124th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

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P R O C E E D I N G S

(8:30 a.m.)

DR. BERGFELD: Thank you very much. We're going to officially open the 124th CIR meeting, and then as all of you know we have met and had a very fruitful day yesterday looking over 17 ingredients, which will be reported on later.

Yesterday I thanked the support staff, the CIR staff, the experts that assist us in these particular preparations and documents, but I wanted to officially put it into the minutes that the documents that we're currently looking at are certainly enhanced. The consistency of the reports and the fact that they are now being -- are very consistent and additive good chemistry, and also the tables which summarize these studies have been exceedingly helpful and have made it clear and easy to read and actually getting to the point in the discussions which have been expanded and are easily read and understandable.

I want to thank all of the staff for all of these efforts, because it certainly

shows a distinctive quality in the reports. So, I again thank you very much, and thank you, panel members, for all your input and participation.

We're going to move onto the minutes, and I'd like to ask for comments on the minutes if there are any. If not, I'd like to have a motion to approve.

DR. LIEBLER: I move to approve.

DR. SLAGA: Second.

DR. BERGFELD: Third. Whatever, back there. Good, I'll call for the vote. All those in favor of approval, please indicate by raising your hand? Thank you, they're approved unanimously.

We're going to move on to our injured Director's Report. (Laughter) And welcome back, Alan. He seems to be not as pale today as he was yesterday.

DR. ANDERSEN: Well, thank you. 68-year olds and golf sometimes don't mix and this was one of those cases, but it's not permanently debilitating, so I have something to look forward to when it finally heals.

We had on the agenda this morning a visit from the chairman of the Council Board of Directors. That is not going to happen. Scott Beattie's schedule just wouldn't allow it to be fit in the final analysis.

But, I was just hugely encouraged - and I think the panel should also feel good at the fact that this was up through a snafu in the schedule. This was something that Scott really wanted to do.

No chairman of the board of the Council has ever visited the CIR expert panel, and the fact that Scott was interested in coming and watching what you do and paying attention is just, I think, a very nice new thing to be happening. I'm sorry that it wasn't able to happen, but now that we know there's an expression of interest I think we'll work in that direction for the future.

For the record, we have had some functionality issues with the website. The part that we use to post material for the panel meetings, thankfully, appears to be working okay but we're going to have to make a

significant effort to ensure that users can find our safety assessments, whether it's 2012, 2002, 1992, or 1982. Our stuff has to be available for people to look at in an easily-searchable way. Right now, that is not working. So this will be a work in progress, no question about that. But as we've been talking about this, I got reminded several times that the game plan all along was that this was a work in progress.

We had taken steps to totally re-vamp the website, and that was an ambitious undertaking. We had a good bit of success, now we've still got some work to do but that was the plan all along. So stay tuned, but we are aware that it isn't perfect and we are committed to taking the next steps.

DR. BELSITO: Just a question regarding the website, because we obviously have access to it. But the dermatologists in general practice if they went to CIR, what would they be able to see about a given chemical?

DR. ANDERSEN: Our goal is for the

user to find first the bottom line. Here's what CIR says about it, and then access to the full safety assessment if you want to see the details. So, that's the game plan.

DR. BELSITO: Free of charge or with a charge?

DR. ANDERSEN: Free of charge. These documents that we're producing have to be available to any interested party at any time. The idea of selling our safety assessments is no longer part of the game plan.

DR. BERGFELD: How about the compendium?

DR. ANDERSEN: Compendium I want to sell, if only because it's a huge amount of work to pull it together and it's a valuable thing. It may be a bit problematic to continue to support that if we're not making some money from it. So.

Now, all you guys -- Kevin is wrapping up the latest update. We're on a -- through June is just about done, and since we're doing it electronically you folks should

be receiving a PDF of it so that you can access it whenever you want, but for the general public our plan was to sell it.

DR. BERGFELD: Are there going to be print copies as well?

DR. ANDERSEN: For you, Wilma, we'll print a copy.

DR. BERGFELD: Thank you.

(Laughter)

DR. ANDERSEN: But that's a one-time deal, the rest of you can use electronics.

I want to look forward to December a bit. There's at least two things that deserve highlighting. First is we're going to be reviewing a hair dye ingredient. I say it that way because I can't remember which one, but there will be a hair dye ingredient that we're looking at and that means we're going to have to address the concerns that have been raised in Europe regarding the risks potentially associated with testing on a small patch of skin before use.

You all recall that we have that incorporated into all of our safety

assessments regarding hair dyes that our expectation is that you will test before you use it to see whether or not you have an allergic reaction to anything in the product. And the question has been raised, is that actually a good practice? So, in addition to the basic safety questions about whichever hair dye it is that's on the agenda, we're also going to have to tackle this question of what do we think about the concerns that have been raised.

Second shoe is there are several new studies regarding phthalates, some of which are in the realm of phthalates linked to diabetes risk in the elderly. I don't know how all of it is going to come down, but you've got -- just like we did for parabens at this meeting, you need to take a look at these data and decide if they have an impact on our safety assessment of phthalates in this particular case. So, that will be another new data review for the December meeting.

And then finally, and my crystal ball is a little fuzzy on this one, we may

receive information from the Professional Keratin Smoothing Council on the impact of their programs to improve the use conditions under which hair smoothing products containing formaldehyde and/or methylene glycol are used. Now, we've repeatedly -- I've repeatedly made the point to the PKSC that just telling you about the wonderful things they plan to do to improve the situation are just not sufficient. We need to see impact, and I don't know when we're going to get that but they are pushing hard to come back and explain to us why we got it wrong -- formaldehyde and methylene glycol. So, whether that will be December or not, I don't -- again, it's a little cloudy but it's coming and if you thought that formaldehyde and methylene glycol were over, it's not. It will be back on your plate again.

And I think that's about it, by way of --

DR. BERGFELD: Do you want to give a forecast of how many ingredients we might be covering in 2013?

DR. ANDERSEN: If we can round out

the priority list as established, we could get almost 600 ingredients in 2013. And my memory is fuzzy -- Monice, for 2012 what might we get to unless they screw something up?

MS. FIUME: Around 600, probably.

DR. ANDERSEN: For this year we could hit around 600. So, we have indeed stepped up the pace. And that was very much our purpose, and we'll see how it really goes, but we're doing good. You're doing good.

DR. MARKS: And the meetings next year are scheduled to be in this hotel, is that correct, Alan? Did I read that correctly?

DR. ANDERSEN: Yeah.

DR. BERGFELD: Any other questions for panel members, others? Before we proceed with the various ingredients? Seeing none, I think we'll go forward, then. We have several final reports, actually 10 of them to take up at this point in time. The Borosilicate glasses, Dr. Marks is going to report on those.

DR. MARKS: I move that we issue a

final safety assessment for the Borosilicate glasses that they are safe as used. There were, I think, five ingredients in this report.

DR. BERGFELD: Is there a second?

DR. BELSITO: Second.

DR. BERGFELD: Any discussion for the discussion? Editorial comments? Don?

DR. BELSITO: Yes, in the summary, Panel Book 14, Page 4 of the report, that last sentence, the panel considered that any spray containing these solids should be formulated to minimize their inhalation, I thought should be deleted. That's really more of a discussion point than a summary of the data.

And then, we extensively re-wrote the aerosol discussion because it went from particle size to other toxicity endpoints and back to particle size, and we just unified it to -- and then Paul in particular did not like in the second paragraph the discussion, the word "leach" in terms of zinc and silver secure in the molecule that will not leach, and we changed that to will not be readily

bioavailable.

DR. BERGFELD: Any other comment? Ron, doctor? Seeing no other comments I'll call for the vote, then. All those in favor of safe, raise your hands. Thank you, unanimous approval of the Borosilicates.

Then moving on to the dialkyl malates, Dr. Belsito.

DR. BELSITO: Yes, in June we issued a safe in the present practice of use and concentration conclusion. There was no new data. We did add in di-octyldodecyl malate in June and there were no comments as to that addition, and I'd like to go ahead with that conclusion safe as used.

DR. BERGFELD: Is there a --

DR. MARKS: Second.

DR. BERGFELD: -- second? Any other comment, discussion? Don?

DR. BELSITO: Again, the aerosol section needed to be rewritten so it was uniform in terms of particle size.

We also in the second paragraph of the discussion was concerned that the reader

that was just skimming through this report might not understand that the concern with the malic acid being a non-aggressive substance for babies was not malic acid, but the contaminant maleic acid. So, we just pointed out that after saying D-malic acid was considered GRAS in baby foods, this was due to nephrotoxicity and growth retardation in rats at 1 percent maleic acid in feed. Maleic acid in feed -- maleic acid may be a contaminant of malic acid, so it's clear that they're two different substances we're talking about.

DR. BERGFELD: I see everyone shaking their head, looks like everyone's agreeing with you. Any other comments? Alright, confident question.

All those approving safe? (Hands raised) Unanimous, okay.

Moving on then to the third ingredient, the Dimethicone crosspolymers. Dr. Marks?

DR. MARKS: I move that we issue a final report that Dimethicone crosspolymers, which are an extensive list of ingredients on

Panel Book Page 29 and Page 30, have a conclusion as safe in the present practices of use and concentration as described in this report.

DR. BELSITO: Second.

DR. BERGFELD: Any discussion regarding this ingredient? Don?

DR. BELSITO: Yeah. Again, we didn't like the listing of the residual monomers. What we did is, we deleted -- this is Panel Book 28 in the discussion. We deleted that paragraph that even though the ingredients were stable to ensure no residual monomer -- with that entire list of various monomers. Instead, what we did in the paragraph above it starting with the third paragraph -- in the book it says, also the properties of the silica backbone. We changed, also the silica backbone is stable under anticipated conditions of use in the ingredients contain levels of residual monomer below the level of toxicologic concern.

DR. BERGFELD: Ron Hill?

DR. HILL: I have no problem with

that, except that it's not a silica backbone so we have to be sure that we get that chemically correct when it's written.

DR. BELSITO: Dan, comment?

DR. LIEBLER: Silicone.

DR. BELSITO: Silicone? Okay.

DR. BERGFELD: Alright, any comment? Dan, are you making another comment? No. Any other comments? Don, June?

DR. MARKS: Don, did you mention in Panel Book Page where the last sentence before the listing of different ingredients -- where it says, are no residual monomers, we said minimize residual monomers.

DR. BELSITO: We got rid of that paragraph completely by saying --

DR. MARKS: Okay.

DR. BELSITO: -- that they're stable and the level would be below the level of toxicologic concern in the paragraph above.

DR. HILL: Can you read that again, then? What you said about what's incumbent on the manufacturers?

DR. BELSITO: Okay. The panel --

okay, so we're in the second paragraph. We've eliminated the entire third paragraph with all the listing. Also, the property -- the silicone backbone -- silicone, right? Silicone backbone is stable under anticipated conditions of use and the ingredients contain levels of residual monomer below the level of toxicologic concern.

DR. HILL: Are you saying that we know that that is the case, or you're asking the suppliers and manufactures to ensure that that is the case?

DR. BELSITO: This is Dan's language, so I'll allow him to answer those questions.

DR. LIEBLER: Is this microphone on?

SPEAKER: Yes, you're on.

DR. LIEBLER: Okay. The method of manufacture and the concentrations of these is used in cosmetic products that would suggest that the levels of residual monomers would be very low. The lack of data on sensitization/irritation would also be consistent with that interpretation.

DR. SHANK: The phrase "below the level of toxicologic concern" is pretty vague. That could be sensitization, it could be cancer, it could be if you develop a toxicity, it could be teratogenicity. It almost sounds like a hedge.

DR. BELSITO: Actually, it's below all those levels is what it means. I mean, my understanding of toxicologic concern is that weakest link and it's below even the weakest link in the chain.

DR. HILL: We didn't have data to assure us of that, that's the point. We did not have data that assures that. That's why I raised the issue last time, and we haven't gotten any new data on that, to my knowledge.

DR. BERGFELD: Dan? Curt?

DR. LIEBLER: So, I simply didn't share Ron's concern about residual monomers that these products -- given the fact that these products are large molecular weight products -- presented in the cosmetic ingredients or used in silicone solvents or non-polar organic solvents. These things are

all going to -- I mean, the residual monomer will be low. The way they're used in the products would further dilute out any small amount of residual monomer that's there, and the thing that I think was significant to me is that as we say in the following sentence, there are multiple animal irritation and sensitization studies that were negative for effects but they didn't test every ingredient by any stretch of the imagination, so we're relying extensively on read-across.

My point was, in the manufacturing process monomers can be entrapped in these large polymeric materials and then the question is, how much is entrapped and how much could be released under conditions in product use? I don't think we're assured by what we have that we know that that's zero.

DR. HILL: Yes, but they read across --

DR. LIEBLER: Well, if they're entrapped, they're entrapped and if they're not --

DR. HILL: Well, then they should

stay entrapped except that most of those monomers written there are volatile materials, so we don't know how much they'll stay entrapped.

DR. LIEBLER: And if they're volatile, that further decreases my concern.

DR. HILL: I'm not convinced with that language. I was fine with some language that suggests that it's incumbent upon the manufacturers to ensure, but then you do have what's the hedge in that case, below the level of toxicologic concern.

I think that's still okay, because that again puts it incumbent on the manufacturers and the product formulators to go out and look at what monomers might be there because the problem with even asking them to divulge the monomers is it generally will say -- it will force them to give up trade secrets on the process of manufacture and I don't think in general we want to force that. But at least it puts it back on them that their monomers -- it's easy enough for them to find out what the toxicologic concerns

are for those monomers, because most of these have been dealt with in some cases extensively, and make sure that under the conditions of use they will not produce conditions where that toxicology would become a concern.

But, that's the language. Somehow that's what I wanted the language to capture myself and I'm not sure that gets it.

DR. BERGFELD: Okay. Ron Shank, you have a comment? Then Curt.

DR. SHANK: My only problem is the phraseology here. One of the monomers is a vinylcyclohexene, and the IARC classifies that as a 2B possible endocarcinogen. There has been carcinogenicity studies on it -- positive weak study, but still positive. That's why it's a 2B.

So with -- and I didn't check out all the monomers, just the few that looked interesting to me. So, just to say vaguely of toxicological concern, what does the manufacturer do? Because for everything, for every monomer?

DR. BERGFELD: Curt, then Don.

DR. KLAASSEN: To go back to your question, Ron, or another way of -- either Ron -- is you like to say that there should be minimal, I guess was the word you're going to put in, instead of no?

DR. MARKS: Minimize.

DR. HILL: Or minimal would mean the same thing. I mean --

DR. KLAASSEN: I was going to say, that's just as bad because it doesn't say anything either. I mean, this is a difficult situation to --

DR. BELSITO: Actually, minimize could be above toxicologic concern.

DR. SHANK: It could.

DR. HILL: Because what I envision is that the people that are making the finished cosmetic products are not in general going to know what those monomers might be. So, I mean, they're potentially accepting a liability, so they have to have some confidence in the information they're getting from big polymer producer - I don't want to

name any specific companies, but they have to have some information from them that this is not going to pose a problem.

The people that manufacture these sophisticated polymers are more than capable of making those determinations and more than capable of knowing which kinds of products those are being used in. But I'm trying to find a way to put it back on them to ensure that under those conditions of use, that some level of assurance is there for safety and that the specific concern is that under the conditions where these polymers are made, the monomers can be entrapped. If they stay entrapped, no problem. If they're released under the conditions of use, I can think of some conditions of use where that might be the case, then these steps need to be taken. Again, I think in all of these cases where there are monomers there is toxicology available enough for them to make those kinds of determinations and seek to minimize it or minimize -- I don't know how you phrase this. I think you can phrase it in a way that this

works.

DR. BERGFELD: So you don't have a phrase we can use at this point in time? You have a concern.

DR. HILL: Yeah, I guess because they're the ones that made a motion and proposed language, that I wasn't quite satisfied with --

DR. BERGFELD: Okay.

DR. HILL: Give me something else that I'm happy with.

DR. BERGFELD: Ron Shank and then Tom?

DR. SHANK: How about saying something like the ingredients should contain no detectable available monomer?

DR. SNYDER: I think that goes to language that we didn't like in the first place as saying no, because I don't think we can demand no residual catalyst or monomer. And so, we were trying to --

DR. SHANK: No detectable, not "no" you can't -- that doesn't make any sense in chemistry. But no detectable means the

methods --

DR. SNYDER: So, two things we didn't like. We didn't like the language of saying no and we didn't like the listing of a select group of impurities, so to speak. And so, we felt that the data that we did have on impurities -- we did have data on impurities, it's just they were all in the parts per million range that we didn't feel there was any reason to think that method manufacturer would be that drastically different from the formulation of other polymers to suggest that they would have higher contaminants of these impurities. And that was a sensitization data, we felt pretty confident that we could go with the language that we used.

We were acknowledging that these could be a problem, but under the methods of manufacture in this report -- and as used, we felt there was not really any issue to raise.

DR. BERGFELD: Halyna?

MS. BRESLAWEC: The language that we proposed to address this issue was that the discussion should indicate that residual

monomers and catalyst should be kept to a minimum in these ingredients.

DR. BERGFELD: Tom.

DR. SLAGA: Well, after rethinking them I don't like the word "no" because that's a function of what history and technology, you know -- sure, I could see if I could pick it up at the tip of my finger and say it's not there, but that's not very accurate. The more I think about it, I don't like "minimize" either because we should watch and learn.

What about going to the most sensitive toxicological concern and emphasize that. Is that a possibility?

DR. BELSITO: I think that's what the threshold of toxicologic concern means.

DR. SLAGA: Since --

DR. BELSITO: It's the first endpoint you hit. What, regardless of whether that's sensitization, reproductive toxicity, or whatever. And speaking from other boards I sit on, they object to the word "detectable" because as science advances that level is going to change.

DR. SLAGA: Change.

DR. BELSITO: So that's a very ambiguous term.

DR. HILL: I would not be satisfied with that, either. Actually, from both directions -- on the word "detectable", even though --

DR. BERGFELD: Okay, Jim, do you want to make a remark?

DR. MARKS: Yeah. I want to ask Ron Shank since he doesn't like the vagueness of "no toxicologic concern", is there another way that you would phrase it that perhaps --

DR. SHANK: Yes, I don't think it's going to be very popular. (Laughter) I split the ingredients into three categories and said that the ones where we have geno tox irritation/sensitization data on the ingredients and their monomers are safe. Those where the ingredients have been found -- the reactants have been found safe, they are safe. And those where we don't have that information are insufficient.

DR. HILL: I mean, that's honestly

how I felt about it but I was trying to come up with a reasonable compromise because again, I think what occurred to me as I was speaking the last meeting -- and certainly in reflecting afterward is, we've developed a situation where we are going to force divulging enough information so that someone else can know more or less how they're manufacturing that polymer, and those are well-kept trade secrets and I'm -- I guess it's a philosophical question. Do we force that or not?

But, there were quite a number of these where we didn't have that detailed information, and that's why I objected to the language that suggested that we in fact know for all of these based on the limited ones that we have. That's not true.

I went through one by one by one and looked at, all right, if you're going to put together a polymer like this, how would you do that chemistry? And that's where some of those monomers in the list came up with. You can make those surmises from the abbreviated

structure, but it's just.

DR. BERGFELD: Don?

DR. BELSITO: I guess if I heard correctly, Ron, you just retracted your vote. Because we voted unanimously that they're safe and we're arguing only over the discussion.

DR. BERGFELD: We didn't vote yet. We didn't vote yet, we've just been in discussion.

DR. MARKS: A motion was made.

DR. BERGFELD: A motion was made, we haven't voted yet.

DR. BELSITO: Okay.

DR. BERGFELD: We've been watching that.

DR. ANDERSEN: Ron Shank, can you go over the three categories you described? Because I didn't catch the middle one. The first one, geno tox and sensitization data, I got.

DR. SHANK: Well, we have geno tox and/or sensitization on data on the ingredients. Safe. For those where we know the reactants, the chemicals used to make the

ingredients are safe, those ingredients would be safe.

For those ingredients made from reactives that are possibly genotoxic or sensitizers, insufficient.

DR. BERGFELD: Don?

DR. BELSITO: Okay, well this brings up the second point that we're going to make after we clarified the language. Our group was not happy with a number of data points, starting on Panel Book Page 23 under Reproductive Toxicity. According to a supplier of a trade name mixture, based on the similar structural analogy to a similar polymer, this would not be expected to be a reproductive toxicant and there was no further data. So, we didn't know the polymer.

That then, under genotox, occurs for dimethicone vinyl trimethylsiloxysilicate crosspolymer, for vinyl dimethyl/trimethylsiloxysilicate stearyl crosspolymer, which we crossed out. Under carcinogenicity it occurs for dimethicone vinyl trimethylsiloxysilicate crosspolymer.

Under irritation and sensitization it occurs for crotonic vinyl C8- 12, iso alkyl esters, V8-bis vinyl dimethicone crosspolymer, and under sensitization it occurs for crotonic acid, vinyl C8- 12, and for dimethicone vinyl trimethylsiloxysilicate crosspolymer.

So, we deleted all that information because it was based upon information on a similar unnamed structure that we could not verify. So, that will significantly change the list as well.

DR. BERGFELD: Well, that does put a hook in this. I'm going to go around the table and ask for comments on both areas, and that is the monomer issue and also this last deletion issue. I'm going to start with Dan.

DR. LIEBLER: On the monomer issue, I think I made my points. We don't have the data, I agree with that. Where we go from the lack of data I disagree with the approach that Ron suggests. I don't think that the available data suggests that we have a problem. Plus, I think the way these things are manufactured, the level of these residual

monomers is going to be low. They're volatile, they're really not going to survive into significant levels in cosmetic products as used.

And as for the second point, it is my suggestion that we delete those references to the essentially non-data data.

DR. BERGFELD: Okay.

DR. LIEBLER: So, I fully support that.

DR. BERGFELD: Paul?

DR. SNYDER: As I stated previously, I thought we had -- while we didn't have a complete data set on the method of manufacture, we had enough data set to suggest that methods of manufacturing and formation of the polymers doesn't appear to result in significant monomer contamination. I was comfortable with that being likely represented, and that's all we ever do in our discussion. We talk about that that represents what data we're looking at and that everything else -- like the same thing we do with the use concentrations, that we expect

that they'll be used in similar concentrations as described in our report. So, I felt it was consistent with our previous genesis of reports and exceptions of some methods of manufacture. Not needing to have every reaction for every possible formulation.

There are a lot of vinyl-containing polymers. There appears in the report -- there appears to be there's not a release of a lot of monomers, so I was comfortable with that, and also in combination with the sensitization data.

DR. BERGFELD: Thank you. Curt?

DR. KLAASSEN: Yes. In regard to the two questions, the first question in regard to the monomers. I think it's appropriate to just -- I can live with the minimal amount of monomers that apparently might be there. There's no indication that we have a problem.

And in regard to the second question, those absolutely have to be removed from the document. That is basically hearsay.

DR. BERGFELD: Don?

DR. BELSITO: Well, in regard to the second question I can say that I would remove them. In regard to the first question, that's not my area of expertise. I trust my colleagues on that.

I do happen to like the word "threshold of toxicologic concern". I think it has a lot more meaning from working on other panels than minimum or levels, and so if my colleagues feel these ingredients are safe the language that I would vote for would be "threshold of toxicologic concern".

DR. BERGFELD: Thank you. Jim?

DR. MARKS: I would concur, actually, with Dan's approach and as long as we capture in the discussion what Dan has elaborated in terms of the concerns with these residual monomers, then I'm content with the way you've worded it.

DR. BERGFELD: Tom?

DR. SLAGA: I agree. I like what Dan has stated. I still have concerns about the toxicological concern. You know, we cop out on conclusions and the formulated to be

non-irritating. I would hate to get to a point that we have a conclusion formulated to be of no toxicological concern, and I think that type -- so, we need some kind of compromise so we don't go to that broadness. That's why I would suggest the specific taking out the most sensitive, just to eliminate.

We all agree there's really no concern.

DR. HILL: We don't all agree. (Laughter)

DR. BERGFELD: You'll get your chance.

DR. HILL: I know, I'm just saying.

DR. BERGFELD: Ron Shank.

DR. SHANK: Some of these are used in leave-ons up to 46 percent. That seems to be high enough where impurities might be of concern, especially if the impurities have genotoxicity.

And without any data on that, perhaps we should ask for a study to find out how much monomer is actually available -- biologically available in the formulation.

DR. KLAASSEN: Which of these chemicals?

DR. BERGFELD: One second.

DR. SHANK: Well, there were far too many for my understanding of chemistry to -- without going through each one and looking it up in the literature. A few I picked out, and the one that I only looked at closely was called vinyl --

DR. LIEBLER: Cyclohexene oxide.

DR. SHANK: Cyclohexene oxide. And vinyl cyclohexene has been studied, has been reviewed by the international agency for research on cancer, and their conclusion was that it is a possible human carcinogen. The animal data were positive, but --

DR. LIEBLER: And that's vinyl cyclohexene.

DR. SHANK: Hexene, yes. Not the oxide.

DR. LIEBLER: Correct.

DR. SHANK: So, there's so many questions about it that I was not at ease saying it's okay to have just a little bit of

a possible carcinogen. It was not the oxide that was tested, it was the hexene. But nonetheless, we don't know what's the active molecule in the carcinogenicity of that compound. That was one, and there are a whole lot more which I'm relying on the chemists to give me an alert if there is any.

So, I finally decided if we really don't know, we should just say "insufficient". And I really don't like -- so long as there's no toxic effect, we could just take all of the ingredients and just say that. So long -- it's safe as formulated to be non-toxic, non-sensitizing, non-irritating, non-genotoxic, non-carcinogen. I mean, then we are not doing our job.

DR. BERGFELD: I'm going to call on Ron Hill and then Don.

DR. HILL: So, on the second question I'm in accord with the rest of the people.

The issue is, after we discussed this last time and even in my preparation I went through but I went and looked carefully

structure by structure what must the likely monomers be in order to assemble that polymer. And then, I looked which ones did we already have some data on in terms of things like sensitization, which is at least a reasonably -- I consider it as a sort of sentinel assay.

And we're missing a large -- first of all, we don't know for sure because there are alternatives in some cases and unless we get information about what those alternatives are then we honestly don't know. We have no studies that show -- other than the biological endpoints -- that show anything about what might be entrapped and under conditions of use what might be released, given the variety of formulations. And I was trying to come up with some sort of compromise rather than demanding that information from the manufacturers, wherein they're going to be basically forced to give up some trade secrets in order to do that.

But we really need to know monomer by monomer how much might be there, and under the conditions of use is there effectively

zero release? Or it's a very small amount, and then we can evaluate based on the toxicology we can evaluate. We're missing a threshold of information on this set of ingredients related to the monomers.

So, I don't think we have enough information without knowing. First of all, there's nothing that suggests in the process of making these monomers that there wouldn't be monomers entrapped, and we don't have any detailed studies for any of them that show what that release level might be and how much might be there in the finished product.

And yeah, some of these are very volatile, but the fact that they're volatile doesn't mean under the methods of manufacture that they still couldn't be entrapped, so how long do they sit there? I have a high degree of confidence in the technical ability of some of these companies to know that they are, in many cases -- but somebody else comes along and starts making it and maybe they're not quite so conscientious, and maybe down the line we have a problem. So I think there's a

lot here we don't know. There's a compromise means of figuring out how to get at that without forcing them to give up a lot of trade secrets, great, but.

DR. BERGFELD: Thank you. Don, did you want to make a comment?

DR. BELSITO: Yeah. Ron, the ingredient that's at -- first of all, most of these are very low levels. The ingredients at 46 percent, dimethicone vinyl, dimethicone crosspolymer, under the impurities states that a mixture product sheet reports that the product mixture containing dimethicone vinyl dimethicone crosspolymer, 4 to 30 percent had less than 20 parts per million heavy metals and less than 2 parts per million arsenic. It says nothing about residual monomers in that.

The other one that's used at 20 percent I'm not finding any statement but it's vinyl dimethicone/methicone silsesquioxane crosspolymer, and about the closest I can get is for dimethicone crosspolymer its manufacturer reports no hazardous impurities.

DR. BERGFELD: Thank you. Now, we

have on the table a motion to approve and we've had a lengthy discussion. I think we've handled the second issue, that is the deletion of some of the studies that had no, I guess, reference point. The second one that we're still dealing with is how to deal with the monomer issue.

So, at this point in time since it was Dr. Marks' presentation I wonder if you have a solution here? And then I'll ask Don to get ready. He's ready.

DR. MARKS: It's interesting the conclusion is not what's up for discussion, it's how to deal with the issue of the residual monomers. At least the sense was that the majority were in favor that these ingredients were safe. The question is in the discussion, how to word the issue of the residual monomers. We don't like -- no, we don't like "minimize", we don't like "detectable", for all very good reasons. What we're trying to convey is that we -- if there is residual monomer, if there is and it's released that it does not cause a significant

-- it's not a significant hazard. I think it's that wording which is tying us up, how to get around the no toxicologic effect.

DR. BERGFELD: Alan, may I call on you?

DR. ANDERSEN: When we put out the tentative report for comment the way in which we captured the concept of concern about monomers was, one, to list them so that it would be hard to ignore what the issues of concern were. And I think maybe subconsciously on purpose we included the concept that there should be none of these left.

But frankly, I think the none in that concept was equivalent to what Dan Liebler is talking about in terms of entrapped, and were that to be the case, who cares? They're entrapped. Or, available but volatile so they disappear pretty quickly. That was what I was thinking of when we wrote the sentence "none". So, that's what we have presented to the public.

Now we have more issues that have

been put on -- there are an absence of data, and I don't quite know how to get over that. But as I have been listening to this, what strikes me is that if we simply -- and I don't care if we keep the list of monomers or not. But if we were to explain that we don't think that any monomers are going to be available for the following reasons, yes it's an opinion but that's what you're charged with giving because they're either going to be entrapped -- these are, after all, cross-linked things, the purpose of which is to create this large gamish and they're huge. And if anything does escape, volatility comes into play.

I'm not sure at the levels that we're thinking about that that isn't adequate.

DR. BERGFELD: Halyna, then Don.

MS. BRESLAWEC: I might suggest considering the concept of a LRA as reasonably achievable, which is a concept that a lot of the European groups use in describing low levels that are below the level of toxicologic concern but also lower than that if technologically achievable.

DR. HILL: And the kind of situation, just to put a hypothetical on this that I'd be most concerned about and then you can figure out how that would play out, is this ingredient is in a hairspray or a leave-on hair conditioner or something along those lines and then somebody hits it with a hair dryer for a while, and then how much of this stuff might they be breathing? You know, so if it's a vinyl something-or-other, that could be a concern. So, however the people who make these things know what those concerns should be know what kinds of products -- I think they know what kinds of products these are likely going into, and deal with it in a LRA fashion, which I'm very comfortable with that kind of concept.

DR. BERGFELD: Don?

DR. BELSITO: Here's another thought. Keep a list, keep the sentence but change it that the panel noted that even though the ingredients are stable, ingredient suppliers should take steps to ensure that there are no detectable bioavailable residual

monomers.

DR. BERGFELD: Comment on that.

DR. HILL: Other than the word "detectable" which is -- that's the --

DR. BELSITO: Well I mean, you know, we're fighting over every phrase we could potentially use.

DR. BERGFELD: Can you repeat your phrase, Halyna?

MS. BRESLAWEC: As low as reasonably achievable.

DR. BERGFELD: Don?

DR. BELSITO: I guess the problem I have with that is as low as reasonably achievable could still be higher than toxicologic concern.

MS. BRESLAWEC: Again, I don't have a problem with making them both. So, the low level of concern and as low as reasonably achievable.

DR. BELSITO: I'd be very happy with that, yes.

DR. BERGFELD: How about a comment from the Marks group? Does that combination

work for you?

DR. MARKS: I could live with that definitely.

DR. BERGFELD: Okay.

DR. SHANK: Can I hear them again?

DR. BERGFELD: Yes.

DR. SHANK: Because you can put them --

DR. BERGFELD: Two things.

DR. BELSITO: So, I guess we're keeping the last paragraph? Are we agreeing to do that?

DR. BERGFELD: Yeah.

DR. BELSITO: We'll keep the list of impurities if you want to.

DR. BERGFELD: Correct.

DR. BELSITO: The panel noted that even though these ingredients are stable, ingredient suppliers should take steps to ensure that the following residual monomers or catalysts are below the level of toxicologic concern or --

MS. BRESLAWEC: As low as reasonably --

DR. BELSITO: Reasonably achievable. Or, if -- and as low as reasonably --

MS. BRESLAWEC: As low as reasonably achievable --

DR. BELSITO: -- achievable. And then the list.

DR. BERGFELD: How does that work for you, Ron Shank? He's got a bad frown.

DR. SHANK: I still don't like to see this toxicological vagueness.

DR. BELSITO: Can we take a vote?

DR. BERGFELD: I think that Alan has captured the sense of this. Have you not, Alan?

DR. ANDERSEN: Well, I've got that last -- sorry -- I've got that last compromise. We have had this discussion several years ago in the safety assessment of acrylate ccopolymers. And one of the hugely important pieces of information was that the monomers used to make the acrylate copolymers are also volatile and they stink. And that was an important finding for the panel because you can't sell the copolymer if, in fact, it

stinks. So, there is a self- limiting process.

That issue has not come up here, and I don't know whether these monomers are smelly or not. I would expect they are.

DR. LIEBLER: Yes. Divinyl benzines, styrine, cyclehexine oxide -- having worked with all of them.

DR. BERGFELD: Smell?

DR. ANDERSEN: I would add to that concept back into the mix of this discussion.

DR. BERGFELD: Isn't that in the line of detectable, though --

DR. ANDERSEN: Well, it's -- yeah.

DR. HILL: And the problem is we don't know what all the monomers are. This was a list I compiled based on looking at the structures one by one by one and saying what monomers are likely based on what the final structure is and surmising from what kinds of reactions one would have to do to get them. It's not necessarily intended to be a complete list because there was no way I could do that.

DR. ANDERSEN: And I think the last

comment I would make in terms of Ron Shank's clear discomfort with the idea of saying below the level of toxicologic concern, I would share that discomfort if we were talking about the ingredients under review. So, if we were saying that one of these crosspolymers is okay as long as it doesn't hurt you -- but we're not saying that. We're down a level and we're saying, levels of the monomers we think are low. We can't prove it in all cases, but it looks like in some combination of they're entrapped or if they get out they're volatile, some global view these monomers are going to be below the level of toxicologic concern.

That I'm much more comfortable with, with opening that door. I would agree with you, I'm not comfortable in opening that door for the parent compound.

DR. BERGFELD: Don?

DR. BELSITO: Well, I think -- you know, it may be helpful at some point if we had someone like Wolfgang DeCant or someone come and talk to us about how scientists look at the threshold of toxicologic concern,

because it is an approach to impurities. It's not an approach to the actual material.

And so just to reiterate what Alan said we're not saying, oh, everything is safe as long as below the threshold of toxicologic concern. There will be impurities, you know, in botanicals. Basically that's what we're saying with kersatin. It's below the level of toxicologic concern. So it's an impurities issue, it's not an ingredient issue.

DR. LIEBLER: You know, this threshold of toxicologic concern is a term that's relatively recent to me, at least. But you know, Paul often says it's the total package when he's talking about the data set surrounding a chemical which has to do with the test data on the chemical that we're reviewing, the ingredient that we're reviewing, which includes whatever impurities are present in that study, the results of the studies, and what we know about the chemical properties of the impurities and the ingredients themselves and the stability. All of that stuff taken together, this

irritation/sensitization data, and it's always got gaps in it.

But you know as Paul says, the total package he can accept. That's essentially what I'm doing, and I'm simply using the term "threshold" -- that these things, these potential impurities, are below the threshold of toxicologic concern for me.

So you know, we can be comfortable or uncomfortable with different language. I think everybody has got different comfort levels with some of the terms, but I think as a panel based on my experience the last few years we're usually able to come to an agreement on the total package. It sounds like that's where we were 20 minutes ago or 30 minutes ago, and we might have had someone with a concern about the monomers per se, but most of the concern was about how to express this issue of being comfortable with the total package.

So, threshold and toxicological concern is an emerging term in regulatory circles to articulate this concept. I think

we are largely in agreement on that concept.

DR. BERGFELD: I think that Alan could take this discussion and condense it down for us. And I think that we need to see this discussion before this particular ingredient group moves forward. Now, what would you suggest, Alan?

DR. ANDERSEN: I don't see a reason not to create that revised discussion and have the panel look at it. This is September. If we do that and can -- you know, I am always thinking about the bottom line and would like to get this done this year. So, I am going to be wanting to close this out come December. But we'll give it one more shot and see if we can come up with a discussion that includes everything.

I don't hear a disagreement that the likely correct conclusion is "safe in the present practices of use", and there is an expectation that comes with that that residual monomers are not going to be a problem. It's how we alert the industry to the need for that that is at issue, and we'll see if we can come

up with some magic.

DR. BERGFELD: Paul, then Don.

DR. SNYDER: I would like to add to that. If we're going to do that, then can we not ask the industry to maybe provide impurities data on the ones that Ron's most concerned with? And so -- or to tell us that vinyl cyclohexine is not -- cannot be generated from vinyl cyclooxide. I mean, to give us some confidence, more weight -- it's still going to be a weight of evidence thing. We're not going to have a full data set on all the monomers, but if we can identify the ones that you're most concerned with, obviously that one, if we get some additional data then maybe we can come -- otherwise I just feel December we're going to be having the same discussion.

DR. HILL: The ones that are listed there I think are from my list, were the ones that I was most concerned might be -- and there's no difinitive data to say these monomers are used at all, that's the thing.

I was working backwards. Here's the

polymer structure, here's what the monomers likely had to be, and I was also looking for ones that had at least some level of biologic concern to me, by which I mean toxicology and also that we didn't have any data for another polymer, any data at all for another polymer that was likely constructed with that monomer. Or at least, difinitive information to know we have data on this polymer, it does include that monomer, so any of the others that are made using that monomer we've resolved that concern.

But even there, because the conditions of polymerization can affect entrapment, without that information polymer by polymer by polymer -- which is what I would like to have and am not going to get -- then we have to have an escape clause, and I think that's what we're looking for in terms of language, for me.

DR. BERGFELD: I think everyone -- Don?

DR. BELSITO: Just one more time and then a suggestion.

First of all, Ron. That's exactly what the term "threshold of toxicologic concern" will take into. Other monomers that you don't know about. And then Haylna's comment, below the threshold of toxicologic concern and at the lowest level achievable, or whatever.

But you can re-write it all you want. If you wanted to get past December I think you should take a straw poll as to whether people are comfortable with the TTC and below or not.

DR. BERGFELD: We can do that right now. Let's do a straw vote on the language that's been proposed. You want to repeat it?

DR. BELSITO: Basically it would be the below the level of toxicologic concern, and the lowest levels achievable -- reasonably achievable.

DR. BERGFELD: Ah -- all those -- and this is regarding the monomers, correct. I'd like to take a straw vote. Those in favor of that terminology or phraseology? Almost unanimous. And you're abstaining or voting

against, Ron?

DR. SHANK: I still don't like the threshold of toxicologic concern.

DR. BERGFELD: So you're voting against?

DR. SHANK: Yes.

DR. BERGFELD: Okay. Well, we have a majority so we could vote on this because the motion is made and seconded, and we could see the discussion at the next meeting.

DR. MARKS: And hopefully vote on it. There's no need -- I'd have to withdraw my motion and propose a new motion that we table it until we see the next rendition.

DR. BERGFELD: But that's another option.

DR. MARKS: Yeah, I think we vote on it and --

DR. BELSITO: At this point we have seven people agreeing with the discussion, so why don't we just move ahead. Because quite honestly, I don't think we're going to get better language that will satisfy everyone.

DR. BERGFELD: Haylna?

MS. BRESLAWEC: You're also not going to get any additional data. And an awful lot of these ingredients are not in use, and manufacturers have asked us to ask that they be removed from this group because they're no longer manufacturing them or they're not manufacturing them. So, there are no additional data and/or information.

DR. BERGFELD: So, the motion has been made and seconded to approve this ingredient. We've taken some lengthy 30 minutes or so to discuss the discussion, particularly the momomers. There was some straw vote indicating some agreement of phraseology to be used in the discussion, so I will go along with Don's request that if there are no more comments we'll call for the question.

All those in favor of safe with the discussion points being elucidated, please indicate by raising your hand. Okay. Well, you don't have to raise your hand, Ron.

DR. SHANK: No, so -- safe is one thing. The way we discuss it is another

thing.

DR. BERGFELD: Yes.

DR. SHANK: I would vote for safe.

DR. BERGFELD: Yes, that's what --

DR. SHANK: My objection was the discussion, but not the conclusion.

DR. BERGFELD: Well, maybe we'll field another motion.

DR. HILL: Because I would have to abstain having the details exactly -- I get the gist of it but --

DR. BERGFELD: Okay.

DR. HILL: The fundamental disagreement I had with Dan the way he put it was that, you know, we have enough information to conclude safe without any provisos. The provisos that we've been haggling on.

DR. BERGFELD: Yes. Are you willing to put a second motion on the table? We've got a vote on this. We had a majority vote. We had two abstaining -- or did you vote positively, Ron?

DR. SHANK: I'll vote for safe.

DR. BERGFELD: For safe. Are you

voting for safe, Ron Hill?

DR. HILL: Bottom line conclusion, yes.

DR. BERGFELD: Yes, that's correct. Alright, so unanimous? It's unanimous for that. Now we're going to prose a second motion.

DR. MARKS: This may be a first. I don't recall we ever -- voting on the discussant.

DR. BERGFELD: Well, we're going to because it's been too hot an issue.

DR. MARKS: My feeling in the discussant point we've already taken straw vote, which was supportive. I would just want to be sure that Paul and Dan's elaboration of why we've -- not the wording, but the reasoning behind being very low levels of the monomer, if there is any there, of not concern -- in terms of adverse effects. The issue of being trapped and the issue of being volatile be explained in the discussion, so it's a more robust discussion than just saying below the toxicologic effects. I hear Ron and

I hear the discomfort, Ron Shank and Ron Hill. I hear the discomfort with that one phrase. If somebody was smart enough to come up with an alternative which would address that for Ron Shank, I think we wouldn't be having this discussion.

So, I just want to be sure in the discussion it's a robust discussion including the points that both Ron -- or, Dan and Paul make, which reassure me about the safety of these monomers and catalysts that could be there, but in levels which are below concern.

DR. KLAASSEN: I'm thinking of all the testing that has been done on some of -- you know, not every chemical has been tested to the degree that we like. But for those that have been tested, this wasn't a problem. And you know, we are kind of making up hypothetical problems.

DR. BERGFELD: I think the motion that I'm asking for is to have the discussion come before the panel again to look at it and to be signed off of.

DR. KLAASSEN: Sure.

DR. BERGFELD: Don, you said --

DR. MARKS: May that be done electronically?

DR. BERGFELD: It can be done.

DR. BELSITO: I think that we spent over 30 minutes and we're not finding agreement. We did a straw poll on six of the eight voting members are comfortable with TTC or -- and below the level -- below whatever the language is.

So, I think we should -- we're not going to satisfy everyone. We've satisfied six of eight people and I think we should just go ahead with it.

DR. HILL: You've satisfied -- I think depending on how it's worded, you've satisfied seven of eight people, because I was in basic agreement provided that the point was that there were these unknowns and they have to be addressed by the vendors, basically.

DR. BERGFELD: We have done this before. Not in a state of motion, but we have held a discussion for sign off, as we're trying to do right now. I think that would be

most appropriate at this time.

Alan, what do you think?

DR. ANDERSEN: I think there is absolutely no reason given the extent of this discussion and the need for very artful and careful wording of a new discussion that this should go back out to the panel electronically for your review and approval.

DR. BERGFELD: Well, I'm going to end the discussion, then, for this ingredient. What will happen is -- I said electronically. Now we're moving on. Dr. Belsito.

DR. BELSITO: So, this is the Panax Ginseng and slight change because we now have to say Panax species rather than genus because there's more than one species in here. But anyway, we ruled that this was safe as used. There's been no new data and I would go ahead with that conclusion.

DR. MARKS: I second that motion.

DR. BERGFELD: Any comment?

DR. MARKS: Yes. On Panel Book Page 27 under the summary, it's the 1, 2, 3, 4th sentence down where it says there were no

dermal pericutaneous inhallation toxiconetic discovered. Rachel pointed out the starkness of that sentence, and actually we have dermal and pericutaneous. So, we limited that sentence to being -- there were no inhalation toxiconetic data discovered, and in subsequent memo receive later than receiving this Panel Book -- the inhalation boilerplate was put in the discussion, so it takes care of that.

DR. BERGFELD: Any other comments?

DR. BELSITO: Just a few minor that I can pick up.

DR. BERGFELD: Okay. Hearing that, I'll call for the question. All those approving this as safe? Unanimous. Okay, moving on to the fifth ingredient, the lanolins. Dr. Marks?

DR. MARKS: I move we issue an amended final report of polyether lanolins with a conclusion they're safe at present practice and use of the ingredients listed.

DR. BERGFELD: Second?

DR. BELSITO: Second.

DR. BERGFELD: Comments, discussion?

DR. BELSITO: Again, the aerosol boilerplate needs to be rearranged.

DR. BERGFELD: Okay.

DR. MARKS: So, we actually had a robust discussion about this report in that Halyna pointed out that most of the report is really a reiteration of exactly what had occurred in previous reports. So, we came to a suggestion that we decrease the length of this report extensively. We keep the abstract, the introduction, have a discussion and summary, and the tables along with the conclusion and not reiterate a great deal of the body of this paper, which is redundant.

DR. BERGFELD: Any comment from the Belsito team?

DR. MARKS: And the onus in here, some of that discussion revolved around whether the journal would publish the same material twice. If they read the previous reports, there would be perhaps an editorial concern about that.

DR. BERGFELD: Lillian, do you wish to comment?

MS. GILL: We've had that discussion in-house as well, and it's a compilation of prior reports. And he's of the opinion they won't want to publish that unless there is something additional, unless there's a change. So, I think that answer is "no".

DR. MARKS: So, then I think we would support decreasing the size of this report and the manner. I suggest it doesn't change the conclusion, it just makes it much more compact.

DR. BERGFELD: Any other discussion points or comments?

DR. LIEBLER: I have no objection to that. Just in terms of our process, what does that mean? Do we need to see this again? That's totally editorial.

DR. MARKS: Yes, totally editorial and I would say if the panel members feel more comfortable that can also be done electronically as we've done with --

DR. LIEBLER: Well then that's below my threshold of editorial concern. (Laughter)

DR. HILL: Mine, too.

DR. BERGFELD: Wow. Agreement between.

DR. LIEBLER: That's right.

DR. BERGFELD: Great.

DR. LIEBLER: Saw right through it.

DR. BERGFELD: Alright, it seems that there's no other comments and we'll call for the question. All those in favor of all of this? Thank you, the lanolins is safe, unanimous.

The next ingredient, Dr. Belsito? This bis-diglyceryl polyacyladipates.

DR. BELSITO: Yeah, so in June we went with a safe for use in cosmetic formulations in the present practice of use in concentration for these materials, and I would like to make that a motion.

DR. MARKS: Second.

DR. BERGFELD: Any comments on this document? Don?

DR. BELSITO: Yeah. The discussion, the first paragraph the CIR panel noted an absence of publicly-available data. We just still needed that entire paragraph. We have

data, doesn't matter if it's public. It will be public when this is published.

DR. BERGFELD: Okay, anything else? Seeing none, I'll call the question. All those in favor indicate by raising your hands. Thank you, unanimous.

Moving on to the next ingredient, then. Dr. Marks, the microbial polysaccharide gums.

DR. MARKS: I move that we issue a final safety assessment of the microbial polysaccharide gums listed on Page 30 and 31 with a conclusion they're safe in the present practice of use and concentration in cosmetics.

DR. BELSITO: Second.

DR. BERGFELD: Comments?

DR. MARKS: Monice, would you read the editorial comment from the Council?

MS. FIUME: The Council had a comment -- and I'll read it as-is -- other than listing the three hydroxypropyl trimonium compounds, this report includes no information about these ingredients or the hydroxypropyl

trimonium group. Perhaps the previous report on the trimonium ingredients should be mentioned in the introduction. In the discussion section, the CIR Expert Panel should then indicate that based on the safety data on the polysaccharide gums and the data on trimonium ingredients included in the previous report, the CIR Expert Panel considered trimonium saccharide gum compounds to also be safe.

DR. MARKS: Okay, and then you have that in the discussion here.

DR. BELSITO: Yeah, we pointed that out also in our meeting and agree. And Monice, I think -- I don't know if everyone saw it as drafted -- a paragraph in the second paragraph of the discussion addressing that.

DR. BERGFELD: So, any further comments? Halyna, anything? Alright, call the question. All those in favor of safe? Unanimous, thank you.

Going on to --

DR. HILL: I would just like to compliment the staff members that worked on

the chemistry, especially the structures and so forth on the good job done on that. Really happy with the final product there.

DR. BERGFELD: Thank you, I'm sure they're glad to hear that.

Looking at the next ingredient, which is a grape- derived ingredients. Dr. Belsito?

DR. BELSITO: In June we actually added two ingredients to the original hydrolized grape fruit and hydrolized grape skin, and went ahead with a safe as used conclusion. And I would make that a motion.

DR. MARKS: We largely agree, other than Dr. Shank had concern about the grape leaf extract, that it's colored and we don't have any phototox data for that. So, for all the other ingredients, yeah, safe. For that one, insufficient for phototox, photosensitization.

I actually felt with clinical experience and no occupational reports, photosensitivity or phototoxicity from harvesting grapes and caring for the

vineyards, that I was reassured about that. But, Don, I would ask for your input. Obviously I don't know whether you've specifically looked at that, but whether you had concerns about --

DR. BELSITO: Which specific one?

DR. MARKS: The leaf extract. Ron, did I characterize what you said correctly?

DR. SHANK: You did. It's a highly-colored extract, and we have no phototoxicity data and it seems up to 3 percent.

DR. BELSITO: If it's colored, then it's absorbing in the visible wavelength, and phototoxicity is driven by UVA. So, I have no clinical concerns. And from the standpoint of understanding phototoxicity, no phototox concerns.

DR. BERGFELD: Ron?

DR. SHANK: If it's colored, it probably has photoactive chemicals in it. You see the color because of the visible, but that doesn't mean there's no UV absorption.

This may be handled in the

discussion.

DR. MARKS: Don, I actually had a conversation with Ron this morning and I thought besides what you said that perhaps it doesn't get -- it doesn't deal with a colored portion, but most of the components you find in one portion of a plant or in the other. It's just different concentrations, and so you take a read-across. Again, the photosensitivity, phototoxicity was less of a concern to me, but I wanted that to be open and perhaps just how would you handle it in the discussion then, Ron? With what we said?

DR. SHANK: I think the discussion could rely on the clinical expertise of the panel members, that they have not seen any problems with grape harvest workers. And that the use of the leaf extract is very low in everything except perfume, and if the amount of a perfume is just very, very small then it would not be a problem. But I think we should recognize that there is a potential there.

DR. BERGFELD: Don?

DR. BELSITO: I would also like to

point out that if you go to Mediterranean cuisine there are lots of foods cooked with grape leaf and if there were a problem you would see it among cooks in Mediterranean restaurants because it's a very sunny area.

DR. SHANK: This is phototoxicity. I don't think they do all their cooking outside, do they?

DR. BELSITO: But they get the materials on their hands and they go outside and they get it on -- you would definitely see it if it were an issue. I can assure you. I mean, you see issues with lime in bartenders, and that's a very dark environment but they have it left -- residual on their skin.

DR. SHANK: Then we can handle this in the discussion based on the clinical expertise.

DR. MARKS: Yeah, I agree with you, Ron. I think what we could do is Ron Shank handle this in the discussion, just say there's no clinical evidence, occupational evidence of phototoxicity in that way.

And so with that in mind, then I

second the motion.

DR. BERGFELD: And Ron Shank is approving of that move?

DR. SHANK: Yes.

DR. BERGFELD: Yeah, so we have it. Motion is made and second to approve safe. Any other discussion? Don?

DR. BELSITO: We just wanted to make sure that in the discussion we noted that there were low levels of carcinogen present and some of the components but they -- ingredients were used at very low concentrations and because of this we were not concerned.

DR. BERGFELD: Okay. Ron Hill?

DR. HILL: I also didn't like stating that phytostearols would not be absorbed because, I mean, if we said the phytostearyls aren't -- I agree if we have long chain esthers. I definitely agree if we have glycocides, but if we say phytostearyls aren't skin-penetrable then neither is hydrocortisone. So, I think -- I propose the small change of language to make sure that we

didn't believe that phytostearyls couldn't be absorbed.

DR. BERGFELD: Okay, any other comment? Seeing none, call the question. All those in favor of safe? Unanimous, thank you. Moving on to the next, chlorphenesin. Dr. Marks?

DR. MARKS: So, depending on where you're raised, this is either chlorphenesin or chlorphenesin. (Laughter)

At any rate, I move that we issue a final report on chlorphenesin with a conclusion that it's safe.

DR. BERGFELD: Is there a second?

DR. BELSITO: Second.

DR. BERGFELD: Any discussion or comment?

DR. MARKS: Yes. On Page 18, Panel Book 18, the first paragraph of the introduction and the last sentence. Based on the use concentration of chlorphenesin in cosmetics, et cetera, we recommend that that sentence be removed and the same sentence under the discussion -- it's the last sentence

of the first paragraph there. We didn't want to imply that the cosmetic ingredient chlorphenesin had any muscle relaxation effects. That, as you recall, was the concern with the FDA and there was that mis-, I guess you would say, - interpretation of what the cosmetic ingredient chlorphenesin is. So, that's the only editorial comments we had.

DR. BERGFELD: Don?

DR. BELSITO: Yeah, we went a little further than that. In the introduction we thought there was no need to point out the confusion that brought this to FDA's attention. So, after the second sentence we actually eliminated the sentence, the Food and Drug Administration, that entire sentence. So, after this ingredient functions in biocides and cosmetic products, we said, the CIR Expert Panel noted that the drug chlorophenesin carbomate CAS number -- also called chlorophenesin -- is a known -- has muscle relaxant effects -- period or comma -- which are not expected for the cosmetic ingredient chlorophenesin with the CAS number

for chlorophenesin.

And then in the discussion, we deleted the entire first paragraph about the FDA.

DR. HILL: The reason I didn't want to go that far is because early in my career we were still teaching chlorophenesin, and at least the folklore surrounding that ingredient can be hydrolized to some extent and that some of the muscle relaxant properties probably trace to chlorophenesin, not the carbomate. And however, the literature searches from that point become very difficult because you have to go back into very old literature and you can't tell in some cases did they experiment with chlorophenesin itself or did they experiment with the carbomate. But you cant rule out that the possibility that this compound has muscle relaxant effects because, as I say, when that was used as a drug at least the folklore was that some of that activity was coming from the hydrolyzed material, chlorophenesin itself, and not the carbomate.

DR. LIEBLER: So that may be true, Ron, but the problem is that we really don't have data to support that and this report is not about chlorophenesin carbomate.

DR. HILL: But chlorophenesin carbomate can be hydrolyzed to chlorophenesin. The question is under drug use -- and of course, at much larger concentrations.

DR. LIEBLER: Exactly, so --

DR. HILL: So I think the use of this ingredient in cosmetics, we're not going to invoke any of that activity. But to make strong statements that say that's totally irrelevant is false. It's misleading.

DR. LIEBLER: Well, we don't say that. We simply say that chlorophenesin carbomate is not the subject of this report.

DR. HILL: I won't object to that, that's true.

DR. BERGFELD: Alright, we have some modification of the abstract, the introductory remarks, and the discussion positioning the muscle relaxant activity of another drug. So, I suspect that's what we've done here.

Everyone agree that we can move forward, then? Alright. Call for the vote, then. All those in favor? Unanimous, thank you.

Moving to amino acids, Dr. Belsito. This is the last and the final report.

DR. BELSITO: So in June we issued a tentative safety assessment for public comment. Safe as used in the present practice of use in concentration in cosmetic products, and I'd like to go ahead with that motion as a final.

DR. BERGFELD: Second?

DR. MARKS: Second.

DR. BERGFELD: Okay, any discussion or comment?

DR. HILL: Amino acids --

DR. BERGFELD: Amino acids?

DR. MARKS: So on Panel Book Page 18 under the discussion, we felt midway into the second paragraph, the bottom of the page, the sentence that begins perhaps most notably, the amino acids and this assessment, et cetera, that sentence could be deleted.

Similarly, on Panel Book Page 19, the last -- yeah, do you see what I'm saying?

DR. BELSITO: No.

DR. MARKS: So if you go in the discussion, the second paragraph right in the middle where --

DR. BELSITO: Perhaps most notably?

DR. MARKS: Yes. We felt that sentence could be deleted as an editorial comment.

And then the same we felt that the last sentence of the discussion, however because the lack of data -- that specifically supports the safety of the D isomers. The Expert Panel -- Ron Hill made the point that if DL is okay, then D is okay. So, he felt that last sentence could be deleted.

DR. BELSITO: Fine.

DR. BERGFELD: Okay, motion has been made and seconded. Any other comments? Seeing none, I call the question. All those in favor of safe for amino acids, raise your hand. Unanimous, thank you.

Now we're going to go to the reports

going to the next level, and the first one there is Dr. Marks and the fatty acid amidopropyl dimethylamines.

DR. MARKS: I suspect this ingredient is going to -- these ingredients are going to elicit another discussion. So, in June the CIR Expert Panel issued an insufficient data announcement. One, getting pericutaneous absorption of the shortest chain fatty acid. For example, the loramidylpropyl dimethylamine. And if absorbed in repro a development toxicity. And also, we wanted sensitization/irritation data.

We've not received this data. However, our team went back and looked at our handling of these ingredients back in June and we actually felt that we could issue a safe as long as it was formulated to be non-sensitizing. That would take care of the issue with the alioamidopropyl dimethylamine, and so we would move that we issue a tentative report on the fatty acid amidopropyl dimethylamines with a conclusion of safe as long as formulated to be non-sensitizing.

And I'll let -- we'll see whether we get a second of that, but I'll let Ron Shank discuss and Ron Hill, if he wants, the issue of repro and developmental toxicity and why we were not concerned about that.

DR. BERGFELD: Ron Shank, then Ron Hill.

DR. MARKS: While Ron's looking for that, I'll mention we had considered table-ing this until we received the REACH data on the stearylmidylpropyl. But we felt even with that data it really wouldn't impact our decision.

DR. BERGFELD: I'll let Don speak and then we'll wait for Ron to get to the place he needs to be.

DR. SHANK: Thank you.

DR. BELSITO: Well, you know, we also considered the memo that we got from Halyna regarding the fact that the REACH dossier was expected on stearamydlpropydimethylamine by May of 2013. But we also considered very strongly the fact that the consortium putting that dossier

together advised us that the read-across approach for these other akylamidyl dipropyldimethylamines is not appropriate because the shorter chains would penetrate and perhaps have a higher sensitization potential.

So, we actually wanted to go insufficient and we changed the ingredient that we wanted. We wanted absorption of cocamydyl propyl, a dimethylamine, and a phosorb reproductive toxicity studies, and we wanted sensitizaiton and irritation on that.

Putting out this insufficient, however, we also wanted to let industry know that we would not bring this back until after May of 2013, so that we could also see the information in the REACH dossier. But we wanted to proceed letting them know that even with the information for the stearamido, we would still have concerns for the smaller size.

DR. BERGFELD: Ron, are you ready? Ron Shank?

DR. SHANK: Yes. It was just the use concentrations are quite low in leave-on

products, and this would not present a toxicological concern. (Laughter)

DR. LIEBLER: I just want to go on the record saying that I'm loving this. (Laughter)

DR. BERGFELD: Ron Hill?

DR. MARKS: Ron Shank, will you rephrase that to below the level of toxicologic concern?

DR. SHANK: No. Below a concern for reproductive and developmental toxicity. That specific. (Laughter)

DR. BERGFELD: Okay.

DR. BELSITO: Well, the cocamydylpropyl is 6.5 in dermal contact.

DR. SHANK: That's in a rinse-off?

DR. BELSITO: No, dermal contact, read-across, white bar.

DR. SHANK: Which one?

DR. BELSITO: Cocamidylpropyl dimethylamine, the one we asked for data on.

DR. SHANK: In my book it says that's in a rinse- off.

DR. BELSITO: Mine says exposure

type dermal contact.

DR. SHANK: Well, dermal contact can be from a rinse-off. But in the leave-ons, it's --

DR. BELSITO: Okay,.03. You're right, sorry. Mea cupla.

DR. BERGFELD: Would that change your opinion, Don, with what you're requesting?

DR. BELSITO: You know, I'm not the repro toxicologist. It would still not change my opinion about the need for sensitization and irritation, whether it would change my need for absorption I'm not in a position to answer.

I mean, basically what -- the consortium who is putting this dermidapropyl is telling us we cannot read across their data to the other one. So from the standpoint of sensitization and irritation, I'm not satisfied that we can go safe as used.

DR. MARKS: That's why we put formulated to be non-sensitizing. And actually, it wasn't the lower one, it was the

-- as in the minutes. The aliomydylpropyl diethylamine I was most concerned about because we have actual case reports with a concentration, with positive patch tests, and that's actually been alerted to us in the North American group that has added it to our patch test screening. So, that was the one I was concerned with and that's why we put on there safe to be non-sensitizing, to address that issue of irritation and sensitization.

DR. BERGFELD: Ron Hill?

DR. HILL: Yeah. I mean, I think what we talked about yesterday, I don't remember that I had anything to add, but what I'd said was if you mandate that it's formulated to be non-sensitizing then the odds of formulating in a leave-on at a high enough concentration that it would cause any reprotox effects are highly unlikely. So we're basically using the sensitization as a sentinel, if you will, for any other potential effects like that. That we would be -- by mandating non-sensitization to get to the levels where you could reasonably expect any

kind of repro tox would certainly, I think, certainly see high levels of sensitization and you wouldn't formulate to that concentration. So it was a sentinel indicator is how I looked at it. I don't know if there's precedent for that or not, but that's the way I was -- that is the mindset we had when we looked at this as an impurity in cocamydyl propyl betaing.

DR. BERGFELD: Don, then Curt.

DR. BELSITO: I mean, if you objected to TTC for impurities, then I have to strongly object to below the level of sensitization.

I think irritation is one thing because irritation is dependent upon so many factors. You know, Ph, what else is in there, yadda, yadda, yadda. But sensitization is sensitization, and we have no data on this. And you know, when we dealt with cocamydyl propylbetane, it was the impurity. So again, it was a TTC approach to these sensitizing impurity.

Now, we're using a TTC approach to the actual chemical, and I strongly object to

that. That is not the use of TTC.

DR. LIEBLER: In view of the fact that we can expect this REACH dossier, which is I think going to be a very helpful document, we know it's coming. And so, you know, I strongly support the idea of tabling this until that material arrives, and also to take advantage of the intervening time to ask about cocamydyl because cocamydyl has the advantage of providing us data on C12, C14, and some C16. And, it's used whereas the lauramydyl which we specified previously is -- I don't think it's used or it's a sensitizer so it's we're not going to get data on that, as Jay pointed out to us in our discussion.

So, Cocamydyl we're more likely to get data and I think if we -- given that the REACH dossier is coming, there's time to generate some data on the cocamydyl. There are uses, so there would be some incentive. Then, we would actually have a nice package to make a decision on and not have to be in this mode of trying to use a threshold of toxicological concern rationale for an

ingredient as opposed to an impurity.

DR. MARKS: I will withdraw my motion, and the only thing I would like to add is the insufficient. I would like to include to get an RIPT on the leomydylpropyl dimethylamine.

DR. BERGFELD: I'm sorry, are you withdrawing to table or insufficient?

DR. MARKS: No, I think I move that it be safe as long as formulating to be non-sensitizing, and --

DR. BERGFELD: You would do that?

DR. MARKS: Well, now I withdraw it. We were having this discussion. Don, if you want to propose your motion I would support the insufficient data announcement but I would also besides the request of data you mentioned, include an RIPT on a lyomydyl propyl dimethylamine.

DR. BELSITO: Actually, yeah. I mean, looking at that I would have no problem. Actually, Dan, when you look -- and as Ron pointed out, I incorrectly read across and thought 6.5 was a leave-on because of the

dermal contact. It's a wash-off. The leave-on for cocamidylpropyl is.003, so I would actually like to see this sensitization and irritation on the oleamydyl propyl dimethylamie, and perhaps the penetration on the cocamydyl propyl dimethylamine, or the absorption, rather. Enough absorbed, then repro toxicicity. Go ahead not with a table but with an insufficient, but with the agreement that we'll wait for the dossier from REACH before bringing it back to the panel. But at least so industry is on alert, that we don't think the dossier is going to answer all our questions, particularly since the consortium has told us that we can't read across from that dossier.

DR. BERGFELD: Halyna?

MS. BRESLAWEC: We simply have no issue with tabling it, that was our proposal.

DR. BELSITO: We're not tabling it.

MS. BRESLAWEC: No, I'm sorry. With waiting for the REACH data.

DR. BELSITO: Right.

MS. BRESLAWEC: For that. With

regard to the additional insufficient information on the cocamydyl propyl dimethylamine, I want to point out that there are nine uses of that. So, we will go back to the manufacturer that does use this and ask for additional data. The Council as a whole will not be generating additional data to support that insufficient.

I would also like to ask Carol to talk about some data that are already in the report.

DR. EISENMANN: I don't know if you saw that there was a summary from the CATB report in there that includes some data in that summary on dimethylamine, which is the cocoa --

MS. BRESLAWEC: Cocoa?

DR. EISENMANN: Right, and in that report we were calling it midoamine. So I'd ask you to look to add those studies to the table, so you have all the studies on these ingredients in one spot. So, you may have missed -- there's a few more sensitization studies in that discussion on those

ingredients themselves now.

MS. BRESLAWEC: While they were in the original part, they just haven't been highlighted so it was easy to miss it.

DR. BELSITO: And you know, before, you know, requested things and then we looked at greater detail from other studies have decided that they weren't --

DR. BERGFELD: Helpful? Paul?

DR. SNYDER: Yeah, we also noted that this report has no absorption, distribution, secretion data and no tox data, as compared to the CATB report which didn't have absorption, distribution in the data but it had lots of tox data. So, we -- that's why we still are going along the lines that we want absorption and the other information that we requested in the insufficiency.

DR. BERGFELD: So, Ron Hill?

DR. HILL: I was just going to add the reason that I thought the sensitization would serve as a reasonable sentinel here is because at least -- yes, we don't know with certainty, but highly likely metabolism of the

amine generates an aldyhyde which leads to heptin generation, and that would be the mechanism most likely for sensitization, and to get above those levels where you weren't seeing sensitization enough systemically to have a possibility of repro tox, which of course I'm always worried about. It seems to be highly unlikely, so I didn't just dream this up in my mind, there's rationale that went with it.

DR. BERGFELD: So we have a motion, and I think it's been seconded to make it insufficient data announcement. We have a list that's been generated, I wonder if you have the list?

DR. ANDERSEN: My problem is that we're well-past that.

DR. BERGFELD: Oh, we are?

DR. ANDERSEN: We previously had issued an insufficient data announcement. It's time now to issue a tentative report. And --

DR. BELSITO: So then I think we have no other option to table it, because I

think we should wait for the dossier but industry should be on alert that when we get the dossier it's possible that the only ingredient that will be approved as safe will be the stearamidyl propyl.

DR. BERGFELD: So, we need a motion to table? That's your motion? A second?

DR. BELSITO: I'll make the motion.

DR. MARKS: Second.

DR. BERGFELD: There's no discussion on the table -- a motion. All those in favor of tabling?

MS. BRESLAWEC: Excuse me, is the stearamydyl and larger or just stearamydyl?

DR. BELSITO: I think, we'll probably feel the larger ones are okay. I mean, the data we're asking for are on the smaller ones.

DR. BERGFELD: So, there's no discussion, again on a tabled motion. All those in favor of tabling, please indicate. So, this ingredient has been tabled awaiting the REACH data. And a special request -- I think we should go through the special request

as Alan understands it.

DR. ANDERSEN: I think there were two areas of information. One is we've retained the request for sensitization/irritation data on alayamydyl propyl dimethylamine, and we'll take another look at Carol's suggestion that in fact maybe there are actually more data on that than needed. And then we added the cocamydyl propyl dimethylamine per cutaneous absorption.

DR. BERGFELD: Okay, alright. Thank you. We'll move on, then, to the next ingredient which is the pegolated oils.

DR. SHANK: These are mixtures? So, how do you do absorption on the mixture?

DR. LIEBLER: It's an ingredient --

DR. SHANK: Technically, how do you do that?

DR. LIEBLER: You mean the cocamydyl propyl?

DR. SHANK: Yes. Is that not a mixture?

DR. HILL: It is a mixture.

DR. LIEBLER: Yeah.

DR. SHANK: So, how do you do the absorption? Technically, how is that done?

DR. LIEBLER: So, what you could do is you could use LCMS to measure the C12 and C14, which are the two major fatty cyl version constituants of that mixture, and those would be representative of the penetration of the mixture. You could go to C16, and I don't think there's anything much below C12, but I mean that's a pretty straightforward assay these days.

DR. BERGFELD: Okay. May we move on to the PEGylated oils. Dr. Belsito?

DR. BELSITO: Yes, in March we agreed to re-open the safety assessment of a limited number of PEG castor oils and PEG hydrogenated castor oils to expand this to a total of 130 ingredients, which I will not read. And we found that these were safe for use when formulated to be non-irritating.

DR. BERGFELD: And that's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: Is there a second?

DR. MARKS: Second, and in the

present practice in use.

DR. BELSITO: Right, of course.

DR. BERGFELD: So there's a little modification of the conclusion, making it a standard conclusion.

DR. BELSITO: Yes.

DR. BERGFELD: Alright, any comment, discussion regarding this document? Don?

DR. BELSITO: Just that we need in the discussion the fact that at least one of these ingredients is a penetration enhancer, and formulators should be aware of that.

DR. BERGFELD: Anything else that's pertinent?

DR. MARKS: We want to clarify why we had dropped the 50 percent limit that had been previous in previous conclusions --

DR. BELSITO: Irritation.

DR. MARKS: Yes, irritation. And now the leave-ons are at a concentration of less than 22 percent, so we just wanted to make sure that was highlighted or put in the discussion, just that you wouldn't have to go back and try to figure that out.

And then, Ron Hill, you had some comments about the ingredient toxicity clarifying the components read-across?

DR. HILL: Right, but I think -- I guess it's probably all editorial. The major issue was that we had in the various sections dealing with, for example -- one example, carcinogenicity. We had components that didn't really need to be written about there, that it suggested that we had toxicology data that we in fact don't have because these are components that aren't relevant to the PEGylated oils themselves. And so what I'd really asked is that that all be pushed to the discussion section and encapsulated precisely so that we had a report that was much closer to truth in advertising here. Actually, adhered to truth in advertising, in that sense.

DR. BERGFELD: Those would be editorial changes?

DR. HILL: It's really all editorial. I think we captured everything yesterday.

DR. BERGFELD: Any other? Alright, call for the question. Again, safe, the PEGylated oils. Raise your hands. Thank you, unanimous.

Moving on to the alkyl esters, Dr. Marks.

DR. MARKS: So, I move that we issue a safety assessment of the alkyl esters as used in cosmetics to a tentative amended report with a conclusion of safe. But, there were some ingredients in the conclusion that we -- particularly Ron Shank -- felt should be deleted, and they were the ones that had all ethyl hexanoate as the last portion of that chemical name.

So, to begin with was like C12, 13 alkyl ehtyl hexanoate, and then going down, tridecyl exyl hexanoate. And there were 1, 2, 3 -- 16 ingredients. And Ron Shank, do you want to give the concern you had about the ehtyl hexanoates?

DR. SHANK: Yes. The European chemical substances information system lists ehtylhexyl, ethylhexonate as a reproductive

risk, and we don't have very much information in the report on the ethyl hexanoates. Therefore, including them I don't think is a no-brainer.

There is a question about a reproductive risk that has been raised. We don't have information, so I don't think we should include them as no-brainers.

DR. BERGFELD: Don?

DR. BELSITO: Well, we actually have some information but we agree that it is not a no-brainer addition, and we also agree to delete them. So, I don't think we have an issue there.

I would --

DR. SNYDER: We do, because also ethylhexyl stearate is also a reproductive toxicant, so we also propose to delete --

DR. BELSITO: No.

DR. SNYDER: -- the ethyl hexyls, I thought.

DR. BELSITO: No. That's the alcohol, remember. We had that discussion.

DR. SNYDER: Oh, that's right. The

ethyl hexyl is the front part of the name, it's the alcohol part we're less concerned about.

DR. BELSITO: But we also in the sheer addition of all these numbers, none of us really had time to look back and see what we're doing in terms of concentration to the ones that we were leaving in. And Monice was kind enough to stay up all night and look at the current concentration of use versus what we had approved, and there were quite a few of the ethyl hexanoates that have significantly increased. For instance, ceteryl ethyl hexanoate was less than 25 percent when we reviewed it. It's now 46 percent. There were several. The cetyl risinalyate and stearate that were less than 10 that are now up to 16, probably -- well, there was one decalyloate that was reported at greater than 50 now at 94. The ethylhexyl palmalotate less than 50, now at 78. I could go on and on.

I, at least, personally did not look at this document in terms of sensitization/irritation, other effects and

levels that were higher than we previously looked at. So, I would actually suggest getting rid of that ethyl hexanoate, getting rid of all the data on that but perhaps tabling this to go back and look at the data to see if it actually supports the higher use concentrations for chemicals that we previously found safe.

DR. BERGFELD: Jim?

DR. MARKS: I withdraw my motion and concur with tabling it until we clarify the point that Don has made.

DR. BERGFELD: So, is that a second for the table?

DR. MARKS: Thank you.

DR. BELSITO: Yes.

DR. BERGFELD: First and second. So, call the question to table this ingredient, please indicate by raising your hands if you agree. So we have -- okay. We have all of you? Okay, unanimous.

I would like to ask a question. If these are to be no-brainers and we have to go and do this level of investigation, why are

they being included?

DR. BELSITO: Because the ones that are the no- brainers have been approved and now are being used at levels that were not approved. So, that's the issue.

DR. BERGFELD: Okay, so that puts before us another level of investigation for all these add-ons. We will need to know the concentrations of use.

DR. BELSITO: Well, we have them and it didn't bother me until it became apparent that ones that we had ruled safe as used were now being used at levels that we had not looked at. So, clearly industry is not following -- they probably have data that support their safety, we just don't have it. So, I would like to see it because we have a significant number that are used on levels that we didn't see data for.

DR. MARKS: So, Monice, could you create a table to that effect?

DR. BELSITO: She has, and she provided it to me. So, the table is essentially done.

DR. MARKS: Okay.

DR. BELSITO: I think what Carol will need to do is probably go back and make sure the ones that are reported as being higher are in fact correct.

DR. EISENMANN: I don't have it.

DR. BELSITO: Oh, you made the table? Monice will give it to you.

DR. MARKS: This is the old concentration.

DR. BERGFELD: Again, I have to state that this does bring up the issue of the concentrations for all the add-ons, you know? So --

DR. MARKS: This isn't -- to me, the more problematic is not the add-ons. It's what do we do in the future if we get a re-review and we find this occurring in there isn't data that support the increased concentration with a lack of sensitivity. We would then have to say insufficient at the present.

DR. BELSITO: Yeah, I mean basically this was a re- review and we've now found in

the re-review that the concentration of use being used is higher than that we originally signed off on. So, it alone is cause to open the document.

DR. BERGFELD: Okay. Well, I think the minutes record all of this concern and we will need to explore this particular group of ingredients as well as future.

DR. HILL: By the way --

DR. BERGFELD: Ron and then Alan. Go ahead.

DR. HILL: By the way, I mean, one of the things that we did last time was group the ingredients and they're now tabulated that we can look at read-across. At least one of the reasons I made that request was that there are some unusually branched or differently branched alcohols and some different carbocylic acids for which we don't have data on either esters or acids, and there are a few of those that I had concerns because there was no systemic toxicology data at all for me, where I said -- are still insufficient in terms of data availability.

And Dan and I disagree about the ability to read across, but an example on decylinic acid component in these esters. We don't have anything for either esters or acids. We know that molecule has anti-fungal activity because decylinic acid is used in over-the-counter powders but we're not capturing any data. That's one example of several. There are some additional alcohols here and I've flagged them. We don't have any information on -- and same with the acids. They're a small handful, but they're unusual and they make it for me difficult to read directly across if they're in high concentrations of use in leave-ons.

DR. BERGFELD: Well, I think that you've flagged them in your document --

DR. HILL: I have.

DR. BERGFELD: -- and the staff can take a look at those and see what they can come up with. The document has been tabled and so there's time to do some work on it. Alright?

Again, Alan?

DR. ANDERSEN: Before we go on, I didn't see the issue of the use concentrations as anything out of the ordinary. Of course we would want to know the current use concentrations when we are adding something to a re-review package. So, it's not a new idea.

The fact that these had previously been found safe in the then-current practices of use and concentration does argue that we need to update that information, but that's a normal thing for us to do.

Laying it out so that you can see it is what's new, and I think message received.

DR. BERGFELD: Okay. Paul?

DR. SNYDER: Last comment. So, Alan. Regarding the ethyl hexanoate report that now we know the maximum concentration is not 25 percent, it's actually 78 percent, so can we consider re-opening that document and then adding in all the hexanoates and then proceeding? Because I think are we somehow obligated to re-open that report knowing that it was safe as then concentration was used? But we know now it's different, because it is

a significant repro toxin.

We did obviate the reproductive toxicity based upon metabolic conversion and exposures, but so now we have three full higher exposure, potentially, and just include all the ethyl hexanoates in that report.

DR. ANDERSEN: Yes.

DR. BERGFELD: Thank you, thank you. Alright, any other comment or suggestions? Alright, moving on to the next, which is methyl glucose, polyethers, and esters. Dr. Belsito?

DR. BELSITO: Yes, this is methyl glucose, polyethers, and esters. And in reviewing this document and speaking with Wilbur, it appears that what was searched were the actual ingredients and in fact we've looked at most of what methyl glucose or methyl glucoside is bound to and we thought that perhaps if we had data on methyl glucose and methyl glucoside that that would allow us to go potentially with a safe as used conclusion. And so, we recommended that this document be tabled to search the scientific

literature for toxicologic data on methyl glucose and methyl glucoside.

DR. MARKS: Our team had a different approach. We thought that we would move forward with an insufficient data announcement, and I'll let Ron Shank in a moment comment your strategy of approaching the safety of these ingredients.

So, if we did move forward with an insufficient data announcement, the data needs we would want are penetration of the ethers. We weren't concerned about the esters in terms of systemic toxicity because they would be hydrolized in the skin. We wanted geno tox data for both the esters and the ethers. We wanted the RIPT details of the methyl glucose susqui-compound on Page 13 where there is a lot of details missing on this susquiterate.

We wanted an RIPT on methyl glucose diolinate. There are case reports of allergic contact, dermatitis of this ingredient, and it's used at 2 percent so we were concerned about sensitivity of that compound. And then lastly, we just wanted impurities to -- that

could have been the first thing.

So, those were our five data needs to move forward. Ron, I will let you or the Rons comment on allowing the tact of tabling and using those comments --

DR. BELSITO: I think we're fine if you want to go with those insufficient data needs, you know, but I think that, you know, we need to incorporate data for methyl glucose and methyl glucoside. I mean, it can be done one way or the other, I guess, by going insufficient. It moves it along, so let's do that. I'll change my motion.

DR. MARKS: Second.

DR. BERGFELD: Any further discussion? Ron Shank, Ron Hill, Dan, Paul, Curt? No? I'll call the question -- oh, sorry, Tom. I missed you.

DR. SLAGA: No, I'm good.

DR. BERGFELD: Oh, you're getting ready to raise your hand. All those in favor, please indicate by raising your hand. Okay, unanimous, it's going insufficient. Do you want to read the insufficient list out loud,

Alan?

DR. ANDERSEN: I'll split impurities first, and saturation of ethers, geno tox for esters and ethers, RIPT details for the sesquitaerate, and an RIPT -- and I didn't capture that.

DR. MARKS: That was methyl glucose diolyenate. Yeah, that was based on case reports of allergy to this ingredient and a 2 percent use concentration.

DR. ANDERSEN: Got it.

DR. BERGFELD: Halyna?

MS. BRESLAWEC: I just wanted to point out in terms of the impurities, that is not enough of a reason to cause insufficient since that information was available in the supplier side. It just wasn't looked for deeply enough. That's in the same category as the additional data request. I don't think it warrants insufficient. The others certainly do, so.

DR. BERGFELD: Okay, so what you're requesting is that the staff look deeper for the impurities taken off the list. I think

that can be done, yes.

Alright, so we'll move on to the last two -- or actually, last three. The tin oxide, Dr. Marks.

DR. MARKS: I move we issue a tentative report on tin oxide with a conclusion this is safe.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion?

DR. BELSITO: Tin (IV) oxide.

DR. MARKS: So, that's the discussion, that we delete or editorial comments. We delete tin in the report itself. There's no need to have tin in the report, and that we confirm that where tin oxide is stated in the report that the valancy is IV. And I don't know how strongly you feel you want to put that tin (IV) -- tin oxide (IV) in the actual title. That certainly highlights it.

DR. LIEBLER: I think that's the smartest way to do it. It communicates very clearly what we're looking at, because I think the speciation issue is very important with

these compounds and we should be as clear as we can.

DR. BERGFELD: I see Ron Hill shaking his head "yes", good. Consensus. I'm going to call the question, then. All those in favor of safe, thank you. Unanimous.

Then, looking at the retinol and retinyl palmatate re-review. Dr. Belsito?

DR. BELSITO: Yes, we looked at this data and there were a couple of things. We didn't really get this usual table on the concentration of use. However, on Page 11 of the Panel Book under cosmetic, the -- one, two, three, four -- fifth line down it says that most products were found to contain either retinol or retinyl palmitate at concentrations of 2.2 percent weight/weight, which is certainly higher than the prior concentrations we had looked at. So, if that is true, it alone would, I think, require that we re-open the document.

I think that other reasons to re-open it is certainly these two have received a large amount of attention and there

are potentially other retinol products that could be added. So, I would vote to re-open it, to find out what the current concentrations of use are. Are they in fact up to 2 percent? And to add the other ingredients that can be added.

DR. MARKS: We second that motion to re-open. We wanted to do a robust review of the photomutogenicity of these compounds, the photocarcinogenicity, and the co-carcinogenicity. Tom, do you want to comment on these? Go ahead, Tom Slaga. And the geno tox.

DR. SLAGA: Yeah, there's really a large amount of new data that we have to scrutinize. And the way the photo co-mutogenicity and the photo co-carcinogenicity. And from the NTP report has a number of issues in it, even though there's a concern about the controls were positive with the claims, there is a publication now from Alan Connie's group that shows that a number of the creams used on humans actually increase the photo

co-carcinogenicity alone, and so we need to really look at all of this in detail.

DR. MARKS: And certainly we agree to open -- to add the seven retinol esters. To alert industry, we would like to see if there is data needs relevant to residual levels of retinol and retinyl palmitate in the epidermis, would be helpful if there were actually -- we know the residual levels. And we'd also like to know what the normal levels of retinyl palmitate are in the epidermis.

DR. BERGFELD: Any other additive comments? We're going to vote to re-open this group of ingredients. Seeing none, I'll call the question. All those in favor of re-opening? Unanimous. Alright, we're moving on to the last -- I would call it ingredient issue, and that's the triclosan and parabens. Dr. Marks.

DR. MARKS: Well, there were health concerns with both of these cosmetic ingredients for the triclosan, particularly the report relevant to increased sensitivity from this compound, and also the issue of

impaired muscle contractivity. We felt that neither one of these reports rose to the level that were of concern, and therefore would not change our previous conclusions of safe, so we move not to re- open triclosan. However, we felt there could be a letter to the editor, a press release, and a website announcement explaining our rationale of not opening the triclosans.

I'll start with that one and then we can move on to the parabens, because there's some other toxicologic concerns with the parabens, although we didn't feel we should re-open that one, either.

DR. BERGFELD: Don?

DR. BELSITO: No, we're fine with that. I think I have a little issue with your phraseology. I think we felt that the data that were presented were not relevant to the use of these products in cosmetics. They were somewhat contradictory in terms of the asthma. There were issues with the fact that while they looked at asthma versus atopic asthma, their definition was patient self-definition

of wheezing, which is a huge issue.

What they didn't look at that I thought was an important issue is atopic dermatitis, because we encourage people who are atopic staph carriers to use antibacterials, so they are likely to use more antibacterial soaps because of that. We don't know that data at all.

In terms of the triclosan on muscle effects, it was given intra-paraneally in much higher doses than people would ever experience in a cosmetic. So, we thought that the data was interesting. There were serious flaws in the one paper that dealt with sensitization, and the paper that dealt with muscle relaxation, which is not relevant to the use in cosmetics.

We would agree that some type of announcement -- that this be looked at -- very seriously be made.

DR. MARKS: To further substantiate that, Don, we also -- there was no link to IgE in the paper with sensitivity or endologic alterations.

There was an unexplained difference in gender that it occurs, sensitivity, in men and not in women, and this was a cross-sectional study which created problems with interpretation, also. So, we concur. We expect that will all be in the letter to the editor and summarized the reasons why we felt there was not -- this report should not be opened and the conclusion should stand.

DR. BERGFELD: So, do you want to make that a motion since that is a vote to re-open or not?

DR. MARKS: I move -- should we do these together or separately? I move not to re-open --

DR. BERGFELD: Separately.

DR. MARKS: -- triclosan.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion? Seeing none, all those in favor of not to re-open? Unanimous. Now, the parabens.

DR. MARKS: The parabens was included in that same paper with the triclosan

concern, where there were allergens to food sensitization. For all the reasons that we discussed were inappropriate for triclosan, it's similar for the parabens. And then, we had some other articles and, Tom Slaga, I'll let you comment about those.

DR. SLAGA: Yeah, the articles are by the same author. Localization of parabens in areas where the accumulation of these parabens. But the concentrations, the levels were so low even though it correlated where cancer would be, if you will, it really -- concentrations were extremely low. And also, they did a study using an immortalized cell line that was not transformed. But if they put estrogens in it, it would become transformed in a soft auger-type assay. And when they put the parabens in, different ones, the levels that they put in were at 10 to the minus 4 to 10 to the minus 5, extremely high levels which would be way beyond what we would find in cosmetics.

DR. BERGFELD: Any further discussion? Is there a motion to not re-open

the parabens?

DR. MARKS: I move that we not re-open the parabens.

DR. BELSITO: Second.

DR. BERGFELD: Second. Any other discussion? None? I'll call the question. All those in favor? Unanimous, not to re-open.

Alan?

DR. ANDERSEN: Did that also include the issue to receive the same level of public presentation or not?

DR. BELSITO: Yes.

DR. BERGFELD: Yes, I think generally speaking both of these fall under that umbrella activity.

Alright, we have the last item and Lillian Gill was going to discuss it because Alan was out for some of this yesterday, and that is the 2013 priority list.

MS. GILL: Yesterday Bart presented the priorities for 2013. We received some editorial comments on those, but I think the list of priorities we have -- let me see if I

can find our notes on that. We had some concerns about the groupings and making sure that the number of uses is supported across the grouping, and some consistency. This was from the Council. The Council also expressed their opinion that the phytosterols was too broad. They recognized that it is in the INCI dictionary but it would be difficult to get data. We continue to feel that because it is listed in the dictionary that phytostearols stay on that list.

The Panel approved the listing as is, suggested that for the magnesium sulfate that we look at the inorganic magnesium salts and not expand to other uses, and they wanted to look at what was on the phytostearol list first before eliminating any from that list.

There was some question about the re-review. In addition to changing that to the 2013 re-review list, there was some question about including the pentyrythril rosinate because this was an insufficient data, and why are we looking at a compound for which we did not receive data initially on?

That's sort of the general gist of the discussion.

DR. BERGFELD: So, the priority list has been presented to you and the teams agreed to what has been stated by Lillian. Alan, do we need to do anything further than just generally approve, or be informed that this is the list?

DR. ANDERSEN: I think that's all that we need?

DR. BERGFELD: Paul?

DR. SNYDER: One question. Should we consider all of the insufficient data for insufficient safety assessments that are based upon irritation -- absence of irritation data at use concentrations? Because those all sit out there as insufficient and by today's standards those no longer would be insufficient. They would go -- the conclusion would be changed as safe when formulated to be non-irritating.

DR. ANDERSEN: Well, that's an interesting proposal.

DR. BERGFELD: Right.

DR. ANDERSEN: What you're saying is certainly true. We have a different view of how we have been handling irritation. It has evolved, and there's no earthly reason why we couldn't when they come up in the normal course, add them to the re-review list and not blindly exclude them because they were insufficient.

It's do-able.

DR. BERGFELD: So we assign you that job.

MS. BRESLAWEC: Dr. Bergfeld, the Council has looked at that list of insufficient data pretty thoroughly and we're not really aware of any that are insufficient for that alone. I mean, maybe one but we're just -- that wasn't one of the correct --

DR. BERGFELD: Well, maybe we could have an official report back at the next meeting as to where all those insufficients reside? That would be good.

Donald?

DR. BELSITO: I guess what I want clarification on is -- because there were some

questions yesterday. First, if we previously found something to be insufficient and it's theoretically up for re-review and no one submitted new data, we don't re-review it?

Okay, number two. If we don't re-review it and find it insufficient again, does that two-year clock where it becomes moving into that other category start or do we have to review it to get it onto that two-year cycle?

DR. BERGFELD: Interesting question. Alan?

DR. ANDERSEN: Last October the clock started on all of the insufficient data ingredients for which there is ongoing use. So, it is started, it's inexorable.

DR. BERGFELD: Would you remind us again what's going to happen at the end of the clock?

DR. ANDERSEN: Well at the end of the clock there -- and I would have to actually look at the procedures to get the exact language, but --

DR. BELSITO: I think they made Don

safe.

DR. ANDERSEN: Well, that's what I wanted to be able to say was the exactly correct language. It goes into a should not be used in cosmetics kind of category --

MS. BRESLAWEC: Safety not substantiated.

DR. ANDERSEN: Thank you. There's the exact words. And that moves them out of insufficient data, and into a clear determination on the part of the Panel, and that is a huge heads-up for any potential manufacturer of cosmetic products who would want to use it that we need data. You know, that's -- so, it's something that will be happening when that two- year clock expires.

DR. BERGFELD: Can you expand on what the FDA was doing or maybe currently doing about that list of insufficient or safety -- what is that term again? So I don't say it incorrectly.

MS. BRESLAWEC: The term is safety not substantiated.

DR. BERGFELD: Safety not

substantiated. Are they acting on that? They were earlier sending out letters, but are they still now?

DR. ANDERSEN: Well, Stan can comment on what --

DR. MILSTEIN: We can look into that. I don't have an answer at this time, but we can certainly get one for you.

DR. BERGFELD: It would be nice to know because there was an activity of the FDA to take the insufficients and certainly the unsafes and send out letters to the industry.

DR. MILSTEIN: It is certainly of interest, continued interest, to us.

DR. BERGFELD: Well, thank you very much. I have come to the end -- okay, Don?

DR. BELSITO: Just one more point, and Jim may want to comment on this as well. Just for industry to be aware of the use of methyl isothyisolone as an individual preservative seems to be giving significant problems very quickly in both Europe and the U.S. and it may need to be something that we will go back to. Watch the literature, the

reports are coming out furiously. The Europeans are very, very upset about the levels that are allowed.

DR. HILL: I already flagged that in one of my books that we look at these. And there's actually a pair of these ingredients, and they're widely used.

DR. BELSITO: Well, the methyl chlorylisothyazilone was thought to be the issue, and in fact what we're seeing now is that the patch tests with MCIM in combination are negative but the MI is positive because the MI is too low in the combination but we've allowed it up to 100 parts per million in leave-ons, whereas the MCIM MI is allowed at 7.5 parts and the MI is only 1/4th of that. So, we significantly increase the concentration of MI, and we're seeing lots of -- well, you'll see our data in a couple years, because we just started looking at it. But the Europeans have been looking at it for a while and we may need to revisit that sooner rather than later.

DR. BERGFELD: Jim, then Curt.

DR. MARKS: Yeah, just for the record. I reclused myself from this discussion in the past, since Roman Halls which is a large manufacturer of this cosmetic preservative sponsored a number of seminars in Hershey which I directed. So, and act as a consultant, actually, with the first time that MCIMI was presented here at the CIR some years ago. So I'll continue to depend on you, Ron, to keep the panel alerted to this, and the comments that I had might be construed as a significant conflict of interest.

DR. BERGFELD: Bart?

DR. BELSITO: When did I become Ron?

DR. HILL: One of us got consulted, I'm not sure who. (Laughter)

DR. BELSITO: I may be two of you.

DR. BERGFELD: Bart?

DR. HELDRETH: I just wanted to ask for one point of clarification back on the priority list. Lillian had alluded to the inorganic sulfates that include the magnesium sulfate. Yesterday, one group had suggested that we keep that group as- is, and the other

half of the panel suggested that we switch that to the inorganic magnesium salts. I just wanted to get clarification on which way we're going to go.

DR. MARKS: I think Lillian presented in the latter. That an inorganic magnesium salts, and that was what our team suggested, unless the Belsito team -- unless Don's team suggests differently.

DR. ANDERSEN: I thought that what I had heard was that this could be left to the next stage. If in fact a broader list were searched and a literature review accomplished and the panel initial review flag some that you didn't want in, you could delete them. But you don't have the opportunity to delete them if they're not there, so that would be my preferred approach.

DR. HILL: I made a fairly strong statement that I didn't want to see sulfate salts with multiple metal ions, that the toxicology from where I sat unless somebody could convince me otherwise would be driven by what the metal was and not the sulfate.

DR. ANDERSEN: That may indeed be the case, and we will be able to demonstrate that based on the literature review, and then make the decision to kick them out.

DR. HILL: Well, that got to the discussion of how actually -- I think Carol was speaking to it. How quickly they'd be able to notify people in industry that this ingredient was going to be out there and that data would be needed, and that they didn't get that -- either she had to do a lot of work to include hundreds and hundreds of ingredients where we might end up with a list of only 20, or like that. So, and then we even asked them -- our procedures, then, such that we give too short of a window once that list is finalized for data to be collected if papers are in Japanese or Chinese and need to be translated, all of that comes into play.

DR. BERGFELD: Don?

DR. BELSITO: Well, since there seems to be such an issue about this, why don't we just put the list together and not put any data and then look at what we feel

should be just kicked out based upon whatever reason?

DR. BERGFELD: I think that's what Alan's proposal was. So, I think that we can generally agree to do that.

So, we have come to the end of the meeting. I want to thank everyone for their hard work and participation.

(Whereupon, at 10:57 a.m., the PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

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I, Christine Allen, notary public in and for the District of Columbia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

Notary Public, in and for the District of Columbia

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