is that not a reactive intermediate?

MS. LORETZ: I don't know what that chemically is.

DR. BELSITO: Well, then you may want to Google Bandrowski's base because it's my understanding that it's a reactive intermediate it PPD and that it's been shown to be a sensitizer. So I think that this whole paragraph is incorrect. I think humans are exposed to the reactive intermediates because the reaction occurs on the scalp on the hair.

MS. LORETZ: I mean this goes back to Julie Skare's presentation and looking at the intermediates and how freely they're formed and how mobile at the time, therefore how low the exposures are. So I don't know exactly what the exact wording is but that's why it becomes -- that's why it's not an issue relative to the exposures to the --

DR. BELSITO: I guess if -- I may have missed that part of her presentation but because again, I think there's data showing that at least for paraphenylenediamine a reactive intermediate has been shown to be a sensitizer in some individuals.

DR. BRESLAWEC: Is this a question --

MR. ANSELL: I think it's --

DR. BRESLAWEC: -- to the writers?

DR. BELSITO: No, this is a question that I'm saying that I disagree with what's written here. That I think it should be deleted. I think that individuals are exposed to reactive intermediates because the reactive intermediates occur on the scalp. So A) there is exposure, there is not no exposure and number two, at least for PPD, I think it's been shown that in some individuals a reactive intermediate that goes by the term Bandrowski's base, and I'm not sure what that actually is, can be a sensitizer.

So A) people are exposed to the reactive intermediate and B) at least in cases of one hair

dye it's been shown to be a sensitizer. So I would delete that entire paragraph.

DR. LIEBLER: So there is a reference I'm looking at on PUBMED which is about paraphenylenediamine allergy and the role of Bandrowski's base. It's from White & Colleagues. It's in clinical and experimental allergy from 2006.

And Bandrowski's base is a trimer derived from paraphenylenediamine oxidation. So it's a quinoid like structure. It's stable enough to isolate and do studies with and it was patch tested in this study and it was approximately 10 times more potent than PPD.

So with the assumption that Bandrowski's base is an intermediate in the hair dye chemistry being discussed then the existence of this sort of suggests that that statement as written can't be correct. It doesn't necessarily mean that we have a major problem with these but --

DR. BELSITO: No, I'm not saying there's a problem. I'm just saying that what's there is

not --

DR. LIEBLER: It's just the language can't be so absolute as to say there's absolutely no issue don't even --

DR. BELSITO: -- is not true. So I mean, I would get rid of that entire paragraph because I don't think what's being said in that paragraph is true. It may be true for this particular hair dye but it's not true for oxidative hair dyes in general because it's not true for PPD at least. And I don't think we need the paragraph. I'm just saying that anyone reading this that's familiar with the literature on Bandrowski's base is going to say, my God, these people are stupid. There's data suggesting that this is not true.

DR. SNYDER: I did have a note to move this part to the intro because the intro we mention it's an oxidative hair dye but that's it. One sentence. We don't talk anything about --

DR. BELSITO: Or we shouldn't move it because it's not true.

DR. SNYDER: Well, I mean but the idea that there are precursors and couplers and reaction products and cause I think that is relevant. Because to a person reading a standalone document because right now we just say it's an oxidative hair dye, that's it.

DR. BELSITO: Yes, but we say that because oxidative hair dyes are covered by the adulteration law. I mean that was the whole purpose for putting that in. That sensitization essentially is a non-issue with an oxidative hair dye when it's label to do testing.

I mean if, in fact, reactive intermediates weren't sensitizers then it may be worth putting in the introduction. I mean I would just delete the entire paragraph is what I'm saying.

DR. BRESLAWEC: I think it was boilerplate lined. I certainly understand what you're saying and it's appropriate (inaudible).

MR. ANSELL: Well, certainly the sentence that says no exposure to the reaction

product intermediates. Some of the other stuff might be more relevant that the exposures are low, absorption into the hair shaft, safety evaluation focused on ingredients more than the reaction products might be relevant in the intro.

DR. BRESLAWEC: Perhaps it would be a good time to revisit that particular boilerplate.

DR. BELSITO: I don't remember ever seeing that boilerplate. That's been a boilerplate in hair dyes? Again, I --

DR. BRESLAWEC: Well --

MS. GILL: The hair dye epidemiology in the hair dye is a boilerplate.

DR. LIEBLER: Could you not deal with this problem by just deleting the second sentence of that paragraph?

MR. ANSELL: Yes, I think --

DR. LIEBLER: Because the first sentence says the use of oxidative hair dye formulations involves exposures to precursor and coupling agents as well as to their reaction product. So that acknowledges that the reaction products are

there. And then if you nix the next sentence --

DR. BELSITO: I'm fine with deleting that, yes.

MR. ANSELL: I think they're low and talk about absorption so I think the second sentence is the part that has to go.

DR. LIEBLER: Yes.

DR. BELSITO: Fine. Okay. And then our conclusion needs to be worded correctly. The CIR concluded it's safe in the present practice of use and concentration as described in the safety assessment period.

MS. BECKER: And we decided a meeting or two ago that somewhere in the conclusion it needs to say in cosmetics.

DR. BELSITO: Is safe in cosmetic in the present practice of use and concentrations as described in the safety assessment.

MS. BECKER: All right.

DR. BELSITO: That was it from me. Paul?

DR. SNYDER: No further.

DR. LIEBLER: That's it for me.

DR. BELSITO: Okay. Phytosterols. I had basically safe as used. Dan, were you okay with the grouping and I guess this is going to be one of those things where we have the question of diosgenin, whether we're going to keep that in. Did council want us to take that out?

DR. BRESLAWEC: Actually what I think what we were hoping for is a more robust search strategy so that diosgenin and beta-sitosterol would be, those terms would be searched as well because the only thing, the search was sitosterols.

DR. BELSITO: Well, that was my next question whether we had all of the appropriate data.

MS. BECKER: When I did the search those two ingredients came up quite often, quite a bit and since they finished with Dr. Marks I did a search and I eked out six more papers that I'm only expecting two of them to be relevant.

DR. LIEBLER: It's good to be thorough.

DR. BELSITO: So this is important in advancing. So.

DR. LIEBLER: So I'm fine with the grouping and I have a modest suggestion for figure 1 and figure 2 is that I suggest sort of about a six to eight structure figure. One that has the structures currently shown in figure 1 and figure 2 plus a few of the other predominant sterol structures so they have a little bit broader representation of the sterols nuclei that make up this group. So that would be easy to do. You've got a lot of white space there as it is and you could fill that with six or eight in two rows.

MS. BECKER: Are you suggesting what structures to add or?

DR. LIEBLER: I would suggest that you choose structure that are most predominantly represented in concentrations or as frequency of mention across the grouping.

DR. BELSITO: Okay, so Dan and I have both said safe as used. We've heard a request for further searches on beta-sitosterol and diosgenin.

There hasn't really been an answer to the question I raised whether we're going to keep diosgenin in here since we decided to get rid of rosmarinic acid from the other report. There's no reported uses for it so I was thinking that at least based upon our discussion before we would drop that.

The same I guess would be true of beta-sitosterol or I don't know how you want to deal with that.

DR. LIEBLER: So perhaps you could clarify for me because in table 8 on pdf page 23 the right-hand column is headed Beta-sitosteryl.

MS. BECKER: Typo.

DR. LIEBLER: Typo? But then we have beta-sito -- if that's beta-sitosterol then we have 48 uses and a range of concentrations.

DR. BELSITO: What page are you on?

DR. LIEBLER: Pdf page 23.

DR. BELSITO: I have a pdf, sorry wrong report. So Paul, you haven't weighed in. Where are you?

DR. SNYDER: I'm fine with the

discussion and grouping if Dan's okay with it.

DR. LIEBLER: So just to clarify we'll keep beta-sitosterol and we have uses and concentrations. Diosgenin we don't so that goes out.

DR. BELSITO: I'm fine with that. So we're going to delete diosgenin and we're going to leave beta- phytosterol in. Safe as used. Do a slightly more rigorous literature search and in terms of discussion obviously plant products of the usual plant boilerplate. I mean these are -- I don't know if the botanical boilerplate is going to be relevant to these as I see the chemical composition of these that are --

MR. ANSELL: I think when we --

DR. BELSITO: They're not going to contain a lot of sensitizers.

MR. ANSELL: I think when we get into the boilerplate it will be generic enough that we can choose it or not. I mean the caution about the constituents should be, well, as a boilerplate it should be broadly relevant to all these

materials.

DR. BELSITO: Okay. So anything in the discussion other than some of form of botanical boilerplate with usual plant caveats?

DR. LIEBLER: No.

DR. SNYDER: None.

DR. BELSITO: Okay. So then I guess that moves us to the botanical boilerplate. So at the last meeting we discussed needing to put this together but it seems to me so abstract in the absence of not dealing with a specific botanical ingredient. This, by the way, is in the admin folder.

DR. SNYDER: I think it's a standalone.

DR. BELSITO: No, it's -- no. Was it a standalone?

DR. SNYDER: I got a separate word document for that.

DR. LIEBLER: It's in the administrative folder.

DR. BELSITO: Yes, that's what I thought. I can't find it. Okay.

MS. BECKER: It's page 33.

DR. BELSITO: Yes, starts on guidance for discussion on page 34. I mean the heavy metal pesticide boilerplate that's fine. I have no comments on that. The aflatoxin I thought was fine. The constituent I thought was fine just really is identifying what constituents we were concerned about. Presumably it would be on the heavy metals and pesticides and aflatoxin if appropriate. And I guess where it started getting confusing for me as to how this would apply was on page 35 where we start looking at all the various options.

If not concentration limit has been specified for the constituents of concern and the threshold of toxicological concern approach was not applied, okay, I mean I guess in the case of H.perforatum what's written sort of makes sense to me.

MR. ANSELL: We had some problems with this as well I think partially because they're mixing boilerplate which should be very short,

useful across a wide variety of botanicals with a structural discussion as to what the elements should be. And then by providing specific examples it drives it down to a unique botanical itself. And when you mash all of those together it's kind of hard to follow.

So we were suggesting that as it relates to the approach as we discussed earlier that we fully agree with the suggestion looking at the major elements in each of these examples that the structure should be what did you review? What did you find? And what were the conclusions? And then these are just illustrative examples of those three elements applied to a couple of botanical examples and I don't know that we would necessarily agree with these particular conclusions. But the idea that it should be what did you review, what did you find and the conclusion we think is entirely appropriate for the botanicals.

As it relates to the boilerplate itself it seems that from the last meeting the issue that

we keep coming on is that botanicals are complex mixtures and that constituents of that complex mixture or that any particular formulation may have a mixture of botanicals which all contribute to one constituent. And so, the presence or the concentration of one constituent to the final product and so we in our recommendation try to capture that and we think that the language is generic enough that it would be useful across essentially most botanicals.

As botanical ingredients derived from natural plant sources are complex mixtures, the panel expressed concern that multiple botanical ingredients may each contribute to the final concentration of a single component. Therefore, when formulated products manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects.

And so, we can certainly wordsmith that but the idea of the boilerplate should be that it's --

DR. BELSITO: I mean I think that's

great. We're just given this document this morning.

MR. ANSELL: Right. So I thought we would kind of explain it. So those were our broad comments on the botanical discussion. We do have some suggestions as it relates to, if we're going to revisit heavy metals and aflatoxin that there's some editorial suggestions we'd like to make there as well.

DR. BELSITO: I mean let's look at them. I mean I think they're all fine. So abstract and pointing out that we have 150 word limit, but you know I like what you say as long as it fits within the limit. Heavy metals, pesticides, limit these impurities, aflatoxin recognizes rather than adopted. I don't have problems with those languages. Dan? Paul?

DR. LIEBLER: So I like the language and again I'm just looking --

DR. BELSITO: These are the new handouts. It's what we got this morning. This is industry's response to the whole thing we

reviewed. You saw that?

DR. LIEBLER: I saw that, yes. So I like the revised version of the language for the abstract. It's just a little bit more economical and saves a few words but it makes the right point. Heavy metals, also agree for the same reason. Aflatoxin, the edit's reasonable. Then the opening paragraph language I haven't had a chance to look at yet. But as long as it's as brief as what's in our admin document.

DR. BELSITO: It's briefer.

DR. LIEBLER: It's briefer, that's better.

DR. BELSITO: It doesn't have all the various permutations and options.

DR. LIEBLER: Yes, good. So I'm fine with these revised versions and I do agree that the examples that were pulled from our other reports where we've already sort of wordsmithed the language, they're examples that probably would have limited generalizability and so it's not really boilerplate anymore. So I think our

boilerplate for botanicals should probably be limited to the abstract metals, pesticides and opening paragraph.

DR. BELSITO: Lillian?

MS. BECKER: One. Let's say framework instead of boilerplate because it is not static yet and it's not meant to be static. And the other thing is the opening paragraph doesn't address multiple products having the same ingredients in there like the shampoo, conditioner and other things that we were talking about for the last several meetings.

DR. BRESLAWEC: That's an issue of aggregate exposure and I'm just not sure that the panel has fully addressed that. And that would be something you'd address not just in the context of botanicals.

DR. BELSITO: Yes.

DR. LIEBLER: Right.

DR. BRESLAWEC: So I'm not sure this is the place to deal with it.

MR. ANSELL: Right. It perhaps

premature to start talking about framework on something we haven't really decided how we're going to address broadly.

DR. BELSITO: Well, yes, I mean I guess it's interesting we've never addressed that and I guess the question is are there reasons to address it? And there probably have been. You know, the fragrance industry does that all the time right upfront in their dossiers is the expected total aggregate exposure of a consumer based upon typical use patterns for that specific fragrance.

And when we've dealt with compounds that we're getting close to sensitization level which is typically the threshold of concern for the fragrance industry maybe we should have looked at aggregate exposure.

DR. BRESLAWEC: Well, when you look at you're not even limited to the botanicals.

DR. BELSITO: Right.

DR. LIEBLER: Yes, I think that's --

DR. BELSITO: And I don't know --

DR. SNYDER: That's a different issue.

DR. BELSITO: Yes, I mean it's a totally different issue that we've never really thought about.

MS. BECKER: But you have discussed it in the last couple of meetings.

DR. BELSITO: No, we did.

MR. ANSELL: Right, we just don't want to tie up this botanical boilerplate and throw a much larger topic on top of it.

DR. SNYDER: So for me this generation of the boilerplate drove a response that I didn't expect. So one is that I think we need to send a loud and clear message to industry and that's kind of what I addressed after which I think encompasses some of the council's concerns about it. I think that, I mean I can really say that because formulations are often complex mixtures of botanic ingredients potentially containing similar constituents of toxicologic concern, formulators must develop strategies to limit their levels in final products.

Central to determining safety is

accurate information on the composition of the specific botanical or plant component potentially from different sources if necessary. Botanicals often contain multiple constituents and therefore the most representative safety data relevant to cosmetic use would be studies that identify toxicities of the most relevant plant components.

We're clipping it and sending a loud message to industry, we need better data. And I think we're trying to develop a framework or a boilerplate in the absence of sending a larger message that we need better data on composition and toxicity studies that look at the actual composition of the ingredients that we're assessing. So I think right now we're really patching things and I'm a little nervous about some of the things that we've done or are continuing to do in regards to what are we actually testing for.

MR. ANSELL: Well, providing that type of guidance is entirely appropriate.

DR. SNYDER: Right.

MR. ANSELL: But do you want that guidance to be in every botanical report? I mean it --

DR. SNYDER: No, no, that's why I'm saying that's why it's conflicted. And I really started to craft this and it was really more a guidance of what the panel really wants from industry rather than a boilerplate. But it could be encompassed in the boilerplate. Perhaps we say that the safety assessment contains what the panel believes to be a robust data set on composition supported by animal studies using constituents of a botanical, blah blah blah. You know what I mean? In their final assessment or something like that but right now I think it's -- I agree with Don.

And I had a really hard time rewriting some of these and crafting these because it just was coming unwound as far as it depended upon what botanical I was talking about or what constituent I was talking about. So you can't generally just say sensitizers. You can't just generally say

liver toxicity. It depends upon the individual ingredient and so the amount of confidence that I have is all driven by the scientific data set that we received. Meaning the composition, what are we looking at, what is those botanicals and what studies support the safety of those components?

DR. LIEBLER: So we can't reduce these discussion paragraphs, these broader discussion paragraphs to boilerplate. It just won't work.

DR. BRESLAWEC: And we agree.

DR. LIEBLER: So we shouldn't even try. I think we should declare victory and go home because we basically got, I think we've got -- I think that the initial versions in our admin document are reasonable and I like the council proposed edits a little better in each case mainly because of clarity and brevity and particularly in the abstract words count. And as well as the more thoroughly rewritten opening discussion paragraph that it conveys the right messages and gets us off this cumulative exposure issue which is a valid issue but not a botanical specific issue.

So I think we're good where we are. I mean if you guys agree with me about the edited versions.

DR. BELSITO: Yes, I mean I'm fine with what council is proposing and the boilerplate for the opening of the discussion paragraph and then as they say, the discussion really will flow from what our concerns were. And you really can't, you know --

DR. BRESLAWEC: But basically the discussion will address what the particular circumstances are, whether a limit was set and if so, how? How will it be changed if you use TTC or something else?

DR. BELSITO: I think it's fine.

DR. LIEBLER: I think if I were a writer doing one of these reports I would probably be thinking about looking at previous reports that the expert panel had agreed on where the situation might be similar and take a look at that as sort of a reference for the language. Not as boilerplate but as (inaudible) that's right. We

can take that approach.

So I mean we're going to have something less than a true boilerplate for most of the meat of these discussions.

DR. BELSITO: Yes.

MS. BECKER: Framework.

DR. LIEBLER: So framework as opposed to a boilerplate.

DR. BELSITO: Okay. Anything else on our framework rather than a boilerplate for botanicals? We got some boilerplate. We got some boilerplates. We got a little action there. Okay. Any other issues before we call it a night? If not, we meet in the lobby at what time? 6:00?

(Whereupon, the PROCEEDINGS were adjourned.)

* * * * *

CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

I, Irene Gray, notary public in and for the District of Columbia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

Notary Public in and for the District of Columbia

My Commission Expires: April 30, 2016