125th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING

MAIN SESSION

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P R O C E E D I N G S

(8:30 a.m.)

DR. BERGFELD: Officially, welcome everyone and good morning to you. This is our 125th CIR Meeting and this is a team day. And I wanted to make a few comments if I could. We're going to have presentations on infant skin and the hair dye patch testing this morning, but we do have 13 documents to go through and two of them have -- an additional two have some new data and we are revising the phthalates again.

Specific comments to the documents themselves, they continue to change and they're very well done. I gather the text is shrinking and that we're adding more information into the tables and the text contains summaries referring you to the tables. We have an increased use of non-animal testing with lymph node assays and the epi ocular human cell cultures and the QSR looking at eye irritation and sensitization. I wonder if we could consider in the teams the following. The read-across, it should occur in the discussion each time and be standardized in some manner. It does not always do that. And in several documents

today in the review pre this meeting in preparation, I noted in the discussion some of the writers had added some discussant points to make sure we were aware of them, and I thought that was exceedingly helpful and I would recommend that it would continue. Also, the Table of Contents varies from document to document and some have human and animal studies; some just have the general category of study. I wonder if we could standardize that. And I really like the table that precedes the document with all the ingredients listed and what studies are available within the text just to make sure we've checked them all. And particularly I want to thank the CIR Science and Support Committee for their valuable input. They appeared to be digging in more and giving us more recommendations, so I certainly want to thank them.

So with that I'm going to turn the meeting over to Alan, who is going to introduce our speakers.

DR. ANDERSEN: Okay. Thank you, Dr. Bergfeld. I think the one additional piece of information that I put out this morning at each

panel member's place and there's copies at the back of the room is a Guidance for Industry that FDA issued last Friday limiting the use of certain phthalates as excipients in drug products. This did not come out of the Center for Food Safety and Applied Nutrition, the Cosmetics group. This is a guidance that was issued by the Center for Drug Evaluation and Research. As I went through it I didn't see any new studies. It does look at the question of phthalates differently than we have. It takes a precautionary principal look and says, well, since there are alternatives we don't want you using phthalates. So that is available for when we get to the phthalates discussion.

We have two presentations this morning and the agenda has hair dye self-testing first. And so we'll do that first. Carsten Goebel, Procter and Gamble, representing the Personal Care Products Council Hair Coloring Technical Committee. And after Dr. Goebel presents I expect a lively discussion from the panel.

DR. GOEBEL: Okay. Thank you very much for inviting me and giving me the possibility to present to you an overview of the work that is

ongoing on the skin allergy alert test. It was announced that I work for Procter and Gamble, but also what we do is we work in Cosmetics Europe on this approach to look more closely into the current skin allergy alert test. And today there has been some concern around this and the presentation today will provide you an overview of how we look at the pros and cons.

So the outline of this presentation is first of all hair dye allergy alert testing, how is the legal situation? Then the criticism to consumer self-testing in general. Then wide testing, the industry objective. And finally, the industry proposal for a harmonized allergy alert test which we do not have yet as you can see from this.

So I think what was already discussed within this team, I do know from my colleague Julie Skary, who did that presentation in the beginning, how is the situation over here in the U.S.? And as you can see down there, the panel advised the cosmetics industry to recommend that the open patch test for (inaudible) hair dye products evaluated 48 hours after application of

the test material. This is more or less one of the pieces that is important to consider in the U.S.

The example of the worldwide use of this test related to what we have just seen for the U.S. this year. So there's a legal requirement to do that test in the U.S., Canada, Japan, Australia, Brazil, and there's a recommendation phrase in the EU until 1992. And this test is also voluntarily practiced in the EU and in Latin America and in Asian countries.

So the first criticism about the test was coming from the EU Scientific Advisory Board, so the SCCP in 2009, and this was about a potential risk that self tests result in indication of sanitization. And the second point was there would be a potential risk that self tests with products give forth negative results. And finally, the proportion of hair dye allergic individuals who have positive reactions to the self test is unknown. So that was starting the debate in 2007.

So let's go back to the idea why do we from an industry perspective think we need an

alert test? So currently the idea is to alert consumers about a potential risk of not tolerating the product which makes sense from our perspective. And also to alert them about any perceived differences versus normal skin condition at the test site that should alert the consumers not to color their hair and to seek medical advice. So this defines already that the alert test, so the (inaudible) is not seen as a diagnosis but just to alert the consumer not to color and to seek further advice. So to avoid adverse reactions that may happen in case of a severe allergy. Along with that the idea is, of course, to protect as many consumers as possible from severe allergic reaction due to product usage as I just said.

And finally, the allergy alert is not intended for consumers with non hair dye allergies, so as you may all know we have clear warnings on the hair dye packages that we hope make clear to the consumer that they should not dye their hair if they have an allergy.

So to put that into a kind of visual, what we have to do as industry now is to establish

equilibrium between three independent variables. And of course, the one variable is the risk of induction of sanitization; and of course, the second key piece is the allergy efficacy; and the third, and I'm not going to talk about this one today is compliance. So the proposal that we are working on now is that the allergy alert test conditions should reflect normal in-use conditions. And so the first step to prove that this is working is a proof of concept study to address points one and two on this slide.

So in addition to what I showed you what the SCCP did in 2007 regarding the criticism, there are recent review articles in contact dermatitis dealing with the so-called consumer self test. And one of the publications is from Tyson et al. and the other one is from Orton and Basketter. And to make that as an overview for all of us and hopefully easy to understand I tried to put together a table to point out the key criticisms. And one, the first one is that the authors didn't consider the current practice as no screening but diagnostic test. And when we look to this from our perspective, we see that

what we would do to understand if the allergy alert test can recognize the cases that are allergic. We consider the proof of concept study advocates control study and generally the allergy alert test is not aiming for diagonals but just to alert consumers to not color in case they would. So this is not a screening test from our perspective.

So the other key point was no validation according to basic scientific criteria related to validation. And, of course, we think that violation against the diagnostic patch test and proven clinical relevance is important because, of course, we are looking into hair dye users and the question is how can we understand the allergy alert test, how it performs, if we do not look into hair dye uses?

And, of course, the other question that is coming along with that is the difference between the biological target population and the target consumer. However, if you want to run a proof of concept study, if you want to understand if this test is performing, then of course you have to look into cases with an allergy.

The next criticism was that no evaluation of the appropriate population group was performed, and again, if we look into the study to be run, we think this is irrelevant to analyze the biological response in allergic cases because again this is what we need to show.

And so the other point that is addressed here is once we run the allergy alert test, taking the hair dye use condagents on application time for a maximum of 45 minutes, there is no higher exposure compared to hair coloring of class except of one additional exposure that you would do 48 hours prior to hair dying.

And finally, this was addressed already also by the SCCS, the risk of sensitization. And so in the proof of concept study that I will describe to you later, this is, of course, relevant to analyze the possibility of active sanitization in controls because we will also expose controls to look into this. And then we'd better understand if there is any risk associated with that.

Finally, the next point was reading of skin reactions by dermatologists and not

consumers, which is, of course, important. And of course, now with that coming study this will look independent or so-so. The reading will be done independently by consumers and by dermatologists.

And finally, the criticism was that there is no harmonization of recommendations, instructions that industry is currently providing on the packages and the leaflets. And of course, the proof of concept to come is to generate a basis for harmonization.

So now let's have a closer look into the key criticisms. So regarding the induction alerts or the allergy alert test, again, if an allergy alert test may be making a news conditions, then of course there is the same inductile risk of the actual condition use because it's rinse off at the same time so the exposure is considered to be the same.

Of course, we cannot exclude that an increased application frequency, however at a different site, due to the performing of the allergy alert, may increase the forming of the allergy alert test may increase the induction

risk. The perspective is that the value of the alert test in providing severe allergic reactions that would be followed -- that would rise after hair coloring, would outweigh this potential risk. And again, we therefore run that proof of concept study now..

So the second key point was the alert efficacy. So the question of false negatives and validation, and so the objective of the allergy alert test is to alert and to prevent reactions to an individual hair coloring production and individual hair dye consumers. So this is no diagnostic patch test, no detection of a subclinical sensitization. It's just the alert function that is important to look at. And we have generated, published evidence that with a 45-minute exposure we can identify at least severe reactions that we need to avoid. And there's another publication from 2005 where it was shown that consumers can identify a reaction. Without dermatological supervision they can identify a reaction.

So now again to put these into perspective for what we will propose, there is a

multi-center proof of concept study for the allergy alert test planned that will address the efficacy of the allergy alert test under use like conditions. And to give you some data of what is published already on this question -- let me see whether this is working here. L'Oreal did a study in 2005 where they looked into positive reactions after contact time of 48 hours. There was no occlusion. There was the history of hair dye reactions with the individuals that were selected. There was no mix with developer. If you look at a product that contained a concentration of 0.1 percent, which is an applied dose of 45.7 micrograms per square centimeter, then they could alert 27 of 34 people. And when they were looking at 34 of 34 --

DR. BOYER: There's a pointer.

DR. GOEBEL: Thank you very much. Perfect. Thanks. And this might be easier.

So, and if they were increasing the concentration to a product that would contain like 1.5 percent with a much higher dose, of course, then they were able to alert all 34 individuals.

We did a study using a fenderben chamber with a 45-minute exposure maximum, so mainly the exposure was between 5 and 30 minutes. And again the individuals had a history of hair dye reactions, and we mixed, as we would do now with developer, to really have the hair dye product as you would apply it to the hair. And again, the exposure period was, in most cases, approximately 30 minutes as you would do for hair dying. Five minutes was only because it was removed if there was a severe reaction upfront. The maximum concentration of PPD in hair dye products was 2 percent, and we just had a higher dose per unit area as the applied dose. And again, this is no difference because anyway, the dose you apply is considered an infinite dose. So as long as you have enough PPD on the skin, the penetration into the skin will not be different.

And I haven't prepared a slide to show this to you. We have data showing this. And more or less the duration of the exposure is, let me say, determining the dose that you get inside the living skin which then would cause the immune response. So the elicitation response in this

case. And with this approach we could alert, let me say, all 3-plus individuals or 2-plus individuals and 12 of 18 1-plus individuals. So this is related to the diagnostic patch test that was known for these individuals with, let me say, use- like exposure.

And finally, we are working on a publication together with KPSS Kao where they only also used 45 minutes and different concentrations. And again, with high concentrations they were able to elicit the reactions in all allergic individuals, so 29 from 29. And not with lower concentrations.

Okay. So now I already talked about the proposal for the allergy alert test. And why did we provide this? The main common allergy alert test parameters should then be, if we come to a harmonized protocol, the product tested as to be used. So the on-hair concentration, skin contact time, test application side, the reading time should be preferably 48 hours, and the additional parameters to be considered would be the test system. So the amount, the dose per unit area, the size of the application side, and this will

be an open test, of course, as hair dying is also open.

And so the aim of the study again is the evaluation of the impact of several parameters influencing the sensitivity and specificity of the new generation allergy alert test. And this is just a repetition of the slide that you have just seen. So open 45 minutes. Product applied. The hair coloring formula mixed with the developer, so the typical in-use ratio, the reading time will be directly after test removal. So after these 45 minutes and in the initial period of 15 to 20 minutes. Day 1, Day 2, Day 4, and later, if necessary. And there will be two test sites, like the retro-auricular region versus the volar aspect of the forearms.

So, and then what is the target group for that proof of concept allergy alert? So when you look at this slide, of course, we have the general population; then we have hair dye consumers; then we have PPD-positive subject that may or may not be hair dye consumers; and then we have our target group, which is PPD-positive subjects with clinical manifestations of allergy

to hair dyes because from them we know that there is the relation to the hair dye allergy.

So then, of course, we will evaluate the robustness of the test. So the robustness is determined against a gold standard, and this is a defined procedure to establish whether someone has the characteristic of interest. And the gold standard for hair dye allergy is defined as the elicitation or not of a clinical reaction of allergic contact dermatitis by the application of a particular hair dye product in the consumer population and not as absence or presence of PPD allergy. So, of course, this test is an alert test and not aiming to diagnose a PPD allergy. So therefore, an allergy alert test should be benchmarked against this clinical reaction and not against the diagnostic patch test. So this is the idea. So the subjects will be individuals with a history of allergic reactions related to hair dyes and a proven allergy to PPD. And so again, the message of application will be that we will use rising concentrations so that they will be representative of shades on the market.

So the evaluation of the allergy alert

test protocol here. So the ability to do a self test correctly -- if the self test correctly classifies individuals into two categories -- positive and negative -- is assessed by two parameters. And I think I don't need to explain sensitivity and specificity. And this kind of the standard how this will go.

These are the increasing concentrations. So what you see here is just the concentration in the products before mixing. So you see from 0.1 to 4 percent. And if you dilute this with a developer as you would do under hair dying conditions, then you have what would be considered the use concentration. So 0.05 up to 2, because this is the highest allowed concentration of hair dyes in the EU. And the dose applied in micrograms per square centime is 27, 135, 405, and 1,080. And so this is then again Product A would be representative of light shades; then 0.5, the concentration is representative of median shades; and 1.5 is dark shades. And this dose, this applied dose is the equivalent dose to the diagnostic patch test approximately. Of course, the difference will be the exposure time.

And, of course, there is a control test material that won't contain the hair dyes.

So the study design, the idea is to have 40 to 50 valued cases. So we will recruit 60. Each PPD-positive subject will contain -- sorry, will be tested consecutively with the product. So with the rising concentrations from product A to D and control product Y because there could also be an allergy to other ingredients in the formula. There will be a rest period from three to six weeks between the test applications if you would need to go up to the rising concentration, of course. If the application of an experimental test product gives rise to a definite allergic reaction as described here, products containing higher concentrations of PPD will not be applied. So if we have identified a positive reaction, then there is no need to use a higher concentration. And, of course, the subject will be regarded as positive. So there will be 15 subjects per experimental group that will serve as PPD-negative subjects so it's controlled. And they will be tested with that control product Y.

So as a follow-up, there will be a

diagnostic patch test to be PPD that will be performed three weeks after a negative or doubtful reaction to product E, which is the product with the highest concentration in the PPD-positive subjects. A diagnostic patch test to PPD and the other ingredients of the hair dye formulations will be carried out three weeks after a positive reaction to product A, B, C, or D in control subjects. The ingredient will be tested -- sorry -- the ingredients will be tested at their usual diagnostic concentration or at product concentration. So depending on what is needed here.

So a diagnostic patch test to the dye ingredients of the control population will be carried out after three weeks in case of a positive reaction. And whenever possible, we will do a use test if there is no reaction with the individuals. So that is just the basis.

And so how will that multi-center look like? So we have clinics. These are the clinics across Europe that have agreed to participate, so it will be Sheffield, Groningen, and Heidelberg, Graz in Austria and Rome, and Krakow is still

talking to us. They may also try and participate. And the planning of the study is currently going on. So, of course, I showed you the selection of the clinical center principal investigator and monitor of budget estimation and all that kind of administrative stuff, if you will, is currently going on. So, and early next year we consider that the study could begin. And then we have the testing phase and the testing of the controls. And finally, the photo op and the statistical analysis, and finally, the final study report. So, of course, because we work with so many clinics and we need to have that certain period of time.

So as a kind of summary, the proof of concept work on the allergy alert test carried out is expected to allow the assessment of variations in the test parameters, the robustness, and the independent evaluation by subjects and dermatologists.

And finally, I would like to thank you for your attention and I'm open for questions..

Yes.

DR. BELSITO: Well, I have several questions. I guess the first is what is product

Y? Because one thing that concerns me is that as we read in today's report and as the dermatologists now, many people who are PPD allergic also react to para-Aminophenol, which is oftentimes combined with PPD in hair dyes. So I'm wondering how this test would pick up that combination allergy?

DR. GOEBEL: So the idea of a test product is to only have one primary. So that would be PPD in this case. So there are products out there that only contain one primary. So no para-Aminophenol would be used. So the couplers that will be used will be resorcinol and (inaudible) aminophenol. So we have an understanding of how allergic reactions to the couplers would look like. So compared to PPD they are considered to be much lower.

DR. BELSITO: But, I mean, I guess my point is it would be important to understand how this test would work when you have cross-reacting substances in your test product, like PPD and para-aminophenol.

DR. GOEBEL: I mean, so you mean regarding the individuals we have chosen? Or you

mean --

DR. BELSITO: Regarding the materials you chose to test to see whether your test was reliable.

DR. GOEBEL: I mean, there are two points, and maybe I'm getting you wrong here. But one key thing that the majority of all individuals we see, they react to PPD. So therefore, we have chosen PPD as the key allergen to run that proof of concept study. And the other thing would be if you -- if, let me say, hair dye consumers on the market would run the alert test with the product they are going to use which may contain then para-Aminophenol or any other dye, they would have that alert in case they would alert to another hair dye ingredient than PPD, for example. So this is the idea behind this.

MR. BELSITO: I mean, again, I guess I'm not sure that they -- your test will show us that they have the alert that it would work for those other ingredients. That's my question. It looks to me like you're studying only PPD and not other ingredients in hair dyes. And we just saw that your test does very well for people with robust

reactions but not as well for people with 1-plus reactions and misses some of them unless you boost the concentration.

DR. GOEBEL: Right.

DR. BELSITO: I guess I'm just a little concerned as to how this would work when you mix PPD with a cross-reactor para-Aminophenol and you boost that concentration a little bit. It's just a thought.

The second issue is are you going to issue people those little templates so they know exactly how much of a skin surface area they're supposed to apply it to? Will that be in the box?

DR. GOEBEL: That is under discussion, so that will also be a consideration once we have the results, to understand how we can make sure that the amount they apply remains, let me say, a thing that is easy for them to do. Right?

But maybe to come back to that question. So how we look at that initial question, how we look to the allergy alert test is so what we want to avoid, what is the key thing is that people get, let me say, severe reactions at the head, for example, because this is what you don't want to

see. And so we would accept with using the exposure time of 45 minutes, if they wouldn't react under the conditions of hair dye, you apply that directly to the skin, for example, leave it there for 45 minutes, and the assumption is then if you would do that on the head and nothing happened here, that nothing would happen because you just tolerate that concentration, which would be true for all dye ingredients in the formula. So what the alert test can do, because it's not a diagnostic test, is that it can alert the individuals at risk. Because once you would detect something, at least you would feel it somehow different. We don't expect consumers to be dermatologists, of course. This should just alert them to go and see the dermatologist or at least to stop using the product. This is the idea.

So if an allergy has no clinical relevance under hair dying use conditions, which would be true for all dye ingredients, we would accept that the test would at this time not alert the individual. And then we wouldn't consider that this individual would get severe reactions because then there was no reaction at least.

However, I understand that this is a compromise. It is not the diagnostic way in looking at it because I think there is the balance we have to keep -- oh, sorry -- a diagnostic test on the one hand side which needs to maximize the exposure and to understand does the individual really have a problem? Or we just want to alert them to go and seek help or stop hair dying.

DR. BELSITO: And I guess my last question/comment is you chose only one center where people have traditionally very dark hair. All of your other centers are in England, two in Germany, and one in Holland. Why didn't you look at Spain and Portugal as centers in addition to Rome?

DR. GOEBEL: Yeah, that's a good question. And we tried. But it's not so easy to get, let me say, centers signing for doing this together with us. So Italy was the only one that really could provide sufficient individuals in one center so we said there must be at least more than 10 they have, best 15, to make it really a reliable thing. Once you look into hair dye -- allergy proven hair dye allergies, so with

problems of the individual related to hair dying, then they don't have that many. So that was easiest to get in the UK, in the Netherlands, for example, and in Germany. I don't know why this is but I agree with you. You would assume darker shades would be used in Spain, but I don't think that's necessarily the case because fashion is also now, let me say, advertising dark shades a lot in the more northern countries in Europe.

DR. BELSITO: Well, if you're interested, you know, Marguerite Gonzalo in Coimbra.

DR. GOEBEL: Yeah.

DR. BELSITO: I'm sure she must have a good number.

DR. GOEBEL: We talked to them..

DR. BELSITO: Ana Jimenez in Barcelona.

DR. GOEBEL: I'm not 100 percent sure whether we also talked to Barcelona, but at least we did -- and we also talked to -- and I've forgotten the name -- to the Lisbon clinics. So, but that was difficult for them. They may didn't want to join for other reasons. It was not only the reason that they didn't have enough hair dye

allergic individuals.

DR. BELSITO: Thank you.

DR. MARKS: So in the last century I did a fair amount of work on this particular question and actually a group of us had a patent on a self-adhesive patch containing PPD. And some of that's published in Contact Dermatitis. You could search it on PA Patch. That's what we named it at the time although we changed.

First, concerning the consumer reading the patches, they were very good. We almost had 100 percent concordance of positive questionable and negative. They could read negatives and positives very easily. Like you, the advantage of this self-impregnated adhesive patch within the acrylic polymer was that you knew exactly what the dose per centimeter square was going to be. There was no question, and the consistency of, as you refer to it, the alert test. My question was, looking back at this now, the main thrust of this was to, again, as you would do in this, put in a package some sort of alert test. I think that in the U.S. probably very few -- I haven't seen any validation of this -- but very few consumers

actually get tested or do a test before the hair dye is applied. I think it's almost nonexistent.

And the other comment, again, I don't know the statistics on this, but at least in my own personal experience, the number of severe reactions is quite rare. Otherwise, obviously, for consumers it would be considered a dangerous procedure and they wouldn't do it.

So when I looked at these articles that were supplied to us, my first question would be is this regulation overregulated, meaning the requirement that consumers be tested prior to hair dye; that the reactions are so infrequent. And in patients, by and large, when they get a more minor reaction, will come in. We have rarely seen the reaction where there's tremendous swelling of the race, the edema of the eyelids, impaired sight, and that sort of thing. So mainly comments, not questions.

DR. GOEBEL: Maybe if you allow me, I think it's a good point that reading for the consumers was in your experience easy for them to understand to do which is a good thing. And I think the other question -- the other comments,

just that severe cases are rare; that's true. They are getting more attention in Europe now. So this is why the situation is open. And I think in Europe what is ongoing is the question regarding induction of sensitization because you have a prolonged exposure period under some of the recommendations, so leaving the product, if you will, either diluted or not diluted, on the skin for 48 hours rather than rising it as you would do under hair dying conditions. And my personal point in here is just to say what you mentioned regarding compliance, which is also very true. I mean, this is to offer people the possibility to check. And again, we clearly recommend not to use in case you have a known allergy, but we don't know how people behave on the market, especially maybe retail consumers. So this is to give them at least a means to help. And in Europe we have a consumer website with a kind of explanation. This is called Color Well, Color Wise. So people can go there and get information on how they should do the test so that they could get help to understand why this is important. So one idea is to really increase the education, also for the hair

dressers to avoid the few, let me say, severe cases we see, to really raise the understanding that in rare cases there might be severe symptoms that you may experience.

DR. MARKS: Don, is your experience the same as mine that seeing severe reactions to hair dye products is uncommon?

DR. BELSITO: I think most of them are mild to moderate.

DR. BERGFELD: Thank you.

DR. GOEBEL: Thank you very much.

DR. MARKS: And what is the statistics on an adult population? What percentage of women dye their hair? So if it were really -- even though we know and test systems that these are strong sensitizers or moderate to strong in the consumer market it seems like it must be very rare because what percentage -- the high percentage of adult women dye their hair with permanent hair dye.

DR. GOEBEL: Yeah. It's a quite high percentage here. I don't know exactly the number but at least I think you can consider like 60 percent or so.

DR. MARKS: Yeah, that's -- and we did like you with this PA patch, had a much reduced exposure time. We could actually dye -- I'd have to go back and look at the data, but if you applied the patch for as little as one hour in some individuals we could make the dye. As you said, the alert test. I forget what we settled upon. It was less than 24 hours as I recall.

DR. GOEBEL: Okay. Thank you.

DR. ANDERSEN: Ivan, I'm going to let you introduce yourself.

DR. BOYER: I just need to get my slides up. Actually, Alan -- Alan asked me to brief you this morning briefly on the infant skin topic. And I'm going to attempt to do that.

And actually, more precisely, the topic is absorption through infant skin. And this includes the development of a couple of factors. The development of the diffusion barrier which is largely -- which is almost exclusively sometimes attributed to the stratum cornea and also the development of the biotransformation enzymes with biotransformation capacities of the skin which can also influence just how much can be

absorbed through the skin into the systemic circulation. We're also going to talk a little bit about diaper rash, which can have the potential to influence absorption through the skin.

This topic emerged as a result of the discussions, the panel discussions at the March 2012 panel meeting. And basically, we were talking about the Council's recommendation, the Council's request to the panel to re-examine a parent's parabens safety assessment in light of two recent SCCS opinions. And one of them in particular, which they refer to as a clarification, addressed specifically the Danish ban on parabens in products intended for use on children less than three years of age. So the panel remarked, the panel noted that the literature on infant skin seems to be pretty much scattered throughout the literature. It's not unified to any great extent. And the panel requested that the CIR staff prepare a summary report or an overview report as a step toward advancing the discussion.

So what I'm going to do is present some

information from the draft report, which we submitted to the panel just last week, and I hope to get some feedback from the panel and some direction about the way forward.

I have a lot of slides, so I'm going to go through them very quickly. They're actually fairly detailed, and I think at the very least they serve as a fairly good outline, a detailed outline of the draft report. So I hope that the slide set itself is going to be helpful.

The skin -- we're going to begin with development of the skin. A lot of this is simply going to be a review, particularly for the dermatologists here. It develops beginning -- during the third trimester -- during the first trimester of pregnancy. And then by the third trimester of pregnancy, the stratum corneum is fairly well defined. The rete ridges are well defined. That's the wavy undulating layer of the skin at the boundary between the dermis and the epidermis. And also there's a development that occurs during the third trimester of the vernix. The vernix is that cream cheese-like substance that covers the skin, and it protects the stratum

corneum from maceration, from getting overly softened by bathing in the amniotic fluid in utero.

Now, a full term baby has all of the skin layers of an adult. And, in fact, from a histological point of view or an ultrastructural point of view, an anatomical point of view, from all of those point of views, the skin really doesn't go through a whole lot of change over time after birth.

The stratum corneum is an effective barrier at birth. And even in premature, even in severely premature infants, preemies are born 10 weeks prematurely. They will develop an effective stratum corneum, an effective diffusion barrier within a matter of a couple of weeks, two or three weeks or so. And, in fact, just for example, phenyleProcter, if it's applied to the skin of a pre-term or a premature newborn, is going to cause a blanching of the skin. And that's a reflection of the ability of the drug to pass quickly through the stratum corneum and stimulate the contraction of the blood vessels in the skin.

On the other hand, two or three weeks after birth, even in the most premature babies, we don't see that effect. There's no blanching effect. And we don't see any of that effect in full-term babies at birth. Or certainly within the matter of a day or two after birth. The stratum corneum, as I said, it is an effective barrier at birth, although it does undergo some additional changes. It does change subtly based on some measures which we'll talk about in a little bit even after a full term birth. And even one year or even two years after birth.

The epidermis continues to thicken for about four months after birth and this is largely due to the proliferation of cells and that basal layer, and proliferating cells cause amounting, a heaping of that layer. And so you get a deepening of the rete ridges.

And there is a hydrolipidic layer on the skin pre- birth, at birth, and from then on. It is an oil in water layer, and it is a protective layer and it is sometimes referred to as a hydrophobic mantle. And it's largely a mixture of sweat and sebum. Sebum secretion begins or

it's actually stimulated by in utero exposure to maternal hormones. So when the baby is born there is no longer that stimulation. Sebum secretion drops, and by about six months of age or so it's relatively low. And it doesn't return to adult levels until around puberty.

The triggers for development of the skin, for the rapid development of the skin, particularly when we're observing a pre-term birth, we know that basically from a drying of the skin that occurs over several hours or so after birth, that increases the frictional forces, the abrasive forces in the skin and that friction, that increase stimulates the proliferation of cells in the outer layers of the skin. And in terms of the molecular mechanisms for the accelerated development, we don't know a whole lot, although it seems pretty clear that skin surface acidity has a role, as do calcium ion gradients and activators of certain receptors. Local activators. Activators in the skin.

And these changes that I'm talking about, these rapid changes that occur during the first month or during the first three months after

birth are largely reflected in measurements of the biophysical parameters like the transepidermal water loss and the skin surface pH, but also in various measures of the total water content of the stratum corneum. And even the gradient of water through the stratum corneum. And parameters like water absorption and desorption rates in the skin.

The skin surface pH is important not only to maintain the normal function and to enable the normal development of the skin. It also fosters the growth of the normal skin microflora in indirect ways and in direct ways an acidified skin surface protects the skin from pathogens.

Hydration, as I mentioned soon after (inaudible), the skin gets fairly dry fairly quickly over the course of the next days and weeks, several weeks or so, and typically the hydration will then increase. It will then build up over the course of the next several months. And based on many of these basic parameters -- hydration, skin hydration, stratum corneum hydration -- seem to plateau around that third month, although there are some measurements indicating that there

are still some subtle changes going on that can continue to change. Some of these parameters, capacitants in particular, at least in one study, capacitants can be statistically significantly lower in children, in infants up to about two years or so of age compared to the capacitants that was measured in that particular study in the adult population.

So in addition, children are prone to developing diaper rash. It's also referred to as diaper contact irritation dermatitis. And they are particularly prone from about six months of life to about a year of life. But it continues to be a significant prevalence up to about two years of life. And the primary cause for diaper rash is the prolonged exposure to that mixture of urine and feces. The urine moisturizes the skin. It keeps it very moist. It keeps it very hydrated, very wet, and it's under the occlusive or the semi-occlusive conditions of the diaper. And what that does is it softens the stratum corneum and it increases the coefficient of friction of the stratum corneum so that even just the inside surface of the diaper rubbing against the skin is

enough to chafe the skin and can chafe the skin.

In addition, there are fecal enzymes that will convert some of the urea in the urine to ammonia. And what that does is it raises the pH and that alkalinity or that move toward alkalinity is going to in turn reactivate lipases and proteases in the feces. And those two types of enzymes in particular can then work together to break down the lipid structures and the protein structures of the stratum corneum. And so the result, the thinking is that this could compromise, could be responsible for a compromise of the barrier function of the stratum cornea.

So in summary, for this particular topic, the stratum corneum is an effective semi-permeable barrier soon after birth, if not right at birth, although there are indications that it continues to change; it continues to evolve; it continues to develop maybe subtly over the course of the next month or two. And based on some of the parameters, this development can continue up to about one year or maybe two years or so. And, of course, episodic diaper dermatitis -- diaper dermatitis is inevitable.

It's going to happen from time to time in infants wearing diapers. That has the potential -- it hasn't been very well investigated as far as I know, as far as I can tell from the literature that I've looked at, but there's no doubt it's plausible that it can have an influence in terms of how much or how quickly something applied to the skin gets absorbed.

And, in fact, there's one author that provided an example. It's a poisoning incident that happened in France in the early 1990s. It involved a talcum powder that had a very high concentration of hexachlorophene. And the observation anecdotal but still the observation was made in a sort of pointed way that the babies with diaper rash, I'm sorry, were more severely affected than the babies without the diaper rash when the product was applied to their skin.

So moving on to the next major topic, we generally think of the stratum corneum as a passive barrier, an inert barrier to diffusion. But it is very clear that the skin can also serve as a kind of metabolism barrier or a metabolic barrier. And the parabens are, in fact, a case

in point.

The skin has all of the major biotransformation enzymes of the liver except almost invariably at lower levels, and in fact, in some cases much lower levels. And so what this means -- one of the things that this means is that the capacity, the biotransformation capacity of the skin is going to be more saturable, more readily saturated than what we see for the same systems, the corresponding systems and the liver.

Even so, the skin still has a substantial capacity to biotransform substances that enter, the pass through the stratum corneum. As long as the substances stay in the epidermis long enough for these enzymes to do their work.

Now, we don't have hardly any information at least that I could find -- possibly we can dig deeper and you may know of some specific sources of this information -- we just don't have a lot information on the development of biotransformation systems in skin, in the skin of babies. We've got a whole lot more information. We've got tons of information on the development of these systems and the liver. So about the best

we can do at this point given the state of the knowledge, is to extrapolate from what we know about development in the liver and use that to support some assumptions about what might be happening by way of development of the skin.

So in the report you'll find that we spend a bit of time talking about the development of enzyme capacities in the liver. And what we know, if we look at it, we try to generalize or try to make some fairly sweeping generalizations which is not necessarily a wise thing to do, is that in general enzyme biotransformation capacity is fairly low. It can be quite low after birth, right after birth, and for the next couple of weeks or so. And then it seems to increase. And it increases up to about adult levels by about six months or age or so. And it can even surpass, and often does surpass, biotransformation capacity, biotransformation rates of adults. And that can last for years, for several years during childhood.

If we take a more granular look, what we'll see is the specific enzymes, specific enzymes each develop in their own time and at

their own pace and they can be very different from one another on that basis from that perspective. And this slide presents one proposed scheme for characterizing these enzymes, development of enzymes. It's one of several that may be out there. And this slide also emphasizes that in terms of variability from individual to individual, it's the enzymes that seem to have their onset at birth or soon after birth that seem to be the most variable during that period. During that perinatal period. And that, of course, can have implications for clinical treatment of neonates and so on.

Glucuronidation, it's very well known. It's very low at birth. In fact, it's responsible. This low glucuronidation capacity is responsible for the common occurrence of bilirubinemia and even jaundice in newborns, and it's also responsible for poisonings, chloramphenicol poisonings and so forth in very young -- in neonates over the course of particularly those first couple of weeks or months. And on the other hand, sulfation rates are quite high from birth and on through childhood. Quite a bit higher than

in adults. And in some cases, in many cases that increased capacity to sulfate, it sort of makes up for it. It can serve as an alternative biotransformation pathway to glucuronidation during childhood while it's very low during that period. There are several examples. Acetaminophen is one. A good example, morphine also, and many others.

Now, in terms of the development of carboxyl esterase activity, we don't have any good studies. These are two fairly recent studies. They're not clear cut. The first study basically finds that you don't find any difference in carboxyl esterase activity in children as young as two years or three years or three months or two months old versus adults or younger children and so forth. They found no difference.

The second city, on the other hand, found that even though the expression was fairly high, even in the very young children, they basically grouped their children to include neonates on one end of the spectrum with children up to about 10 years old. They found that expression was quite high in that group but the

actual enzyme rates, the hydrolysis rates measured in vitro were fairly low. Were substantially lower than in their adult population.

They did not find any real correlation with age except when they took the few children that they had in their child group who were less than one year of age, grouped those together, put those together as a subgroup. They did find a statistically significant correlation for one of the enzymes that they looked at.

These studies both have real problems, and one of the major problems is that many of the subjects were ill and they were being treated with drugs. And we don't know what drugs they were treated with. We don't know what illnesses they were treated for but it's clear there's a possibility of inducing enzymes in the liver that can be complicating the results.

So in summary, enzyme systems in general tend to mature very rapidly in newborns. The major exception is glucuronidation, the enzymes that catalyze glucuronidation reactions. And these enzymes apart from glucuronidation,

enzymes that catalyze other reactions can increase substantially by about six months or so and even exceed biotransformation rates during childhood.

The skin, to the extent that development of biotransformation in the skin, to the extent that we can assume that that development parallels development in the liver, we can say that this is probably the case that for many enzyme systems in the skin, development is fairly mature. It's fairly well developed by about six months of age. So that takes us back to the parabens topic.

It's very clear that in adults parabens can penetrate the stratum corneum very quickly and esterases in the skin are very good at breaking down that hydrolyzing parabens and, in fact, it's been suggested that that hydrolysis is likely to be complete in the skin so that no (inaudible) paraben is going to get through and enter the systemic circulation. It's also very reasonable to expect that if, in fact, our metabolized parabens get past the epidermis and do enter the systemic circulation that they're

going to be broken down. They're going to be metabolized fairly quickly in the liver. That's what happens in adults.

Now, in children, the concerns that have been raised by the Dutch in particular in the Boberg reports are based on -- they stem from a very large number of assumptions. And this is just a short list on this slide of some of the assumptions. And the one I'll point out is that it could very well be that esterases in the skin of children, of infants and neonates, could exhibit lower activity than in adults. And if that's the case then we might have to think about the potential that parabens can get through intact, unmetabolized. They're more likely to get through infant skin than through the skin of adults.

On the other hand, again, if we use what we know about development of biotransformation systems and the liver to make some assumptions, we can say that probably by about six months of age or so the esterases, the other enzyme systems, they play a role in the skin of infants and by about six months of age will probably be

comparable to the rates, the biotransformation capacities that are characteristic of the adults.

So that basically is the summary, a quick outline of the report. And I'll turn it over to the panel. If there are any questions or hopefully some discussion, we'd like to know. One thing we'd like to know is based on the report, maybe you did have a chance to look it over, or based on what you've heard in this presentation, one, do you think we ought to go forward and continue to develop something like a precedence document to address this issue? And if that's the consensus, then what are we missing? What should we focus on in terms of researching this a little bit further? How should we make this come together? And what is your vision for what it should look like?

DR. BERGFELD: Don.

DR. BELSITO: That was excellent, Ivan. And I'm assuming you were at least one of the authors in the report we received which I thought was superb.

I think there's one little bit of information that you had on your slide that you

didn't talk about, and that is that the capillary loops are absent in newborns and don't develop until about four to six months of age, which means anything that does get into the epidermis will be less likely to be absorbed systemically. It's almost like a protective mechanism.

And then I guess the question for Kurt, since he was referenced in some of the articles we read, is do we know anything about, I mean, enzymes are induced and it's more likely that the skin will be exposed to things than the liver during the first four to six months of life about the inducibility of these glucuronidation enzymes so that the skin may be ahead of the liver because it's exposed to substances that will induce them?

DR. KLAASSEN: That's actually an excellent question. And to the best of my knowledge there's very little data on that topic. What we do know now about the induction of these enzymes and, of course, most of the work comes from the liver because that's where the highest concentration of the enzymes are, but to induce these enzymes you need to have not just the

inducer but we now know you need to have the transcription factor. And very important ones are PXR and CAR, which are nuclear receptors. And chemicals have to interact with them to go to the DNA to turn it on; to turn on the synthesis. So to the best of my knowledge there's not, although hardly anyone that works in this area, unfortunately, works mainly with the liver. And secondly, maybe with the kidney. And thirdly, maybe with the lung. But once you get past those three organs, there's very, very little data. And some of this data would not be too difficult to obtain. I think, you know, your major problem of trying to write a definitive document is that you're not going to find very much definitive data in the literature which is kind of the problem that you ran into. You had to kind of take data from the liver and assume maybe certain similar things are happening at the skin and it actually turns out that even with drugs in children that are given orally or intravenously to children, the data isn't even that good for them. And some things seem to metabolize faster. Some slower. Actually, the NIH right now is trying to put

together a group to study transporters, for example, in the developing organism in humans more specifically. So I guess what is really needed here is more research rather than -- I think -- I'm not saying that putting together a white paper wouldn't be important, because a white paper maybe could indicate the data that's missing. And then maybe that would be an impetus for somebody or some groups to come and try to fill in those gaps. But there's tremendous gaps when you come to the skin developmentally as far as drug transport, drug absorption, drug metabolism, to the best of my knowledge.

DR. BERGFELD: Tom.

DR. SLAGA: There's a good bit of literature on sensitivity of newborn animals, not humans obviously, like mice to carcinogens and tumor promoters. That would be an important thing I think you should include in a write-up.

You mentioned that the parabens may increase estrogen by inhibiting sulfotransferaces. Is there any really strong data on that or is that just -- because that would be interesting since, you know, sulfation is one

of the main ways to detoxify in newborns and if you look at the androgen and estrogen pathways in newborns that there's a lot more of the intermediates that are formed and it slows down to the formation of estrogens and androgens, like DHEA and all of those to go through sulfation. And so sulfotransferase is extremely important. So if you would inhibit that, that would create very little ability to change things into water soluble compounds to get rid of it.

DR. BOYER: Right. As far as I can tell, that literature is just emerging. There are not a lot of studies on it. It was emphasized in the Boberg reports though. It may be that in addition to the hypothesis, the parabens can maybe in a relatively weak way interact with estrogen receptors. There are other mechanisms that maybe bypass the estrogen -- direct interaction with the estrogen receptor. And sulfation, as one study I think, has pretty much done in vitro using microsomes. It's not a well developed area in the literature at this point.

DR. HILL: And I'm not sure that it's very safe to extrapolate from liver either

because one major difference developmentally is the placenta has a very rich array of drug metabolizing -- Well, I say drug metabolizing, enzymes such as P450s. So that protects the infant circulation at least from external xenobiotics. And I'm not sure that that would develop in the same way and have the same function in the skin. So it might be a little dangerous to extrapolate developmental, what goes on in the liver versus what goes on in the skin.

In terms of looking at this in terms of parabens, I mean, I came into this as a medicinal chemist looking at a substance derived from parabens that might be estrogenic. If you had P450 mediated metabolism on the alcoholic moiety of butylparaben -- isobutylparaben, for example. Then you could generate compounds that look a lot like DES, for example, whereas if in adult skin or more mature skin, if esterases and glycosyltransferase and sulfotransferase are the major roots but in certain circumstances P450, so if that alcohol moiety were to come into play, then you might can generate estrogenic substances that wouldn't happen in anybody else. So I think,

again, there's just this big vacuum of research that needs done that I don't think has been done yet.

DR. BOYER: Right. Absolutely. In the risk assessment, I know, having worked in it for a while that, in fact, we make a lot of assumptions, and sometimes we make big leaps. And we also try to make sure that we discuss the uncertainties so they're associated with that. So again, given the development of the literature at this point, the best we can do, and maybe that's not adequate at all, is to make that extrapolation from the liver.

DR. BERGFELD: I wonder if in summary, overlooking what you've presented and obviously understanding there are big gaps, if you were to say a child at six months has fairly functionable skin, not equal to an adult but functional skin, that is somewhat protected?

DR. BOYER: I think that you can probably say that. You can be fairly confident that that's going to be the case in terms of the stratum corneum barrier. You can also be fairly certain if you have information specific for the particular substrate, a drug or the ingredient

that you're talking about, if you get some information you know pretty much how it might be metabolized. You know, for instance, it's not exclusively glucuronidated. And of course, that can work both ways. Glucuronidation or metabolism in general can work both ways. It can activate tox skin from the parent compound and so forth. So we need to keep that in mind.

If it's sulfated by the liver you can probably make the assumption, again, that in a skin of neonates by about six months -- infants by about six months of age, that's going to be a fairly competent biotransformation pathway for that set of substrate.

DR. SNYDER: Ivan, I, too, thought this was a very fruitful effort, and I think it gave me greater confidence in what the panel does from a CIR perspective in that from what I read, we already were aware of the exposures. We know the body's surface area of the skin in infants is higher than in an adult. So we already take that into consideration, any exposure to any toxin. And I thought that your research, while there might be gaps, didn't really identify any unique

toxicities or toxicities that would be unique to the infant that we wouldn't have detected in an adult. And that was my concern. Was there anything unique about the bowel transformation process or the barrier, the physical chemical barrier of the skin that would make the infant susceptible to unique toxicities that wouldn't be seen in adults? I didn't really see that and I felt that that gave me more confidence in what we're doing is in fact valid.

I think a bigger issue becomes in that relatively narrow window from newborn to about -- I don't know, we can probably argue this until the cows come home -- six months of age in which there does appear to be some differences. Now, whether those represent individual differences that we see in adults or are in fact true differences between the infant and the adult, I think that's what we need to determine. And so that was the only thing that I thought. I thought it was a very fruitful effort. I think this will be a nice thing for us to draft and to utilize because the only reason I mention the infant to six months is that now are we going to start having

to ask for data based upon the use data to say is this being used on up to six months of age and beyond six months. So I think we can drive ourselves crazy with trying to do that but I think we're doing a very good job, at least the data that I saw. I didn't see anything that was a red flag or a red alert that we're not doing things appropriately.

DR. BERGFELD: Don.

DR. BELSITO: And just to follow up on that, we also had the EPA papers. And I agree with you, Paul. I mean, in fact, you know, I didn't see anything and then I saw decreased capillary loops meaning that even if things did get through they'd be less likely to be absorbed. And, you know, reading the EPA factors were applying a 10x factor for a susceptible population, I think that at this point I would agree. I think it's important that we go ahead and publish this document, you know, pointing out where there are data gaps, hoping people will fill this in and keep abreast of it like we do with hair dye, but I'm quite comfortable that, you know, if we're concerned at all from adult data, adding a 10x

margin of safety when we're looking at infant products I think will protect that population.

DR. BERGFELD: Dan.

DR. LIEBLER: Yeah. I think if this document goes forward, I think it's really important that we explicitly identify the questions that this is intended to address because I think we're identifying data and identifying sort of areas where there's a lack of data and other areas where there's probably reasonable data. And perhaps the panel needs to agree on what are the most important questions that this document would address. In my mind one of them is are there barrier function differences in the skin that influence ingredient safety in infants. And I think the answer to that question is much more straightforward than the answer to the second question which is are there metabolism differences or metabolic differences in function in infant skin that affects susceptibility or affect safety responses to cosmetic ingredients. And there there are huge data gaps. Nothing, almost nothing but speculation and hand waving.

And then perhaps the third question is

the key for us going forward, which is what are the relative weights of those two issues in determining safety of ingredients use in infants? And, you know, because we don't know that much about metabolism, how important is the metabolism piece in our decision-making process? And I think we need to address those questions. And perhaps there are questions that I haven't even identified here that should be asked. But that, I think, should be the basis that guides us in developing a document.

DR. BERGFELD: Don.

DR. BELSITO: And I agree with you, Dan, but we sort of now have a sense that although we don't know for the skin, certainly we know for the liver. Sulfation is clearly increased. Glucuronidation is decreased. So I think we get metabolism data typically. You know, if we're concerned that the metabolism that we're seeing could either protect and that's a glucuronidation pathway and we're looking at products that are being used in infants, we'll probably be, you know, that will be an alert that we need to really look at how these products are being used. Are they

being used in the diaper area? What are the concentrations? You know, or if glucuronidation results in a toxic product, you know, it might make us feel more comfortable in infant skin.

So, I think we at least have a sense that the barrier is really pretty much intact at birth, so the ability of things to get through is probably about the same. And to get actually absorbed is probably less because they don't have the capillary loops until about six months of age and then it really comes down to, you know, what are the metabolic pathways of concern, if there are any?

DR. BERGFELD: Halyna.

MS. BRESLAWEC: We very much welcome the development of a precedence document on this subject. It's a very important one. We would like to have the opportunity to be able to review it and comment on it before anything is finalized.

Just some thoughts I think that parallel some of Dan's in terms of what the document itself should address. I think it should provide some guidance to the panel and points to consider in evaluating a cosmetic ingredient for

use in children. A reminder that protective creams for diaper rash are drugs; they are not cosmetics. So many of the products that I think we're immediately concerned about are regulated as drugs.

With respect to the inclusion of information on parabens in the document, I think the scenario where there has been expressed concern and an area where there's been some literature published and certainly a lot of speculation, I'm not sure that that belongs except as an example in a document like this. I think it should be more general. So I think we're likely to have more comments as we have a chance to review it in a little more detail. So we would welcome some time and the opportunity to comment on it..

DR. BERGFELD: Ron.

DR. HILL: One of the things that I remember came up in the thing we looked at in March was the specifics of the diaper area, the nappy area they called it in the European area, and potential for greater absorption. And then we were thinking, I think, in terms of things that

might be used in that area that are not regulated as drugs. And I'm not sure besides maybe sunscreens what else that might be, but maybe we can include what things might likely be used in that area specifically where the absorption is likely to be considerably increased under circumstances of an extreme rash. Because to me that would probably be the main points where we might have real concern.

And then the other thing I said earlier I think we still need to keep in the back of our mind which is if something like esterase that is substantially different in the skin, and I think there we need research. And the lesser access to capillaries and the possibility of something being retained in skin for a longer period of time and either being subject to greater, maybe P450 mediated biotransformation so it takes it down a different path or even photometabolism because it's not being carried away as quickly might need to be considered sometimes.

DR. BERGFELD: Halyna.

MS. BRESLAWEC: Just a reminder without stealing Dan's joke coming up, that the

sunscreens are also regulated as drugs.

DR. HILL: All sunscreens are regulated in the U.S.?

MS. BRESLAWEC: All sunscreens are regulated in the U.S. as drugs.

DR. BERGFELD: I thought it might be worthwhile looking at what the pediatrician advises young mothers to do with their babies' skin just to get an idea because it's my sense that pediatricians say put nothing on these kids. And don't expose your child at an early age to the sun in any form.

DR. MARKS: So my comment would be you address diaper dermatitis, which is both a compromised barrier and occlusion, but a large percentage of children have atopic dermatitis of varying degrees so all this discussion is about normal skin, yet we have a significant subset of infants and children who have varying total body surfaces areas of atopic dermatitis. So the barrier is probably totally is markedly compromised. I don't know what that percentage is but it's pretty significant -- maybe 5, 10 percent of the general population.

And then the other -- so I don't know how you address that. I just want to -- after we feel comfortable that intact infant skin or children's skin is okay but now we have this large subset of compromised barrier in infants and children.

The suggestion about what do pediatricians do I might consult Peter Elias and his wife, Mary Williams. They've been studying the skin barrier forever, or at least for their adult lives, and it would be interesting to get their input perhaps.

DR. BERGFELD: Curt.

DR. KLAASSEN: Yeah. I was just going to say I suspect you ran into this but there is a report that was put out by the National Academy of Science about 10 years ago. Phil Azalean was the leader of that document which really came about to increase what eventually was used by EPA to add this tenfold safety factor for children for pesticides in particular. Make sure you look at that review because they reviewed a lot of the literature. Probably very little bit about skin in there but again, it was a good document 10 years

ago.

DR. BOYER: And I think some of the more recent publications by Renwick in particular, that group, sort of extended that work or they've attempted to extend that work.

DR. BERGFELD: Any other questions or comments? Thank you, Ivan.

DR. BOYER: Thank you.

DR. MARKS: So what are we going to do going forward?

DR. BERGFELD: It sounds like we're going to develop a policy, a precautionary policy, document.

MS. BRESLAWEC: Will we have the opportunity to comment formally on it?

DR. BERGFELD: Yes.

MR. ANSELL: I don't think it's a policy.

DR. BERGFELD: I was going to the FDA industry policy, precautionary document, whatever..

DR. MARKS: Is that what you -- I didn't hear precautionary, Dan. I almost heard a request for the state- of-the-art right now and what could

be done in the future.

DR. LIEBLER: Right. I assume this to be something along the lines -- is this similar to our -- not to our respiratory boiler plate, obviously, but a document that helps to essentially guide our approach to issues involving infant skin.

DR. ANDERSEN: I think it's fair to say that there's input from any interested party that we have to allow the opportunity to provide. Tom raised the question about including a chunk of tumor promotion data that makes sense to add to it. So there's going to be a period of evolution, but I think it's more in the venue of a white paper that reviews this area of science and is then available on the website so that people know what we're looking at. And you will apply it as needed. There are going to be individual chemicals for which this is going to be important. There are going to be chemicals for which this is a yawn. And you're going to have to make that determination chemical by chemical. But I think having the background information allows you to do that.

DR. BERGFELD: How is that going to differ from our hair information and our pulmonary inhalation? Wouldn't it be the same, whatever we've called that?

DR. ANDERSEN: I think they have different impacts. The hair dying epidemiology as a body of information is where the panel has looked at everything and reached a conclusion that the epi data do not support a causal link between hair dye use and cancer, and that is a huge body of data that you don't want to have to repeat each time you look at the safety of a hair dye. You've got that now captured and you simply reference it that, well, yes, there's epidemiology but no, it doesn't at this point in time suggest that hair dyes are linked; that hair dyes cause cancer.

For the inhalation toxicity boilerplate, that has a decidedly different flavor than hair dye epidemiology. It is to address the possibility that there's going to be inhalation exposure. And it goes through the data and a logic argument that says that either we have everything we need in terms of inhalation

toxicity or we have missing information and here's how we're going to interpret it in the absence of that information. And it includes factoring in the available systemic toxicity from other routes of exposure to act as a barometer of, well, how toxic could this be? So it has a very different flavor. And this would be a third piece that wouldn't be like either of those two.

DR. BERGFELD: But how is it attached to the website?

Is it attached as informational pieces? What is the category that these groups of three now items would fall into? Are they all separate?

DR. ANDERSEN: They're separate and it's -- it is particularly problematic. We are into redoing and improving the functionality of the website. And as I've gotten much more intimately involved in that, the focus has been bimodal. One focus on your meetings so that material relative to this meeting can be easily found, downloaded, and digested. That's going to be even more important in the future as we try to get away from paper. But that's one focus that we have.

The other focus is ingredient by ingredient. And that also has to be a functionality on the website because somebody out in Podunk, Idaho wants to know what you said about formaldehyde. And they really don't want to have to figure out at what meeting did you say that. So that's the second area of functionality. What we're talking about doesn't link up easily to either of those, and I think we're still struggling with it. They have to be available clearly to any interested person on the website; just how we're going to do that is a little bit up in the air right now.

DR. BERGFELD: Don.

DR. BELSITO: I guess I would like to see it available in whatever fashion the hair dye epi and the respiratory statements are and how I would see it being used is, at least I personally am very comfortable that the stratum corneum barrier is fairly efficient at birth. And so if we're dealing with a chemical where there aren't issues of absorption across the stratum corneum, then we can refer to that document that we noted it was used in the same concentration in babies

as adults but we're not concerned because the stratum corneum barrier is intact. If it's passing the stratum corneum and we're basing our safety assessment on the ability of the skin to biotransform it, you know, then we'll have to go into that document and say, well, you know, biotransformation is by sulfation. Sulfation, in fact, is higher in infants, so it didn't bother us. Or biotransformation is by glucuronidation. You know, we're not sure about that. And so we're adding this 10x safety factor if, in fact, it gets down to calculating margin of safety, which is exactly really what we did with parabens. I mean, we were very present there. We did those margins of safety for children. So that's how I would see using the document as supporting evidence. The barrier function is one thing and biotransformation is another and therein lies the difference.

DR. BERGFELD: But in the respiratory we have the opportunity to pick and choose parts of that as well. So I see them all sort of the same, as informational pieces that are accessible to the public and ourselves and for us to link and

specific documents as well. But I was wondering how we got to that on the website because in all the documents, especially the hair documents, it says see this link. Is it easy? I haven't gone to that link. I don't know.

DR. BELSITO: (OFF MIC)

DR. BERGFELD: No, but I haven't done that. Is it easy if someone was searching the CIR site?

DR. BELSITO: If you're viewing the documents electronically and you hit the link it just pops up.

DR. LIEBLER: As long as you click the link and it doesn't say
404 -- (Laughter) -- you're good to go.

Seriously, I think that this is actually going to end up being important because it's like the long exercise because we could generate some document, either publish it or put it on the website and it would simply be another review on top of the pile of reviews. And I think it would be of relatively limited value frankly. But where it would have a real value to us, which is most important I think is that it helps

standardize our approach to infant skin issues when we consider ingredients. And it would have a combination of literature documentation and appropriate language that we could use in reports to address infant skin issues for specific chemicals. And it's going to differ from one chemical to another. So a review isn't going to be able to be comprehensive enough to be very useful. But a document that guides our consideration of infant issues is going to be incredibly useful for this panel and that's the most important reason I think for this exercise.

DR. MARKS: What Ivan did this morning was really great, but as we've done in previous issues like this, whether it's the endocrine disruptors or inhalation and all that, we had expert -- outside experts come in who are at the top of their field. So perhaps I mentioned Peter Elias and Mary Williams, but certainly J&J has somebody who has looked into this in great depth. And a sunscreen, yes, is not made to put on. It's regulated by the FDA in terms of a drug but it's in a moisturizer. So they've looked at the ingredients in that moisturizer.

MS. BRESLAWEC: We host a fall symposium each year, and this year one of the keynote speakers was actually from P&G, not J&J, and addressed the issue of infant skin. And if you would like, we'd be glad to provide a speaker like that to the panel.

DR. BERGFELD: Great. Thank you. We'd like that.

MS. WEINTRAUB: I also just want to say I think this presentation and this document as it develops is very important. One thing that really hasn't been mentioned but it's been alluded to by different people is -- I'm trying to figure out the best way to describe it would be dosage and the fact that the concentration of use in a product, in a baby lotion which is probably most likely what it would be in terms of cosmetics, what the implication is for a baby and the amount that you would put on a baby's skin in terms of the proportion of weight of the product to the amount of skin of the baby considering their weight. So that's just something that I don't think was really highlighted or pulled out from the PowerPoint presentation but I think it's

something that should be covered because I think it's something we discuss or at least I think about, and I think others probably do as we think about the impact of specific ingredients in baby products.

MS. BRESLAWEC: We can have somebody talk about that when they come because that's something that they spend an awful lot of time on.

DR. BERGFELD: All right. We're ready for the break and the assignments..

Alan.

DR. ANDERSEN: I think we are. And the winner is Dr. Marks gets to pack up and move.

DR. BERGFELD: And he's moving where?

DR. ANDERSEN: I have no idea. As you go out, Carla will tell you where to go.

(Recess)

DR. BELSITO: Okay. Are we ready?

DR. SNYDER: I have one comment before we start.

DR. BELSITO: Go ahead.

DR. SNYDER: The discussion of the infant document is not on our individual team meeting agendas but I would like if we could

spend -- at least at some point to discuss that a little bit more.

DR. BELSITO: Why don't we do that now? Okay. Go ahead.

DR. SNYDER: So I thought it might be enhanced by a little bit of a -- well, you have some background information but maybe a preamble emphatically stating that the purview of the cosmetics panel and what we deal with, some of that was addressed during the open comments, and that we are only looking at use on normal skin. By that, it's my opinion that the damaged skin section, it doesn't belong in that document in my opinion, as does I don't believe the paraben. So I wanted to relay that before we go to another draft that goes into a tremendous amount of detail in that regard. And so I think that marquis publication had a nice figure which I thought was interesting and it kind of went against the idea of using the liver data to support what happens to the skin because if you actually looked at all the systems, they looked at the liver, the skin, the GI, there's quite a bit of differences in the bowel transformation parameters that come on and

to what degree. I think we just have to go with what data we do have and really focus on that. And we can identify the gaps. But basically it comes down to the physical and chemical barrier, which is attributed to the stratum corneum which I think you've done a very good job of documenting. And so that goes to exposures. And then once we do have exposures, then there's a bowel transformation issue. And so I think that's another important component.

And then as I stated previously, the conclusion of all this is there are no uniquenesses to the infant, though it would make us suspicious that there would be unique toxicities that would not be seen in adults. And so that's kind of the way I would envision the document to ultimately look like.

DR. BELSITO: I tend to think with the exception of -- what was it, the PEGs where we happened to have this report of nephrotoxicity in a burn patient who had it applied to a full thickness burn, I think we almost always assume that a cosmetic product is being applied to relatively normal skin. Otherwise, I mean, I

don't think we look at, you know, what happens when you tape stripped skin and then do sensitization and irritation studies. But I mean, if it concerns you, I mean, you can say, you know, what are you going to do, isolate our baby products and see for baby products safety of this undamaged skin is unknown. I mean, then the truth is we really don't know the safety of it in adult skin either.

DR. SNYDER: No. That was only in reference to the diaper dermatitis section which was quite lengthy, and I thought we started to drift a little bit away from what we're really looking at. Because we're not really looking at cosmetics that are used on damaged skin. We may become aware of case reports or reports like that example you gave where they may raise concerns and we may want to emphasize or something, but as our standard procedure document, we don't take issue with cosmetics on damaged skin.

DR. BELSITO: Right. And maybe to follow up on that in this document that we're talking about devising for infant skin, perhaps the whole notion of diaper dermatitis should not

be included in that since we're really talking -- it would give the misconception that we're looking at products that are used to treat diaper dermatitis. And as Halyna said, those are OTC drugs regulated by the FDA and not by us.

MS. BRESLAWEC: I don't have any issue including that information in if you want to include it for completeness. It's just that I think if you do, you do have to mention very clearly that products used in that context are drugs and not cosmetics.

DR. LIEBLER: So I agree with Paul's suggestion that right up front to say this report says that we're really focused on nondamaged skin primarily; however, we acknowledge the issue of diaper dermatitis that point out that most of the products that are reviewed by this panel are not used -- none of the products are used to treat diaper dermatitis but they could easily be confused with products that are.

DR. SNYDER: And the only other conundrum to me is the issue of -- it almost goes back to the CIR overarching document in what defines baby. Because we do have this designation

as baby. We don't say infant; we don't say newborn. It's baby. It depends upon what the document is going to look like at the end. Is that going to send into a domino effect of other subcategories that we want or we don't want? In my opinion, I don't think we need them because like I said in the full meting there, that I don't think there's any unique exposures because the physical and chemical barrier of the stratum corneum is formed at birth and there are no unique enzyme systems either present or absent that are known to present any unique toxicities -- susceptibilities to toxicities. And so I'm not a proponent of cutting this into minutia detail but I think it's something that we will have to -- and that preamble could state what we consider to be the cutoffs or something. I mean, I'm just opening it up for discussion, I guess.

DR. BERGFELD: Well, it's in development so all that can be taken into consideration.

DR. BELSITO: I mean, basically I think what is defined as a baby is how the company wants to market the product and label it as a baby powder

or whatever. I don't think there are any age definitions, and I think we probably all know adults who use baby powder, you know, and they're not babies. So I think, you know, at that point I think one has to assume that if it's labeled as a baby product it could potentially be used on a child that's just brought home from the hospital; and therefore, anything -- I mean, in fact, adult products could be used on a child brought back from the hospital. So I really don't -- I think trying to define that is really irrelevant to what we're looking at.

Anything else? Curt?

DR. KLAASSEN: No.

DR. BELSITO: Dan? Okay. So let's move on with the agenda. First is Buff Book 2-Amino-6-chloro-4-nitrophenol.

It's a re-review. We looked at it in '97 and we said that it and its hydrochloride salt were safe up to 2 percent concentration. At that point we weren't getting concentrations of use so we were setting concentration limits, and that was based upon a guinea pig maximization test. There is new concentration of use data suggesting

it's used only up to 1.5 percent, so below the 2 we gave in '97. There's new sensitization, phototox, and genotox data but it really doesn't differ from what we've seen before. And furthermore, there are no ingredients to add even if we were to reopen it. So I personally thought we did not need to reopen. I guess that's the first issue for you guys to comment on.

DR. LIEBLER: I agree.

DR. KLAASSEN: I agree.

DR. SNYDER: I agree.

DR. BELSITO: Okay. Then the --

DR. BERGFELD: I have a question..

DR. BELSITO: Okay.

DR. BERGFELD: You have -- we have two documents that have reduced use concentrations, and the next one you may consider reopening. I wonder with the difference in use concentrations if you would make a comment to that.

DR. BELSITO: Well, I think when the use concentration increases beyond what we said was safe or there are hundreds more uses, then that might be a reason to reopen. But, you know, we said safe when used up to 2 percent. It's used

up to 1.5 percent. That's still within our parameters. And they didn't show us any information to show that it was unsafe to use between the 1.5 and 2 percent range. So I really don't see the need to reopen. I mean, particularly, you know, since the current use is at 1.5 and is within that level. I mean, that was my own personal viewpoint. Had they showed me something that 2 percent was bad and we had said you could use it up to 2 percent, then I would think we would need to reopen it. But I didn't really see that data.

And then I guess the second question is, of course, the self testing. And I don't think that we're going to get that resolved I think at this point. Probably just keep the current caveat. I mean, it appears to be an FDA regulation as a result of interpretation of the Delaney Act. So I think we just need to keep an eye on what industry is doing and decide how we want to proceed.

DR. SNYDER: I had one comment to you as a dermatologist and to Wilma as a dermatologist. When you do see cases of contact sensitization to

hair dyes, do the patients oftentimes have evidence of other allergies or have a history of other allergies?

DR. BELSITO: Well, that's a confusing issue, okay, particularly with para-phenylenediamine. But most patients really it's pretty much hair dyes, although there is broadening as I was mentioning, you know, you'll see patients who are allergic to PPD and para-Aminophenol and para-tyrinesufonamide. And then the other issue is occasionally you'll see patients who are allergic to PPD and to the aminobenzoid anesthetics like benzocaine. And then you can almost predict those patients will have sulfa allergies because the molecular structures are such. But I don't know if that answers your question.

DR. SNYDER: Well, it does because I was wondering if they were going to have inclusion or exclusion criteria for the patients for the self testing because it seems to me that it would also be informative to the potential consumer, not only the self test but if you have a history of any allergies to -- and I was thinking about the

anesthetic -- to other things that may be similar, that that would also be used as an alert rather than just the test, just the patch test.

DR. BELSITO: Right.

DR. BERGFELD: Well, the allergies, I deal with a lot of scalp problems, too. The dyes are very rare and frequently not an allergic individual when they're present but I'm not sure we have a number on that. The cross reactivity though is another story as Don mentioned.

DR. SNYDER: And one last comment on this report. The margin of safety calculation was based upon a NOEL, not a NOAEL. So it's even more conservative and I think that should be highlighted.

DR. BELSITO: I'm sorry about the margin of safety because I didn't have any paper to keep records of what you were saying so I was focused on something else.

DR. SNYDER: I believe the margin of safety calculation is based on a NOEL, not a NOAEL as indicated in the report. Therefore, it's a more conservative estimate.

DR. BELSITO: Okay. So we're not

reopening and we're just keeping the boilerplate as it is until industry comes back and lets us know about their current study that's going on trying to assess consumer use of their test.

Rachel.

MS. WEINTRAUB: So I had a question. And as I reviewed, I noticed there's an inconsistency with carcinogenicity. Sometimes it's included and then it's mentioned that there is no data and sometimes it's not included at all. So that's just sort of a procedural issue that should be consistent. But secondly, I think the panel should respond substantively if there is no carcinogenicity data, why that doesn't impact the decision and whether other information about genotoxicity or mutagenicity or whatever it is answers what may be the lack of data on carcinogenicity. And I didn't see that here in the discussion. And I think that's something that will come up across a number of documents where there is no carcinogenicity data.

DR. KLAASSEN: I agree with you. If there is no carcinogenicity, it should state so. And that might be because some of these are kind

of older documents. It's maybe the rationale for that. And then we should have in the discussion, and if we say it's safe, why we think it's safe. So I agree with you 100 percent.

DR. BERGFELD: I'd like to speak to those older documents. We always looked at carcinogenicity. The one that we missed initially was reproductive only and that was corrected very quickly.

DR. BELSITO: I mean, I think what Rachel is saying is that we didn't bring into the discussion in this document the fact that we had no carcinogenicity. Why did we not worry about that? And that's because the genotox was negative. So.

MS. WEINTRAUB: And I think that just that phrase -- that phrase I think needs to be in there especially because that's an endpoint that so many consumers especially consider to be something that they look for.

DR. BELSITO: Agreed. Anything else on the nitrophenol?

DR. ANDERSEN: Yeah, Don, I'm not going to let you off quite so easily on the question of

self testing. I get it from the presentation this morning that industry is going to examine the proof of concept that self testing actually works. I'm more than happy to wait for those data.

The flipside of the question, however, was might self testing induce sensitization. And that has not been touched on. Now, it's not fundamentally for the panel to resolve so I'll give you -- let you off the hook a little bit because it's an FDA problem. FDA is exempted. Hair dye color added from the color additive provisions if this warning or the self test language is provided. So it's a regulatory issue. And as long as FDA maintains that coal tar derivative hair dyes are exempt only when they have this language, that language is going to stay there. I mean, there's no company that's going to not put it on because otherwise the product isn't exempt from the Delaney Clause.

So that's an FDA internal issue that's -- I don't know whether they're going to resolve or not resolve. But if you as a panel wanted to raise a red flag that you think self testing may induce sensitization, then now would

be a good time to do that. Or if contrary you think that it's unlikely, that would be good to get on the record as well.

DR. BELSITO: Well, I think if you, I mean, can you induce sensitization through patch testing? The answer is yes. But, I mean, I believe that you're genetically susceptible and it's only a matter of exposure that brings it out. So if you're going to expose yourself to this product, then you know, so you induce it with a little patch behind your ear or you induce it with a reaction over your scalp, number one. Number two, I mean, you know, I like, you know, Tyson, they're very bright people, but I was sort of curious why they're doing this because not only is 2 percent PPD part of the American standard, but it's part of the European standard patch test which is put on everyone regardless of whether you suspect they have a hair dye allergy or not.

And I guess the third part of the equation is, you know, when you ask what do we think, I was thinking, well, you know, manufacturers maybe should supply patch test material as we test it, you know, 2 percent PPD

in para-Aminophenol but actually what's being recommended is even better. It's that the product be applied at the concentration that it actually will be applied for 45 minutes in an open test. You know, I think that's even a stronger argument to say, you know, in a more limited area that the consumer self test will be less likely to cause an issue than the actual dying of the entire scalp. So I don't buy that argument.

On the other hand, I mean, I totally agree with Jim. I don't think most consumers do it, particularly if you're, I mean, most of the women that I see who dye their hair have it done at a salon. I can guarantee you they're not going there 48 hours before their dye job to get a test. So.

DR. SNYDER: Yeah. My idea on that is that no test that they do will be 100 percent sensitive and 100 percent specific. And so it's going to have issues. And some of the issues will be the false positives and false negatives. So just by nature of that I think it's the best they can do, and I do agree with Don that using it under the conditions of its use intent is probably the

best to identify those susceptible individuals.

DR. ANDERSEN: I'm okay with the idea of gathering data on whether the self test actually identifies the people that you want to identify. It's the other piece that if you had thought that there actually was a significant risk of the self test inducing sensitization then it would be appropriate to raise that question. From what Don's saying, he's not that concerned.

DR. LIEBLER: Yeah. I would say that if we were to embrace that based on the available data we would damage our own credibility as an expert panel.

DR. BERGFELD: I believe it's premature.

DR. BELSITO: I guess the other piece above it would be that I've been patch testing for over 30 years. I have a database that goes back to '95. I've tested over 3,000 people with 2 percent PPD. I have induced sensitization to a small number of chemicals, and to my knowledge I've never induced sensitization to PPD with patch testing.

DR. ANDERSEN: Thank you.

MS. WEINTRAUB: As I reviewed this information I also wondered what percentage of consumers actually patch tested themselves, which raises the question first of all, well, if it's not happening, how can it induce sensitization. But second of all, if you're supposed to patch test for a reason, which is to see, you know, if there is an allergy, well, is this system effective for that? So I think there's sort of a broader question that if it's not happening and if patch testing in salons isn't happening, if patch testing when people are using these products at home isn't happening, well, should there be another mechanism? You know, that seems to raise other questions as well.

DR. BELSITO: I mean, the whole arena of dying the hair is to me always very interesting because I have a number of patients who are known to be allergic to hair dye and pop prednisone for the day before and the day of and a couple days after so they can get their hair dyed. Now, I don't give them the prednisone. I don't know where they get it, but the fact is that dying hair is very important to a huge segment of the

population, and they're willing to take the risk of a little bit of skin reactivity so they don't have any gray or they have a color different than the color that they naturally would have.

And in terms of whether the testing that's done or not, I mean, I don't know how you can -- you can say that it should be done, but I don't know how you can regulate the behavior of the consumer.

MS. WEINTRAUB: That's why, I mean, is the self testing the answer? You know, should there be another way? I mean, I don't think it's ones that industry necessarily supports but, you know, more premarket testing before or an entirely other mechanism.

DR. BELSITO: I guess what the Europeans are saying is that what industry should do is come up with dyes that don't have these allergenic capabilities. I'm not a dye expert. I don't know that they exist. I'm sure if they did, industry probably would have them out on the market. You know, I guess one thing we could do is take a Texas governor approach and say instead of everyone should be HPV vaccinated, that everyone who is

going to get their hair dyed has to get a note from a dermatologist that they were PPD negative on patch testing. But I don't think we want to go that far in government.

DR. BERGFELD: I think that the limited numbers of sensitization are such that the patch testing isn't driven by sensitization in the practical sense.

DR. ANDERSEN: I think there's an oxymoron in terms of the rationale and the endpoint here. FDA made a pronouncement that said you're exempt from the Delaney Clause which says don't use anything that causes cancer. So you're exempt from that clause of the act if you put a label on your product that says "test for sensitization." Wait a minute. Those two don't have anything to do with each other arguably. So what's going on? And that oxymoron has never been resolved. It just exists.

The benefit of doing a self test that might just uncover individuals who are sensitive is a bonus that maybe if it does indeed work you'll avoid some people having an adverse reaction to the hair dye. It just doesn't have much to do with

carcinogenesis.

DR. BELSITO: Anything else? Okay. So I think, let me summarize. We're not going to reopen and at this point we're not going to change our boilerplate regarding self testing. Is that a fair assumption? Okay.

So moving on to the alkyl ethylhexanoates, if you remember back in September we were looking at this as a member of a larger family but decided to split out the ethylhexanoates in particular because of repro toxicity for two ethylhexanoic acid moiety. And in the process of splitting that out in the original report with cetearyl ethylhexanoate we've been able to add 15 additional ingredients. I think Monice has done a great job of splitting both reports together or apart, rather, and keeping the information intact. And I thought we could go ahead with a safe as used when formulated to be nonirritating with this and I welcome comments by other members of the team.

DR. LIEBLER: So I agree with that. The only couple of points I wanted to raise is in the -- let's see, this is Panel Book page 30 report

page 3, the animal toxicology basically says refer to Table 1. But then in the discussion the issues of ethylhexanoic acid animal toxicity is brought up there and it sort of comes at you out of the blue with any citations. I realize it's already been a part of another report but that much probably should be recapitulated under the animal tox section with appropriate citations so that the citations -- the original data citations are there for the reader. So that's one point.

And then another point is in the -- under the items for consideration for possible inclusion in the draft discussion, in the second paragraph, refer to the -- you talk actually about the animal tox issues and sort of the mouse- specific issue regarding (inaudible) binding, you also end up by saying that the process of metabolic conversion results in a time course that allows clearance of 2- ethylhexanoic acid before sufficient levels can arise to produce toxicity. This outcome, in addition to the fact that alkyl ethylhexanoates would have to pass through the stratum corneum precluded risk of developmental tox. I think actually some alkyl

ethylhexanoates would be significantly absorbed and others probably wouldn't. And the ones that probably would be would be like the isodecyl, the lauryl, and the myristyl, as well as the ethylhexyl. And I realize it's not a black and white distinction between what's absorbed and what's not absorbed, but if ethylhexyl is, then I would expect the other three -- isodecyl, lauryl, and myristyl to probably have some absorption. So maybe that should be rephrased a little bit.

MS. FIUME: Do you have any suggestions?

DR. LIEBLER: Well, you could simply say that the longer chain alkyl hexanoates would have to pass or that alkyl -- sorry. Let me get back to you with some specific language on that. Okay? But I think the point is that some of them would, and some of them wouldn't be very well absorbed. But I agree with safe as used.

DR. BELSITO: Yeah. I agree with Dan. That was my only comment that suddenly in the discussion the 2AEHA comes up and there was never any mention before so we need to put a little bit of that data into the document as well as in the discussion. And the discussion was totally

unreferenced so we didn't know where that came from. But otherwise really good.

DR. BERGFELD: I'd like to make a comment about the discussion. The second paragraph regarding read-across is excellent and I'd like to see that appear in other discussions.

DR. LIEBLER: Wilma, can you clarify what you were just referring to?

DR. BERGFELD: Well, although there are gaps -- it's the second paragraph under Draft Discussion on page --

DR. LIEBLER: Oh, third paragraph. Okay.

DR. BERGFELD: I guess it would be the third paragraph.

DR. LIEBLER: You know, you made the point earlier, Wilma, about having a standardized way of describing read- across. I think that's appropriate only to the extent that we have a standardized way of doing read-across and we do not.

DR. BERGFELD: Well, we have a pattern though, and it might have to be altered for each one but at least to address it in some form. Like,

the beginnings of this, although there are data gaps, similar chemical structures, physiochemical properties, functions, et cetera, I'm sure that that applies to most, that part of it.

DR. LIEBLER: That much is true. I guess I'm making -- I'm referring to the comments I made before. It was probably about a year, year and a half ago, is that we still have a pretty intuitive approach to read-across. It's not very standardized. There aren't really clear rules for doing this. So that led to the workshop that we had on chemical inference and tools. And that was a useful workshop. But not a lot really came of that so far. We haven't turned that into a method and approach. You know, this is something that's not an easy problem to solve. So when you said we needed a standardized way of describing read-across, to the extent we use this verbiage I guess that's okay. But it tends to mask the fact that we approach this more intuitively and I think Ron and I are good examples of people with very similar training in chemistry but approach this very differently. Not to say that one's right and

one's not; it's simply more of an issue. It sort of illustrates that we really don't have a standardized way of doing this.

DR. BERGFELD: Well, more than not, sometimes it's not even mentioned.

DR. LIEBLER: Oh, yeah. Yeah.

DR. BERGFELD: That there's a read-across happening here. So I think it always has to be here because in all these larger documents that's exactly what's happening.

DR. LIEBLER: But this nice language, it's okay as far as it goes but it papers over a real --

DR. BERGFELD: Gap.

DR. LIEBLER: -- high degree of variability in what read-across amounts to.

DR. BERGFELD: I agree with you..

DR. ANDERSEN: I think from my standpoint the alert on the need for something in the summary/discussion goes all the way back to the data profile and this one is a perfect example. If you look across there are lots of data on cetearyl ethylhexanoate, and that's marvelous. Where we're having to wing it is taking any of

those columns and looking vertical for the other chemicals. There isn't much. So the onus should be on us to explain why that's okay. And I think that's what Wilma is getting at is there is some need to offer an explanation of why that is true.

In other cases, the question will be left to right. Some data but not full, yet some data on a lot of chemicals that form a body of data on which you can rely. Very different circumstance but it's all dependent on what the picture is in that data profile, and I think we just developed a new thought that as we write these we're going to write a paragraph that describes that data profile and explains why we think it's okay.

DR. BELSITO: Anything else? Okay. Moving on to the second and larger half of this group that was split out, the alky esters as used in cosmetics. Again, I think Monice did a superb job in splitting them, reviewing it safe as used when formulated to be nonirritating. I thought the discussion was great and have no additional comments. And I turn it over to my team.

DR. SNYDER: I second that. I also made

a comment that I thought the introduction and the discussion were very well drafted with regards to dealing with the point that was just made about the read-across and the justification for using data from other points and what data was present in this report. And it was very clear to the reader that certain data things where you were going to have to go to other reports to retrieve those but it was used in the panel's deliberations for consideration of safety. So I thought this was a very well done report, Monice.

MS. FIUME: Thank you.

DR. LIEBLER: I concur. This was terrific. I really didn't have anything to add.

DR. BERGFELD: I'd like to ask a question if I might. I was impressed with the shrinkage of the text in all the documents and the enlarged attended pieces, tables, et cetera. Is that going to be the format for now and the future? It seems to be.

DR. BELSITO: When you say shrinkage of text, you're not talking about font size?

DR. BERGFELD: No.

DR. BELSITO: You mean that we're

replacing text with tables?

DR. BERGFELD: Correct.

DR. BELSITO: We've asked for that.

DR. BERGFELD: This one is, what, four pages.

DR. BELSITO: I understand. But I think it's much easier for us to get a good sense of what's going on by looking at data with tables rather than paragraph after paragraph.

DR. BERGFELD: I totally agree but I was quite struck this time with so many being four or five pages long.

DR. BELSITO: And I thought it was great personally.

DR. ANDERSEN: As for the future, you betcha.

DR. BERGFELD: You betcha. And may I ask another question? Is there a new editor of the Journal because the format of the summary statements that lead into these topics have been done away with.

DR. ANDERSEN: I think, yes, there is a new editor to the Journal and our understanding at the moment is she will also be pleased with the

shortness of the text and that we're not reiterating what we published in six other previous publications. So this is -- we're certainly marching to the panel's drummer but we also think that this marches to the Journal editor's desires as well.

DR. SNYDER: And I just want to emphasize that you can decrease on the front end but still include on the back end, provide those relevant -- all the safety assessments and data sets to us because I still want to review those even though they're not in the text in great length but don't short us on the other side because then it makes it more problematic.

DR. ANDERSEN: Well, I agree. We're gambling that the editor will find those short summaries in the tables perfectly acceptable.

DR. BERGFELD: Is that what you're referring to or do you want the actual text put in there from the other documents?

DR. SNYDER: No. I want the data section in the back of the report. The report can be shorter but I still want that data to support that report. I don't want to not -- are you

understanding? Sometimes --

DR. BELSITO: You want the old report as part of the --

DR. SNYDER: As relevant to significant issues that we might have to address.

DR. BELSITO: In what we get?

DR. SNYDER: Just like this one.

DR. BELSITO: Right. Because sometimes the old reports were not in with the report and you had to go back. And if you're reading it on the plane and don't have access to Wi-Fi it can be a problem.

DR. SNYDER: And also, sometimes there's -- sometimes the writers take things out of context or transpose things maybe slightly different. What happened in the last report was it was transposed as a NOAEL but the actual old report was actually NOEL. And so --

DR. BELSITO: Right.

DR. SNYDER: -- there are some things that we need to catch because that's what we're supposed to do.

DR. BELSITO: Dan? No? Curt?

DR. KLAASSEN: No problems.

DR. BELSITO: Okay, good. So next we move on to talc. And this is a new report. The scientific literature review was just issued in August 2012. And over the many decades talc has gone under a number of -- sort of for lack of a better word restrictions in terms of making sure there are no asbestiform particles, et cetera. And when I look at this document I guess before I make any further comments, this is yours, Monice?

MS. FIUME: Yes.

DR. BELSITO: Could you clarify the 36 percent in sprays that is given in Table 2?

MS. FIUME: Is there a particular line you're looking at, Dr. Belsito?

DR. BELSITO: Let me get it. There are so many tables here.

DR. BERGFELD: It's on page 31. Page 31 and --

DR. BELSITO: Yeah. Incidental sprays.

DR. BERGFELD: Under summary information exposure type. Spray is there. The second grouping.

DR. BELSITO: It's actually 0.3 to 35

percent and then it says B, use of talc in spray products in which companies were asked whether or not they used it in spray products.

MS. FIUME: So the council has submitted a second survey where they went out specifically and asked the companies. Because the concentration of use data that are in here I believe were 2010 when this report was originally going to become a table a while ago. Rather than re-review, and Carol, correct me if I'm wrong on anything, rather than re- review all of the concentration of use data, they went out and specifically asked for the concentration of use of talc in spray products. And if you look under makeup bases, they've come back that there's a 35 percent aerosol spray. And that's where I got the number from.

DR. BELSITO: Okay.

MS. FIUME: Did it not match with what you saw?

DR. EISENMANN: On page 100 of the panel book is the result as I provided to Monice if you want to look at where I got it. And I also asked the companies that were reporting spray use to

give me the maximum concentration in a non-spray use if they also had the same product category of both spray and non-spray. And one of the reasons why I decided not to do a complete survey is because you have 100 percent products. It just didn't seem to -- you're not going to get any higher. Certainly, powders haven't changed so I decided that really what you wanted to know is the spray uses.

DR. BELSITO: Well, I mean, really what I want to know is because my assumption is that that high percentage is in a fungal foot spray and it's not in a hairspray that's going to be sprayed directly into the breathing zone.

DR. EISENMANN: It surprised me there were a few companies that had makeup spray products.

MS. BRESLAWEC: Fungal foot sprays would be drugs.

DR. BELSITO: Well, then a deodorant foot spray. I don't know. But I can't imagine 35 percent talc in a hairspray. I mean, it doesn't make --

DR. EISENMANN: It's not a hairspray.

It's a --

MS. BRESLAWEC: Makeup base.

DR. EISENMANN: Makeup base.

DR. BELSITO: Okay. Anyway, I just, you know, I guess when I was looking at it I was thinking that, you know, as we categorize and do this condensation of products it would be nice to separate out spray products from those used about the face. So foundation spray, hairspray versus spray products that are used in other areas of the body. That was just my point and what I wanted clarification. Having said that I think that we can go ahead and say safe as used but not on damaged skin due to granulomas. That was my assumption of reading all the data, but I will open it up to my fellow team members.

DR. LIEBLER: So I agree with your overall assessment. I think the part was really quite well done. I have -- I guess one of the issues about the sort of persistent concern about potential ovarian cancer risk and potentially other cancer risk revolved around this issue of characterizing impurities in talc; whether there's asbestos-like material in it. And it

looks like from the "literature" that you were able to review and cite that there's not a lot of recent literature characterizing much of the talc that's used in current cosmetic products. Is that correct?

MS. FIUME: The specification that came out in 1976 is still current. So it is my understanding from the research that I have done that it's a cosmetic use talc. It will be asbestos free.

DR. LIEBLER: So that's the specification?

MS. FIUME: Yes.

DR. LIEBLER: And then there's the relatively recent study, I think it was a 2012 study where the FDA asked nine suppliers to provide material. It was analyzed and it was found to be within specification essentially, but it's a relatively small sampling. That's what I'm talking about, the difference between the specification and the data supporting impurities.

I guess we're not going to do any better than that on impurities. In other words, will

there be documentation that the specifications actually met? Do we need that? How important is that for us? I ask my other colleagues on the panel how they feel about that.

DR. BELSITO: What do you mean?

DR. LIEBLER: Well, there's the specification that says here's what it should or should not contain, and then there are the data to support that it actually doesn't contain asbestos material.

DR. BELSITO: I mean, that's all we can go by. I mean, we do this all the time. We say it shouldn't contain, you know, a certain percentage of heavy metals. I mean, if a company wants to adulterate their product we can't control that. All we can say is that asbestos form like particles should not be present in cosmetic grade talc. The FDA has already said that. If they were to be present it would be an adulterated product and it would be up to the FDA to go after them.

MS. BRESLAWEC: Dr. Belsito, we have a manufacturer here that could address your concerns if you wish. Make a statement.

DR. BELSITO: Always willing to hear. Sure.

MS. PIER: Hi. I'm Julie Pier. I work for a talc manufacturer. And the standard has been in place since the '70s and the manufacturers do comply with that. And I guess we don't publish our data for the general public but it's -- most of the suppliers do comply with that. We have the Mining Safety and Health Administration comes in and does air testing of our mines and makes sure that at least the environment is free of asbestos, but it's up to the suppliers and we're very sensitive to that and do a lot of internal testing. I know for a fact our company has copious records of testing on all of our products.

Concerning the FDA study, I know that we complied with that, our company complied with sending samples to the FDA and I know the other major companies in the U.S. also complied. I haven't seen the final study from the FDA. It hasn't been published yet. We're trying to get that to know who was requested but I have information that some of the people who supposedly didn't comply with sending samples

into that study were actually distributors and that the major companies that produce the talc did comply with that. And I actually know the lab that did the analysis and they found absolutely no fibers of any kind in any of -- there were hundreds of samples tested from the companies themselves plus off-the-shelf cosmetic products that they pulled to do the analysis.

DR. ANDERSEN: Do you certify to the purchaser of your talc that it's asbestiform free?

MS. PIER: We do kind of an internal statement that we send to our customers and that is actually requested quite often.

DR. BELSITO: Curt.

DR. KLAASSEN: Yeah. I was just going to say that we probably have better evidence that this regulation is being used by the cosmetic industry much more than many of the others that we state. So I think we're in fine shape.

DR. LIEBLER: Well, the reason I bring this up is because of this persistent buzz, whether it's substantiated or not about asbestos contamination in talc. And I think it's important

for this panel to have as thorough documentation of the available data. Now, in our reports we often use data that are not published in the peer review literature but are supplied by industry to describe contaminants or at least what measurements were used and what -- you know, if nothing was detected, what was the limited detection of the method used and so forth. And it sounds like you just said those data are there.

MS. PIER: Yes.

DR. LIEBLER: And if those could be provided so that we could incorporate representative data into this report, it would strengthen this because much of what's referred to in this report is pre-1976, before the specification was in place.

MS. PIER: Before the standard. Yes.

DR. LIEBLER: And I think that it's important that we are able to document in this report to the extent that the data are available what is the routine compliance with the standard, what are the analytic methods that are used to ensure that the products comply with the standard.

DR. SNYDER: Monice has in the report almost a little over a page of impurity information which is quite a lot, and she does address the 1976 requirement and then also the 2012 results of the screening by the FDA. So I think she has that all captured.

DR. BELSITO: I think what Dan is asking for is some data from some representative companies as to exactly how they screen to assure that it is, in fact, asbestiform particle free.

DR. LIEBLER: Exactly.

MS. PIER: We can absolutely provide the methodology that we use.

DR. LIEBLER: Yeah.

MS. PIER: That would be speaking for ourselves.

DR. LIEBLER: And then the flipside of this is that there's I think a lot of or there's some space devoted to what looks like sort of a little controversy in a box about these guys who got together at Bowling Green or wherever it was and whipped together this little study that basically said there was a lot of asbestos contamination in talc and then we're citing these

personal communications, Caneer to Ashton, June 1973, that are entertaining but they're not particularly useful for us. You know, I'm not even sure if the original study is actually in the literature in anything that could be considered the scientific literature, much less peer reviewed. And I'm not sure if we should be devoting space in this report to that because I think it blows that up beyond its merit.

DR. BELSITO: So which page is it?

DR. LIEBLER: Well, so I'm actually referring to on Panel Book 11, under constituents and impurities, there's the, let's see, fourth paragraph, "Personal communication from Caneer to Ashton referred to previously published study that stated that the analysis of 18 commercial talcum powders found 4 to 46 percent asbestiform mineral." And the old -- the letter from Caneer to Ashton documents, I guess, that these gentlemen visited the group, and I think it was at Bowling Green or wherever this was done, someplace like that and presented them with -- presented the authors of this with a number of problems that were evident from their

analysis, and they basically said, oops, yeah, I guess we goofed. And that's kind of where it sits. But I don't know if that initial report actually appeared in the peer review literature or if it's something we should even take seriously, much less the rebuttal to it. Is this all really stale beer basically?

MS. FIUME: Dr. Liebler, I think for me part of that information was that they were stating that the methodology used to examine the talc played an important role in whether or not the analysis was correct. Currently under analytical methods I do have what the industry recommends for looking at talc. So if none of that plays a role as well I'm more than happy to take it out so that I know that this should definitely come out. On the bottom of Panel Book page 11 and the top of Panel Book page 12, basically both of those two bullets can be removed. And then the few paragraphs above it.

DR. LIEBLER: Yeah. I would suggest that that stuff just be deleted.

MS. FIUME: But leave that third bullet which will now be by itself -- can remain there

because that's the 2012 FDA.

DR. LIEBLER: Right. Right. I think this would be much stronger if we had the data from industry documenting the analytical methods and typical values found for the product. That would be much more informative for describing what are the data -- what are the characteristics of the materials in current use.

DR. BELSITO: So then are we all in agreement, Paul and Curt, with Dan's motion that Panel Book page 11, actually report page 4, if I followed Dan correctly, you're asking that the next to the last paragraph starting with the personal communication from Caneer to Ashton, the first bullet and 1973 and the second bullet on Panel Book 12 in 1979, that all of that be struck from this report; is that correct?

DR. LIEBLER: That's what I'm suggesting.

DR. BELSITO: Paul? Curt?

DR. SNYDER: I'm okay with striking the amount of text that's given to that but I think either in the discussion or under constituents there needs to be an introductory statement

saying that the panel recognizes that analysis and methodologies used to evaluate talc prior to the 1976 regulation were wrought with errors and methodology and the issue or something. We have to have something that we were aware of that because, again, part of our responsibility here is that we can't appear that we completely ignored that or why we chose to ignore that. I think we have to at least address it somewhere in here, either in the discussion or in just one or two sentences at the beginning of the constituents. I'm not comfortable with taking it completely out because consumers may read that from some source and not understand why we didn't address it or what we thought about it.

DR. LIEBLER: I would certainly be okay with that, Paul. One sentence. Refer to that. You could have the citations of the study, even including this letter, personal communication there and simply say, look, this was -- there was some controversy about the methods used to characterize talc and contaminants of talc. There were, as Paul said, there were a number of reports with questionable reliability and here we

cite current data on the products as supplied.

DR. BELSITO: Curt?

DR. KLAASSEN: I agree with that..

DR. BELSITO: Yeah. I definitely wouldn't want it deleted because I think that's what raises the whole issue of asbestos that we then go on to address and then it's like out of context. Why did we address it? I think it can be shorted to something to say like in 1973 Caneer questioned the presence of asbestiform material in talc. In that year the FDA requested analysis of 195 samples. They found this. And then in '79 they analyzed samples, found this, and as the analytical methods improved in 2012 this is where we're at.

DR. LIEBLER: So if you can just minimize that, just the way the report currently reads, that's the best data we have. That's given most of the emphasis whereas we actually do have good data and we should have those in the report. This should be perhaps condensed considerably.

DR. BERGFELD: Do you think in your discussion that you have to consider pulmonary fibrosis and take up the ovarian studies in some

way just to bring all those together?

DR. BELSITO: Well, the ovarian studies I think are --

DR. BERGFELD: Then why do we give them so many pages?

DR. BELSITO: Because is think they're out in the literature. I mean, in the discussion. I mean, I think that --

DR. BERGFELD: But you can negate them. You can negate them in the discussion. You can address them and negate them.

DR. BELSITO: Didn't we address the --

DR. SNYDER: Yeah. It's addressed in the summary.

DR. BELSITO: In the summary.

DR. SNYDER: I think the discussion could be much more abbreviated.

DR. BERGFELD: Yeah.

DR. SNYDER: In that it's a clearance, you know, issue. That it's an overload issue in the lung and the root of exposure in the reproductive tract. So I'm okay with that. I think what's a bigger issue in the discussion is what Don raised earlier, the 35 percent in

aerosolized makeup foundation and that we still think that that is below issues that would cause concern for inhalation exposures.

DR. BELSITO: The discussion hasn't been developed yet, but I mean, I think the whole issue of ovarian cancer, I'm not even sure that needs to be in the discussion. I mean, in all the studies it didn't really seem to get there even when applied to the perineal area and that whole --

DR. BERGFELD: But you spend a lot of time in the document on it so you do need to bring it an end somewhere.

DR. BELSITO: Because we have that -- I think it's brought to an end in the document, you know, when you look at absorption of black whatever and everything else, it's not getting up there. So I don't know how the talc got there. Maybe it got there when they got an appendectomy in 1963 with talc-containing gloves. I mean, I'm not sure but applying it to the perineal area, all the data that is in the document would suggest that it doesn't migrate from the vulva up to your ovary.

DR. LIEBLER: So we've got I think over four full pages on ovarian cancer epidemiology and talc in this report. So we've got to at least mention it in the discussion.

DR. BELSITO: Fine.

DR. LIEBLER: To the extent we simply say that the data are inconclusive which I think is basically done.

DR. BELSITO: I don't think the data are inconclusive. The data are pretty conclusive that when you apply talc to the perineal area it doesn't get to the ovary. You know, what's inconclusive is how the hell they got the ovary they were examining. I mean, I think that's inconclusive, but I think it's fairly conclusive that application of talc to the perineal area doesn't result in migration to the ovaries.

DR. SNYDER: I agree with that..

DR. BERGFELD: Are you going to address baby sprays in the discussion?

DR. BELSITO: Oh, my God, someone spraying foundation on their baby. It must be that lady from Colorado.

MS. BRESLAWEC: I'm not sure that there

are any uses for this ingredient in the baby area. We can check.

DR. BERGFELD: Well, in your table you have creams, lotions, powders, sprays.

DR. EISENMANN: They're not powders.

MS. BRESLAWEC: They're powders but not sprays.

DR. EISENMANN: Correct.

MS. FIUME: But on that same note can I ask for the discussion how you would like to address -- it's used up to 99 percent in fragrant powders, dusting, and talcum. So how would you like that addressed in the discussion?

MS. BRESLAWEC: I'm not sure what your question is. Do you want us -- is the question do you want us to refer to powders as a spray?

DR. ANDERSEN: You're asking the panel?

MS. FIUME: I'm asking the panel as far as inhalation goes how they would like that addressed in the discussion..

DR. SNYDER: I think it's simply an exposure. I still don't think even in a powder that you're going to get to those levels where they exceed pulmonary clearance mechanisms. I

think that's clearly the basis in pulmonary. So that could be how we deal with that, at least in my opinion.

DR. BELSITO: You know, in general, I think the use of fragrance, dusting powders at least in my experience of reviewing cosmetics that consumers bring in when I'm patch testing them has decreased. Powders are very messy. They get on clothing. They cause white discoloration of clothing. So I think they're probably more important in terms of applications to young children and babies. But I agree with Paul. I don't see the use of a powder for most people. You always may get that odd ball is going to create any issues of respiratory overload. I mean, they're messy. You start putting powders all around, suddenly you've got powder all over your bathroom.

DR. BERGFELD: Pediatricians now suggest strongly no powders for children and babies.

DR. BELSITO: You know, I obviously didn't have any issues with it since I started off with a safe as used when applied to undamaged skin

with the issue being that one study that when it was put on broken skin --

DR. EISENMANN: One question about the broken skin rather than damaged skin because when you use the term damaged skin people might think it's sunburned skin or, you know, intact skin that's a little bit diseased. So do you mean broken skin? That would be a better term than damaged. Or some term, you know, barrier-compromised skin. But this word damaged got us into trouble before and --

DR. BELSITO: Well, barrier compromised gets us into trouble with atopics and then I don't think it's going to be a problem for atopics. I mean, I guess what you'd really want to say is, you know, where there's first degree or more burn but then can the general public interpret that in the absence of epidermis, I mean, you know, can the general public interpret that? And that was actually one of the things I was thinking about when we were talking about the hair dye. For my institution review board I have to put language that a sixth grader would understand. So I think, you know, when they're writing these hair dye

instructions, you know, at what level are we going to gauge it?

DR. EISENMANN: This is in a scientific journal so it doesn't have to be a sixth grade level. So it can be --

SPEAKER: Eighth grade level.

DR. BELSITO: Twelfth grade. Okay.

DR. EISENMANN: Right.

DR. BELSITO: When the epidermal barrier is removed.

DR. EISENMANN: Okay.

DR. BERGFELD: Or compromised?

DR. BELSITO: No. Because it's compromised when the stratum corneum is compromised and I'm not concerned about that. I'm concerned about when you're putting talc on dermal tissue and forming granulomas. So when the epidermal barrier --

DR. SNYDER: Or ulceration because that means complete loss of the epidermis.

DR. BELSITO: Well, I mean, well, but then there are, you know, there's a first degree burn, which is epidermal; second degree burn into the dermis. I think anything, you know, first

degree or beyond. So when the epidermal barrier has been removed.

DR. EISENMANN: I have one more issue that I would like to raise. On page -- on Panel Book page 31-32, this co- carcinogenicity section with BAP. I'm not sure that that's an effect specific to talc. I think if you put BAP observed to other particles it changes the distribution of the BAP in the lungs. And I'm not sure. I think these studies could come out of the report.

DR. SNYDER: In my book I indicated to strike that.

DR. BELSITO: So we are talking about all of the co- carcinogenicity studies eliminating?

Dan? Curt?

DR. LIEBLER: Yeah. I'm okay with that, actually, all the studies, basically two citations from one laboratory, right? Stenbock and Roland ('78); Stenbock (86). That's two paragraphs. Two big paragraphs on studies that are obviously not very well designed to evaluate an effect of talc. Either it could be eliminated or shrunk down to a very shot paragraph. Pointing

out the weakness of the study. They don't really have an appropriate control..

DR. BELSITO: Well, I mean, I think that, you know, I mean, carcinogenicity is the hot button consumer issue with talc, and even though we might think that there's explanations as to why there was this co-carcinogenic effect that is totally irrelevant, I would not like to see it completely struck from the document. If you think there's too much emphasis I would condense the study. And then in the discussion say the CIR panel noted these two studies, indicating the potential for co-carcinogenicity. We think that this is such and such in effect and it's not relevant to the use of talc in cosmetic products. Period and Amen.

But, you know, I think that sometimes we get rid of material and I'm okay with it because it's not hot button public issues. But I think anything -- getting rid of anything that has to do with carcinogens, sitting on talc completely from this when it's been out in the literature would be a mistake on our part and we could be accused of not looking at the data when, in fact,

we looked at it and decided it was not relevant.

So I think you can condense the paragraphs. I don't have a problem with that.

DR. LIEBLER: Yeah, that is what I was suggesting as well. I mean, I think that we need to point out this study has major flaws. We can simply acknowledge it in a couple of sentences.

DR. BELSITO: And then in the discussion point out the flaws and why we dismissed it.

DR. LIEBLER: Right.

MS. FIUME: So then for clarification for the discussion items to make sure that I have everything, I had four main points, I believe. It was talking about the ovarian cancer studies and why they aren't relevant to the safety of cosmetic talc; inhalation discussing would the skin barrier be intact and the safety of talc. And then the BAP and talc who did carcinogenicity studies.

DR. LIEBLER: And the issue of impurities and the standard and the supporting data.

DR. BELSITO: So you have impurities, ovarian carcinoma, the co-carcinogenicity,

and --

MS. FIUME: The fact of use on intact skin.

DR. BELSITO: Right.

MS. FIUME: Or the epidermal barrier is attacked and then the respiratory. And then since -- for report page 19, Panel Book 26, some of that ovarian cancer risk and the epidemiological studies, do you want that section reduced or is it okay as is. Or do you feel that it gives too much emphasis if it's not reduced some?

DR. LIEBLER: Well, my first reaction to it is if we're going to basically say in the discussion that these studies do not support a role for talc and ovarian cancer, then we probably don't need to devote four and a half pages to it. On the other hand, we want to make sure that it's clear that these were thoroughly reviewed in our report. So I think it could be cut. It would -- I didn't try and suggest what text should be cut, but I think this could be edited down to perhaps by half.

DR. BELSITO: I'm fine with cutting it

down a bit. I mean, I sort of like the fact that, you know, we detailed all of the studies. There again, because it's another hot- button issue. And then I liked the idea that we looked at, you know, all the studies that are looked at -- talc migration from the genital area and basically it doesn't migrate. So. Yeah. Maybe there's some talc in some of these ovarian cancers but it didn't get there more than likely by a perineal application.

DR. SNYDER: I think it goes to what you said before about the other section and that you have to have some of that evidence of what drove the studies. And so I think how long that is remains to be determined but I think we need to have the full spectrum of the early on thinking, the studies that refute that that was a migration from perineal application, et cetera. So I think that all can be shortened somewhat. And dealt with very briefly and succinctly in the discussion.

DR. BELSITO: But I wouldn't shorten it just to put it in a table. I think it needs some words to go with it.

DR. LIEBLER: There are plenty of tables anyway. No, it's just the text. It's just the text I'm referring to. And actually one part of this that was really good was the closing set of bullets that outlined the main conclusions drawn. So I definitely would keep that. That's really very effective.

DR. BERGFELD: In use of the text, just in the tables --

DR. BELSITO: Yeah, I know.

DR. BERGFELD: -- back on page 75 in the Panel Book.

DR. BELSITO: Yeah. But what I'm saying is I wouldn't say that there have been a number of reports of linking or suggesting a linkage between perineal talc use and ovarian cancer, Table 5. I wouldn't shorten it that much.

Anything else? Okay, so.

DR. BERGFELD: I just want to ask one question of you, Don, and perhaps of Paul. On page -- under animal studies and application of talc to the animal, it talks about just applying the talc to the surface of the animal, and it didn't say it was an abraded animal. It's on Panel

Book 33, sixth paragraph down, "Dermal application." Do you think it resulted in dryness of skin and skin erosion. Do you think that was rubbed on or they were just powdered? That would make a difference.

DR. SNYDER: My interpretation is they were just shaved and the powder was applied; that's it.

DR. BERGFELD: Okay.

DR. BELSITO: I didn't have any problem with that. I mean, I thought it was just all just a desiccant effect of talc. I mean, at least when I used to shave guinea pigs they were slightly bloody and their skin was already somewhat abraded. So. Okay.

DR. SNYDER: That reflects your technique more than anything else.

DR. BELSITO: Yes. That's right.

DR. SNYDER: Always operator error.

DR. BELSITO: So we're going with talc being safe as used. We're asking industry to submit a little data as to how they now analyze talc to assure that it is free of asbestiform particles. We are going to minimize the 73 and

7 analyses on page 11 and 12 but not eliminate them. We're going to really condense the co-carcinogenicity studies and mention very briefly in the discussion why we believe they are irrelevant. We're going to cut down the ovarian carcinoma and again very briefly in the discussion why we didn't feel that was relevant. And in the discussion include issues of respiratory. And we do not believe the current uses would result in respiratory overload.

Does that summarize everything?

DR. SNYDER: Very well. You left out safe as used.

DR. BELSITO: Self as used; should not be used --

DR. SNYDER: But should not be used on skin.

DR. BELSITO: Right.

DR. SNYDER: Until the epidermal barrier is removed.

DR. BELSITO: Right. Exactly. Thank you. Okay. We have time for a few more here. So let's at least start the phthalate discussion. And I guess since Alan is here and he had a chance

to review this guidance for industry document and it was just sitting here when I got here and I haven't even seen it yet, basically this came from the FDA Center for Drug Evaluation and Research.

MR. ANDERSEN: That's correct.

DR. BELSITO: So, not from cosmetics.

MR. ANDERSEN: Right.

DR. BELSITO: And their recommendation is in drugs to do what?

MR. ANDERSEN: Phthalates in particular dibutyl phthalate and diethylhexyl phthalate have uses as excipients in drugs, and because there are alternatives to perform those excipient functions at the Center for Drug Evaluation and Research is recommending that the two phthalates not be used. And the science behind it is nothing different than what you have reviewed. There's really no new data. What's different is that the Center for Drugs Evaluation and Research has applied the precautionary principle and not a risk assessment. What you guys have done is a risk assessment with large margins of safety vis a vis cosmetics. So, I would argue that this doesn't have any real impact on the phthalate question,

but you needed to know it exists.

DR. BELSITO: Okay.

MS. BRESLAWEC: Dr. Belsito? I might point out that the FDA guidance specifically states that the recommendations in this guidance do not address the use of DBP or DEHB in other types of FDA regulated products.

DR. BELSITO: Well, diethylhexyl phthalate is not a cosmetic ingredient anyway, right? I mean, because we deal with what, dibutyl, diethyl, and --

MR. ANDERSEN: Butyl benzyl.

DR. BELSITO: Butyl benzyl.

MR. ANDERSEN: Yeah, that's correct but I think that sentence in the guidance document was written more for the Center for Devices and Radiological Health, which does have diethylhexyl phthalate as a cross to bear because of its use in tubing to keep it flexible.

DR. BELSITO: Okay. So anyway, what we're presented here were three different studies. One done on a South Bronx population of children looking at phthalates in airway inflammation as measured by nitric oxide, and then two studies

looking at diabetic populations. One from Uppsala, Sweden and the other based upon the NHANES data in the United States.

I thought the phthalates and airway inflammation -- I mean, they were able to draw some lines but when I looked at the scattergrams it looked like it was all over the place and I had a real hard time making any sense of it.

The diabetic studies -- I'm not a statistician and I was just sort of overwhelmed with the statistical analysis of these studies, but also impressed that there did seem to be somewhat of a correlation with urinary phthalates and diabetes. And then a possible explanation for this, you know, based upon the nuclear praxisome proliferating activity and the fact that there are drugs that target that to treat diabetes.

So, I don't know if that's cause for re-opening because I'm not sure that phthalates from cosmetic preparations are absorbed to a level where that will reasonably occur. Also, they were looking at phthalates that aren't used in cosmetics, so I really thought that when I was looking at those levels of non-cosmetic

phthalates that there were other sources that were likely more important if this was even real, which I'm not sure it is. But there were sources of phthalate exposure such as freezing plastic water bottles or microwaving in plastic whatever that probably were more important than what we were seeing in terms of exposure from cosmetics.

But that was my own personal view, so I open it up to people who know more about phthalates and diabetes and airway inflammation than I do.

DR. SNYDER: Who would that be? (Laughter) Yeah, I read the data on all these. I thought they both did a good bit of addressing the study limitations of both studies. I still think that the big missing link is what's the underlying mechanism. You know, we have these associations but how does that link that they're related, I think is one issue.

I did want to know that we did not have -- I didn't understand why we did not have the Gaithera, 2004 reference was not in our document, in our report previously. But I thought that we had addressed the issues related to -- in

the old report we did address the metabolism issues and the enzyme systems as it pertained to the diabetes report. So, I thought we had addressed some of that even though it wasn't directly linked maybe at the time to diabetes, but we were already aware of those issues about the enzyme systems regarding the metabolism of the phthalates.

So, I wasn't all that concerned about the new data set in regards to what we already know about the phthalates.

DR. LIEBLER: I think the papers establish that there is a relationship between the parameters measured and nothing more. I -- you know, for example between exhaled nitric oxide and urinary phthalate metabolites. There is a statistically significant relationship that may or may not be biologically significant, and so I felt that way about all three of these papers. Essentially there are three variations on the same type of study.

And so I said, okay, well if we did use this to re- open what the heck would we do once we did that? Because we can't interpret these

studies at any level mechanistically that would inform our evaluation of our prior conclusion. So for that reason I felt that we really can't use these studies to really re-evaluate our conclusion because they provide really no mechanistic insight as to whether or not there's any causal relationship between these ubiquitous environmental contaminants and the disease states -- either airway disease or diabetes.

So I felt if we did re-open it we'd have no place to go and we wouldn't really end up being able to change our conclusion. So for that reason, I suggest we do not re-open.

DR. KLASSEN: I'll basically second what Dan said. You know, these are -- these three studies kind of show a weak association. You know, the data is not that impressive. You know, they are statistical associations. I mean, we know that the -- what the phthalates do biologically, and that's been covered before.

I question that it is a biological significance, or even if it might be reproduce-able in another study. So, there are many explanations for why these associations

might occur and to suspect that they really are important is premature at this stage. And I think we should not re-open, because of these papers or anything else.

We also have another paper, I guess, on our desk this morning in regard to the sulfation with the phthalates that we might want to address.

DR. BELSITO: I didn't see that.

DR. KLASSEN: It had to do with sulfation.

DR. BELSITO: Oh, that was part of the child/infant report.

DR. KLASSEN: Yeah, might use it two different ways.

DR. BELSITO: Oh, okay. So we acknowledge the papers, we've read them and don't want to do anything with them. So, Alan, how do we communicate to the public that we did this?

I mean, were we being asked to potentially re-open this on the basis of this data? I thought this was like a panel FYI.

MR. ANDERSEN: Well, it's a panel FYI but you do need to make the decision if the information crosses the threshold to re-open.

DR. BELSITO: Okay.

MR. ANDERSEN: By saying that it doesn't, we'll capture that in the minutes of the meeting and it will become a matter of public record.

DR. BELSITO: Okay.

DR. BERGFELD: But also, it will be in our record and the annual report, will it not? That which we have not re-opened and the reasons given.

SPEAKER: Yes.

DR. BELSITO: I guess the only thing that I have a slight discrepancy with is, you know, when we say, you know, we have no mechanistic clue. I would agree with the airway inflammation but, you know, I thought the argument for the peroxisome proliferator receptors in diabetes was pretty cogent. So, I think they offered a potential mechanism there, so I think we have to come up more with then just a statement we don't think there's any mechanism that helps us.

You know, my point was that they were looking at levels of phthalates that aren't used in cosmetics and in fact the -- as I interpreted the data, the burden from cosmetic use was

insignificant compared to burdens from other exposures, particularly given the levels of non-cosmetic phthalates that were found in the urine. So, that was my point. Not that, you know, these were interesting articles. You know, there was an association, there was a potentially plausible explanation for a link. The issue was, we don't think the exposure is largely from cosmetics, we think the cosmetic exposure is negligible and that -- number one, and number two there needs to be further investigations. You know, there were limitations in the study, as the authors readily acknowledge. These studies had limitations, yadda, yadda, yadda.

But to simply say there was no mechanistic explanation for airways, I would agree. But for diabetes, I would have a little bit of a pause.

DR. SNYDER: I agree. I think they did address, and very well -- they said this could potentially be a plausible mechanism, but they even conclude themselves that their data set is insufficient at this time to conclude that that is a mechanism action that further studies are

required.

I think it's the same conclusion that we would come up with if they hadn't written that, or that's what we're saying, is that we are aware of these associations but at this time there's no data to support they're nothing more than associations.

DR. BELSITO: I'm sure you can wordsmith it.

MR. ANDERSEN: Message received..

DR. BELSITO: Five minutes -- do we have a chance to look at PEGS cocamine? This is new data, it's Round 2 on the PEGs cocamine.

The first go-around we basically -- this was an insufficient report and CIR came back to us with some structural activity relationship software and we basically said we don't like it, it's not good enough, and -- number one. And number 2, we would like to understand how SAR works, and so Phase 2 was that series of speakers were brought in March and June and it wasn't just for our education, per se, but it was a way of re-introducing SAR data to support the PEGs cocamine.

So, it's coming back to us, I think, with a lot of additional data, very structured response from industry, and a look at how other groups are approaching this using SAR data, what's out there, and we're not being asked, really, safe or unsafe based upon this but at least from what we've seen is there good grounds to proceed and re-open it? And when we do that, add in other PEGs cocamine -- and I certainly thought there was adequate data to suggest that we could re-open it and probably come with some safety.

Question I had -- and I don't know, not being a chemist -- is that in my review of the data it appeared that the trialkylamines might be problematic because of lack of data to extrapolate from a number of biological endpoints, and I didn't know if any of the ingredients were being able -- being asked to look at were trialkylamines -- so my question to Dan is, are they? And then if they are, my answer to industry would be, at least based upon my review of this SAR data we may not be able to extrapolate using SAR data for trialkylamines.

DR. LIEBLER: I'm not sure how strong the data are for the trialkylamines. I think that we could re-open the attempt to use SAR to cover PEG-2 cocamine is, in my view, unsatisfactory. It's unconvincing. But so if we re-open, we need to be able to cover PEG-2, PEG-4 data. We have sort of a big chemical space gap between the longer PEGs and these small derivatives.

DR. EISENMANN: Is that for all inputs? Because there was some data for PET-2 talamenes and systemic geno- toxicity data on the PEG-2 talamenes.

DR. LIEBLER: Yeah, mainly on the sensitization and irritation.

DR. EISENMANN: Okay.

DR. LIEBLER: So, that shouldn't be too hard to generate.

You know, so that -- I am okay with re-opening it but that's what we're going to need, in my view.

DR. BELSITO: So, you feel we need data on PEGs 2 and 4 cocamine for sensitization and irritation?

DR. LIEBLER: I think so, yes.

DR. BELSITO: And that the other endpoints would be okay.

DR. LIEBLER: Well, I'll tell you what. If we re- open it we'll take an even more careful look.

DR. BELSITO: And are any of these trialkylamines? Because if you read through the report there's basically, again, a lot of endpoints where there were no data on trialkylamines. I think that was best done -- and this I did a while ago. But, was there one that was done by a high- production volume group, EU group, or something?

SPEAKER: The EPA.

DR. BELSITO: The EPA, yeah, that one. Where they went endpoint-by-endpoint and said whether there was sufficient data. That was my only question. I thought that, you know, the arguments were very cogent. I'm actually not that concerned with PEGs cocamine causing sensitization and irritation, but --

DR. SNYDER: Yeah, I just took it as far as re-open and explore expanding to include all those ingredients. But until we see the data, I

can't identify what the specifics might be to data needs to include everything.

So, I mean, I didn't go into this in as much detail as you seem to be expecting because I think the issue is re- open or not. And if we re-open, then we can address the data needs.

DR. BELSITO: Okay. So, we're going to re-open and that's all we're going to say at this point. Industry should be alert that Dr. Liebler is a little concerned about PEGs 2 and 4 cocamine for various reasons, and I'm a little concerned about SARUs if there are any trialkylamines in this group, and I don't have a clue as to whether there is or not.

MS. BRESLAWEC: Dr. Liebler, if I could characterize your concern on the SAR, it's specifically regarding sensitization, that you will consider the SAR for the geno-tox separately -- will give more detail.

DR. LIEBLER: Yeah, that's a good point. I actually made a comment here on my copy of the document.

I think an alert for sensitization potential is a little less meaningful than alerts

for geno-tox or other endpoints like that, because we have a much better mechanistic understanding of the geno-tox than we do of the sensitization. So, just to flag a structure and say sensitization potential, I have less confidence in that.

MS. BRESLAWEC: I appreciate that, because I mean as you know we've been proponents of trying to get the panel to consider the SAR data, especially in this one for the geno- tox. So, appreciate that.

DR. LIEBLER: Don, we just need to clarify. The basis for re-opening is to expand, not for any safety issue.

DR. BELSITO: Right, okay. Let's do one more, since it's a final. Tin(IV) oxide. I mean, I have report looks fine. Does anyone have issues with the final?

So, safe in the present practice of use and concentration. Don.

DR. LIEBLER: To be abstract, the panel concluded that chlorphenesin is safe.

DR. BELSITO: Yeah.

DR. LIEBLER: Busted.

DR. BELSITO: I picked that up also. Okay.

SPEAKER: Lunch.

DR. BELSITO: Let's end it here and we'll start with another hair dye when we come back from lunch.

(Recess)

DR. BELSITO: I saw Alan go into the other room, so I'm assuming he's not coming back with us.

Okay, so next ingredient is m-phenylenediamine and its sulfated salt, and so this is a re-review. Again, in '97 we went with a safe as used up to 10 percent conclusion. Again, at that point we were putting percentages on because we were no longer getting the information on concentrations of use.

There is basically some new sensitization data, new geno-tox data, and the question is whether we need to re-open it based upon that new data. I didn't think so, but I was just curious because there is a statement that the EU has banned these and I didn't understand why.

DR. EISENMANN: This is one of the

ingredients that industry decided not to support.

DR. BELSITO: In what way?

MS. BRESLAWEC: In Europe, the industry was required to submit additional information in support of hair dyes and they chose to do so for quite a number of hair dyes, and this was one where they did not. And the likelihood of additional data being generated right now on this particular compound are pretty much nil because of the animal test ban that's going into effect early next year.

DR. BELSITO: Right, okay. So, I guess you know, when you make a statement like that, particularly if the statement is going to appear in our decision not to re-open an ingredient that we have found to be safe, it would be important to put the reason why that, you know, in the EU there has been a regulation or whatever or a request for this additional data to support the safety of this chemical. Industry chose not to submit it, and rather than banned -- because banned implies to me that, you know, there's something bad about it that's known and therefore you can't use it. You know, that this ingredient is not to be used in cosmetic products in Europe.

But just to simply give me a sentence that says it's band, I'm going -- you know, what the heck is going on here?

DR. BERGFELD: Could I ask you a question? Does the request apply to all the hair dyes in the EU? Or just to specifically this one? The request for more documentation or?

DR. EISENMANN: Yes, it is applied to all of them. They were reviewed all of them, and industry decided this is the -- these are the ones we're going to support and these are the ones we're not going to support. And the ones they're not going to support they put on the Annex 2, which is -- they call it the Banned List.

MS. BRESLAWEC: The list --

DR. BERGFELD: I would think that would also be important, because if you pull this one out means they are not supporting it means different than they applied the recommendation to all and they -- industry decided not to look into XX number of --

DR. BELSITO: Well, that's what happened.

DR. BERGFELD: I know, but you're asking

for a statement to clarify the banding. But it's even more than the banding. They made a selection of which ones they would support and which ones they wouldn't, but it wasn't specific to this one. It was specific to a group and this one was within it.

DR. BELSITO: Well, I'm assuming it was specific to each ingredient and how economically viable they thought it was for their particular cosmetic products.

DR. BERGFELD: But if the public reading this thinks it was this item only or this chemical only, it puts a different slant on it.

DR. SNYDER: If I'm not mistaken, we've dealt with another hair dye that was also banned for the EU multiple times -- this is not the first time this has happened, correct?

MS. BRESLAWEC: Correct. There are a number of hair dyes that are in this category, which are Annex 2 in Europe and where CIR has determined them to be safe for use.

DR. LIEBLER: So does this -- I'm not sure I completely understand how these considerations effect our decision whether to

re-open.

DR. BELSITO: They don't.

DR. LIEBLER: So -- okay, so this is really a sidebar.

DR. BELSITO: Well, I mean they would only if -- when I said, why was this banned, you know, because they have carcinogenicity --

DR. LIEBLER: Right. Yeah, yeah.

DR. BELSITO: -- and you know, then where is it here?

DR. LIEBLER: And clearly that's not the case.

DR. BELSITO: Right. You're not seeing --

DR. LIEBLER: Strategic decision, a whole bunch of these got put on a list and they said, basically defend these or not. Industry made strategic decisions what to defend for whatever reasons --

DR. BELSITO: Right.

DR. LIEBLER: -- and this wasn't defended but it's a sidebar to our -- I support you on do not re-open. I don't think that -- available --

DR. BELSITO: And it's really moot, because quite honestly --

DR. LIEBLER: Yeah.

DR. BELSITO: -- major hair coloring companies are international. If they can't market in Europe, they're not going to make a special hair dye just for the U.S. So, like methyl dibromil glutaronitrile, which has been banned in Europe, this is probably going to go away from U.S. Cosmetics.

MS. BRESLAWEC: Well, if you look at the usage, it's gone from 162 to 46 for phenylenediamine and 28 to 19 for the m-phenylenediamine sulfate. But there are manufacturers that are using it still, reporting usage in the United States.

DR. BELSITO: Yeah, but we've seen reported usage before where it doesn't exist. But I mean, I'm not disagreeing with you that we need to look at the data even if we think it's going to disappear from the market because of what Europe has decided, but I don't think there's any need to re-open it. I just think when we make that decision if we're going to get that statement,

that it is not allowed in Europe, that we don't use the word "banned", and that it's simply not allowed for cosmetic use in Europe because the companies made a strategic decision not to support the submission of data that would be required for it to be used.

DR. SNYDER: My only other thing was, I think the report -- I would like to -- still like to see in the report a table that has the past use and the current use, even though it was in the text but there's no table that parallels the use concentrations and frequency of use.

DR. EISENMANN: But, is it all right if it's just one line? Because it's only used -- I mean, in some ways it's misleading to put it in deodorants and -- because, you know, it's hair dyes.

DR. SNYDER: But it's not even in the text now.

DR. EISENMANN: No, I think it's in the text. Just the text. There's no table, because it's just hair dye use, so a table -- if you use the regular format, it's kind of misleading because it has deodorants, the baby

powders -- it's a hair dye.

DR. SNYDER: But it has the 2012, but it doesn't have this re-reveiw. So what was the past use, because I want -- we need to document that it is being -- that the use hasn't gone up.

MS. BRESLAWEC: Yes, we certainly will provide that.

DR. BELSITO: Anything else? Okay.

DR. BERGFELD: I would like to ask a question. Are you going to say when you don't re-open in a little bit of a discussion about the current use being 0.1 to 0.2 percent, rather than the 10 percent which it was approved for? I mean, some statement as to the difference in concentration being so much lower now. Not that you're changing the concentration --

DR. BELSITO: We don't actually know that the concentration is lower. Again, at the point where we're making these recommendations we didn't know the concentration. That's why we started -- I mean, we started -- we went through that phase of three or four years where we would take the weakest link and set a concentration limit based upon that, even though if it was

totally unrelated to how it was used.

I mean, you know, we could make a point in the discussion that back when we allowed the 10 percent it was at a time when we had no clue what the percentage was in the product, and this was based off of sensitization and irritation, and in fact now that we know it's only used at.2, if anything, it's even safer. But I'm not sure that you need to get into that much detail for something that we're not re- opening. I mean, that's my own personal bias.

DR. BERGFELD: Well --

DR. BELSITO: I mean, it will be there in the table where it's currently used.

DR. BERGFELD: Well, we have two ingredients that we're looking at that have reduced concentrations of use. Both we're not reopening. But I just think it's sort of an interesting trend downward, and that we need to make some kind of comment about that..

DR. BELSITO: But it's not a trend downward, Wilma. We don't know --

DR. BERGFELD: I understand what you just said, but at least --

DR. BELSITO: We submitted it, we didn't know what the concentration was.

DR. BERGFELD: Looks like a trend downward.

DR. BELSITO: Well, then make that -- I mean, we could make that comment, I suppose. I mean, at some point in the discussion, but then you know, it has to be explained that the 10 percent wasn't what was being used. We didn't know what was being used, and the 10 percent --

DR. BERGFELD: But the patch testing reflected that --

DR. BELSITO: Right.

DR. BERGFELD: -- in the human studies, so.

DR. LIEBLER: I think if we had a situation where we actually knew the use concentration and then over the passage of time -- with the passage of time the use concentration is actually going down, that's the time to bring it up.

When we have essentially an upper bound based on some type of testing where we actually didn't have a record of the use concentration,

then we can't say it's going down.

DR. BELSITO: Yeah.

DR. BERGFELD: Well, that's true, of course. But these were products dye containing, and they were actually measurements of what was being tested was a product. And what we had in -- how much PPD was in it, so it -- well, either way --

DR. LIEBLER: So if we know that it's going down --

DR. BERGFELD: -- makes a note of it.

DR. LIEBLER: -- then it becomes reasonable to note it because that actually -- particularly if we're not going to re-open, because that helps to add to the logic of not re- opening.

DR. BERGFELD: Yeah.

DR. SNYDER: I think it's just a conundrum of the old report philosophy, basically putting the limitation based upon the highest concentration patch tested.

DR. BERGFELD: All these product formulations, so it was in use at that concentration. That's what the point is.

MS. BRESLAWEC: Actually, if you look at the old report in Panel Book 28, it says that CTFA provided information in '95 saying that they were used in hair colorants at concentrations of up to 3 percent.

DR. BELSITO: Well. And, Wilma, they weren't formulations. I mean, if you look at Panel Book 47, skin irritation and sensitization potential, there were occlusive patch tests done in petrolatum. So, we weren't using product formulations to base our values off of.

I mean, if you feel strongly we can make a slight mention of it but I think it's misleading because it would make people think that it was being used up to 10 percent. And as Halyna just pointed out, the data we had was that even at that point it wasn't. But it was that weird two or three year error in the panel where we had nothing to go by, we could no longer say safe as used because we didn't know how it was used, and we're just putting limits on everything.

DR. SNYDER: Alan isn't here to address this, but I mean I'm sure that would then be re-opened and change the conclusion without a

limitation and just say safe as used.

DR. BELSITO: I don't think it's going to be used up to 10 percent, I don't think we need to re-open it.

MR. JOHNSON: Dr. Belsito?

DR. BELSITO: Yes.

MR. JOHNSON: Is there any specific language that you would like to be included in the discussion section?

DR. BELSITO: I mean, not me. I don't think we, you know -- other than the fact that it needs to be very clear that it -- when you say it was banned for use in Europe, I guess that's true. I would get rid of the "banned", though, and say "not allowed for use" in Europe, since industry failed to submit the required dossier that would have allowed it to have been reviewed, which I think -- is that an accurate statement?

MR. JOHNSON: Do we have a reference for that?

DR. BELSITO: I'm sure that Halyna can provide a reference that industry declined to submit a dossier.

MS. BRESLAWEC: We will provide

something along those lines.

DR. SNYDER: I mean, it could just be simple terminology -- failed to provide the necessary documentation, according to the --

DR. BELSITO: Elected not to --

DR. SNYDER: Elected not to, according to the Annex regulation, or something. Whatever that is specifically referred as.

DR. BELSITO: Okay. Anything else? Okay. So, moving on to methyl glucose polyethers and esters. So, back in September we issued an insufficient data announcement and we wanted skin penetration on the polyethers, and if there was evidence of absorption, repro and developmental tox. We wanted geno-tox, we wanted RIPT on methyl glucose dioleate, at a use concentration of 2 percent, and study details for the RIPT on methyl glucose sesquistearate and the safety assessment. And then, we asked Wilbur to go out and get whatever information there was on methyl glucose and methyl glucoside, since they were in the background of this. Although, I actually didn't see much if any information on methyl glucose or glucoside.

So, what did we get? We got penetration data suggesting that it's limited, and that these are not water- soluble. We've gotten geno-tox data, but only on PEG-120 methyl glucose di- and trioleates. So the question is, whether that will cover the other members of this group, and I'll leave that to Dan to discuss first in terms of chemical similarities, and Curt and Paul to chime in.

And so, if in fact the geno-tox data is okay, I think the sensitization and the irritation data is okay, and the other part of the equation in addition to whether the geno-tox data is okay are the impurity data that we have now okay-ed to go forward. And I'll open the floor to Dan, if you want to comment on chemical similarities and your view on generalizing the geno-tox data.

DR. LIEBLER: Yeah, I didn't have a concern about that. I think the concern about that arose in the discussion from the other teams of reviewing the minutes from last year -- last month -- last meeting.

We actually didn't get any data on

penetration. What we got was a statement from the manufacturer saying that they didn't think penetration was likely because of the molecular weights of these compounds. I basically agree with that. Again, the concern about dermal absorption didn't come from this team, it came from the discussion with the other team and it was part of the list that we agreed on when we had our full panel meeting.

I think that on Panel Book Page 17 under toxicokinetics, the content -- the underlined, added content on molecular weight and absorption -- it's basically not data, so it doesn't belong there. When we say that, you know, that there's a statement that these shouldn't be absorbed, that's not the same as having data that it's not absorbed.

I tend to agree that the molecular weights of these are going to preclude any significant absorption. That can go in the discussion, because the molecular weight information if it's not already in the tables, it should be. And it's --

DR. BELSITO: So what do you want

struck?

DR. LIEBLER: So, it's actually the new content on Panel Book 17 --

DR. BELSITO: Right.

DR. LIEBLER: -- under toxicokinetics, the first paragraph.

DR. BELSITO: Right.

DR. LIEBLER: The underline -- all the underlined stuff in the first paragraph, it's not really data. It's just a statement from the manufacturer.

DR. BELSITO: So that should -- you want that moved to physical chemical properties with molecular weight?

DR. LIEBLER: The molecular weight can be incorporated in the tables describing the ingredients --

DR. BELSITO: Right.

DR. LIEBLER: And the rest of that verbiage just goes, because we can say that in the discussion that we feel that the molecular weights of these compounds are going to preclude any significant dermal absorption.

So, essentially in essence we're

striking all of that. So all that's going to be left is what is in the original draft. The report, I think, will -- where it basically says, studies on the absorption, distribution, metabolism, et cetera, were not found in the published literature, period.

Now, you can leave in the pulmonary absorption part because there's actually data there.

MR. JOHNSON: On methylglucoside?

DR. LIEBLER: Yeah, of the methylglucoside. There's also a paragraph on enzymatic activity on Panel Book Page 19. It's about 2/3 of the way down. I think that's just sort of borderline interesting phenomenon that doesn't really have anything to do with the effects of these materials, so I would -- I didn't see what that was relevant to. I would suggest that that be deleted.

And then, Don, as far as your question about the -- whether these compounds in the current report can all be grouped together? I didn't have a problem with any of them being there.

DR. BELSITO: I guess my question was, can the geno- tox for the two we have be used to cover the others? Because it's for the high molecular weight PEGs, PEG-120.

DR. LIEBLER: I don't think that these compounds look like they should have any geno-toxic potential. The high molecular weight PEGs are really the highest molecular weight compounds in the whole group. Some of these smaller compounds might not have the same physical properties as the high molecular weight PEGs. I don't think they have geno-toxic potential. They don't carry any functional group that would suggest that that would be an issue.

DR. BELSITO: I mean --

DR. LIEBLER: So I don't think we need to request additional data.

DR. BELSITO: My feeling was that we've looked at PEGs of smaller molecular weight and haven't seemed to be concerned. So that, you know --

DR. LIEBLER: Yeah, it wouldn't be the PEG part --

DR. BELSITO: It would be the methyl

glucoside?

DR. LIEBLER: The glucoside part, either. You know, I don't just see --

DR. BELSITO: So it would be neither part?

DR. LIEBLER: No, right.

DR. KLASSEN: There's nothing left when you get rid of the two parts.

DR. LIEBLER: Exactly right.

DR. BELSITO: So, they're an infertile couple, you know? There are problems.

DR. LIEBLER: I really don't see an issue there.

DR. BELSITO: Okay.

DR. LIEBLER: If somebody wants to raise it tomorrow you can argue it, but I just don't see the point.

DR. BELSITO: Okay, you will argue it.

DR. LIEBLER: That's fine.

DR. BELSITO: So be prepared. Okay, so then if we have no absorption data but we have molecular weights and we're comfortable in the discussion saying they're not going to get absorbed, and we have enzymatic activity deleted

and it didn't really make a difference, and we're comfortable with the geno-toxicity based upon our knowledge of PEGs, methyl glucoside, the glucose, and the two data points we have, and we're comfortable with the sensitization and irritation, then we're comfortable with going ahead as safe as used. And discussion points would be lack of absorption based upon molecular weight.

And Rachel now will say that since we have no carcinogenicity data we need to say something about why we weren't concerned about that, which we will do. Anything else to go in the discussion?

DR. SNYDER: Not a discussion point, but I had a question for you about the two RIPT tests that we had. One was at 25 percent. Is that 25 percent of the PEG-120 methyl dioleate?

MR. JOHNSON: What page are you on?

DR. SNYDER: It's on Page 115 of the Panel Book. We had one at.59 percent, but then this second one I couldn't -- it was written in, I wasn't certain where the number 25 percent -- Page 115 of the book.

MR. JOHNSON: In the raw data?

DR. SNYDER: Yeah. So, we didn't specify our insufficient data announcement, we just said at the maximum use for methyl. They gave us a PEG-120, and then --

So the one was just methyl glucose dioleate at .59 percent, but it wasn't at the 2 percent we asked for. But the 2 percent we asked for is of the PEG-120, methyl dioleate. So is that sufficient in your mind to alleviate that?

DR. BELSITO: I was fine with that. It --

DR. SNYDER: Because we can ask for 2 percent of the methyl glucose dioleate.

DR. BELSITO: Yeah, and then going back and looking at that at I didn't understand why because the highest use concentration was 0.6 percent, and then we have a study at 0.59 percent. So, I thought that that was sufficient although I'm having trouble locating it now. I think it was in the tables, right?

I mean, if you look at the table, I saw that, too, and I couldn't -- unless you change the concentrations of use.

DR. EISENMANN: I think when I went back to somebody who was reporting 2 percent in a leave-on they said, oh, that was a mistake. And that frequently happens.

DR. BELSITO: Yeah.

DR. EISENMANN: So that's the 2 percent leave-on --

DR. BELSITO: So, the new leave-on was.6 for the dioleate. We had RIPT at.59, which is essentially the same. So I was very comfortable with the sensitization and irritation data. So, any other discussion points? Really the biggie is, we don't have penetration data but we're not worried about it because of the molecular weights and the polarity. Is that the answer?

DR. LIEBLER: Correct.

DR. BELSITO: Okay. Another one bites the dust.

DR. BERGFELD: Can I ask you a question?

DR. BELSITO: Yes, ma'am.

DR. BERGFELD: In your experience in the contact dermatitis world on these ingredients, you patch test any of these ingredients?

DR. BELSITO: You know, I do in

formulation but they're not ingredients that have been pointed out as really as significant issue in terms of allergy. So, do I test for these like I test for methylchloroisothiazolinone with a pure allergen? No. But, typically I'll look at what patients are using and I will test product as-is. I really haven't seen anything.

DR. BERGFELD: Okay.

DR. BELSITO: Okay. I sort of like the name of this. Hydrolyzed source protein.

MS. BRESLAWEC: (OFF MIC)

DR. BELSITO: Oh, source amino acids. Oh, I'm going the wrong direction. Okay, so source amino acids.

Okay, so these are amino acids. We already looked at amino acids, but now we're looking at the racemic mixtures of D- and L-amino acids and they're derived from different sources. And I think that -- you know, I think we can use the L- for amino acid report. I thought we could bring in some of the sensitization and irritation data or at least summarize it from that report, because we've already said the big issue is going to be skin.

Yeah, the aerosol issues we can deal with. The PKU and the glutamate issues we deal with the same way we dealt in the amino acid report. I guess the big issue here was, for me, what were the sources of collagen, elastin, and the non- human hair keratin that were sources and, therefore, we have the whole virus prion issue that we need to raise in discussion because all we're told is that it's the, you know, source amino acids from collagen. Well, where's the collagen come from?

So, I think we can cover that all in discussion and just go ahead with a safe as used by bringing in some of the skin -- or summarizing the skin stuff from the amino alpha, amino acid report. And that's where I was.

DR. BERGFELD: Do you remember what they did with those animal-based materials before that purified them? It seemed to me we've had this issue before.

DR. BELSITO: We just restricted the -- you know, that they should not contain the --

DR. BERGFELD: Contain -- yeah, and I

think FDA has some pretty specific directions on this in terms of how they're processed and how they're manufactured. And if they are, then they're okay and if they're not, then they're not. So --

DR. BELSITO: Right.

DR. BERGFELD: -- it's been dealt with before.

DR. LIEBLER: These appear to be pretty much uniformly generated by complete acid hydrolysis followed by ultra-filtration, and I don't know if those comport with the FDA recommendations on purification methods to minimize contaminants but the -- to the extent that those methods are used to attain consistent purity and avoid un-hydrolyzed proteins as impurities, then I think it's probably fine.

MS. BRESLAWEC: We've not submitted a lot of manufacturing information yet, and we will look for data where it's available.

DR. LIEBLER: That would be helpful, because the only -- I agree with Don about bringing the L-amino acid report into the sensitization/irritation section just so that in

can be clear that there are data. And then, simply to add maybe in the discussion that the main -- any main source of irritation/sensitization here could possibly be contaminants from incompletely hydrolyzed proteins.

DR. BERGFELD: So, where would that leave this document?

DR. BELSITO: I don't -- moving ahead as a tentative final safe as used.

DR. BERGFELD: And you're agreeable all this will be added and you'll look at again or you won't look at it again?

DR. BELSITO: Well, we always look at it again as it comes back as a final document. I mean, basically --

DR. BERGFELD: It'll go out without you looking at it and then come back as a --

DR. BELSITO: Right, I mean I have no problem --

DR. BERGFELD: You have some data being added. Is it --

DR. BELSITO: Well, I mean we're adding a summary of irritation and sensitization data from the alpha-amino acid report, and you know I

mean, it'll come back as a tentative final. Or I mean, it can come back as a green. I don't really care, but I don't really think there's a lot that needs to be done to this report, other than you know, pretty much add the sensitization and irritation data, pretty much take the discussion from the -- in terms of, you know, PKU and glutamate issues. And we must have dealt with the amino acid report on animal sources, so essentially take the exact same language from that discussion and put it into this discussion.

I don't really see the need to re-review it.

DR. LIEBLER: I think there's not animal sources with the alpha-amino acids. Those are mostly bacterial fermentation products, right?

DR. EISENMANN: Yes.

DR. BELSITO: Okay.

DR. BERGFELD: That's why we separated them.

DR. LIEBLER: Yeah.

DR. BELSITO: Well, so then we just take it from another -- any of the other animal reports we did on how we phrased that it should be free

of infectious particles.

DR. LIEBLER: But I think the part about including the data on irritation and sensitization isn't a big stretch for us because we just did that on the alpha-amino acids report and, you know, I think that's --

DR. BELSITO: I think can come back as a tentative final, I mean --

DR. LIEBLER: Which would be --

DR. BELSITO: All we're going to do is editorialize, possibly, the discussion. I think we're all comfortable with the conclusion, which is the one thing that can't change. There's not really a lot that needs to be added to this.

DR. EISENMANN: Well, unless you want more information about, like, what Dr. Liebler -- if there's any hydrolysis proteins, if you want more information on method of manufacture, if you say "safe" I might have trouble getting that from companies because you've said "safe".

DR. BELSITO: Dan?

DR. LIEBLER: The only reason I bit was because Halyna suggested that it was there for the

taking.

MS. BRESLAWEC: I withdraw my offer.

DR. LIEBLER: I mean, I think we're okay with what we have, but if there was even more substantial documentation I certainly wouldn't say "no" to it.

DR. BELSITO: Okay, so let's get this straight. Are we going with a safe as used, we want it to come back as a blue document, we want some of the summary of the sensitization and irritation data, and essentially the discussion from the alpha-amino acid paper. And we want it added -- the boilerplate that we've already decided upon for cosmetic products that are animal-derived added into the discussion as well. At one point we were doing viruses and prions and then we changed to just infectious materials, but there's a recent boilerplate that we approved that that be brought into the discussion and then we're done with it.

So, that's what we're recommending.

DR. SNYDER: I had re-worded the -- on Page 8, the top of the page, the toxicological studies? So I had written down some language to

re-word that, saying the toxicities from dermal exposure would not be expected to be different from oral exposures, and as such are not of concern by the CIR Panel. Irritation and sensitization are of a concern, and the focus in this report -- and then follow with the, but data from the alpha-amino acids support that these would not likely be sensitizers, irritants, or sensitizers. So I have that written in here for you, Christina, to improve upon that language a little bit.

DR. BELSITO: Okay. So, Christina, you'll pick up Dr. Snyder's Paul-smithing. Okay.

So now can we move on to source proteins? Okay. So, this also is a new document coming to us, hydrolyzed source proteins. So as opposed to what we just looked at, these are going to be sort of oligopeptides rather than pure amino acids.

And I guess some of the issues that I had as I was reading through this is, one of the sources is spinal cord?

MS. BRESLAWEC: We would suggest taking that one out.

DR. BELSITO: Okay, thank you. That

makes it.

MS. BRESLAWEC: That would be our suggestion.

DR. BELSITO: Good, well I was going to suggest that, too. Okay.

MS. WEINTRAUB: Because it's not (inaudible)?

MS. BRESLAWEC: No, because it's not permitted for use.

DR. BELSITO: Okay, so delete "spinal cord source". Then on Page 4 of the document, I guess it's Panel Book 10, brought up a concern I had even before I saw it with biologically-active peptides derived from soy protein.

And you know, it's not an area that I follow, but I know that oligopeptides have been reported to have a number of different biological activities, and so I wonder now that we've gotten beyond just amino acids, you know, here's one report of hydrolyzed soy having an angio-tensing converting enzyme in hippitory activity. But you know, we have no clue as to what these oligopeptides are and you know, I mean, I know enough that you can get, you know, nine, you know,

amino acids linked together and they can have a biological function and you knock two of them out and they no longer have that function. So I'm just very worried that I have this group of chemicals that, you know, it's worse than the botanicals because I don't know what's in it and I, in my very naïve way, have heard reports that these oligopeptides can have various functions depending upon their length.

So, that was what my two concerns -- I'm not comfortable going with a safe as used, and I am not even comfortable knowing what I need to know to make them safe as used because I don't know what I'm looking at.

DR. SNYDER: I ping-ed the document for similar reasons because the FDA defines amino acids as a single amino acid, and then they define peptides up to 40 amino acids, and then proteins or anything over 40 amino acids. So, is it our definition of a protein? So is this report only dealing with not the smaller peptides, only dealing with -- I mean, is that a common -- I'm not aware of that being a common designation as -- when you talk about a protein versus a

peptide.

DR. LIEBLER: So, really a protein is any peptide, really, could also be called a protein. So, you know, two amino acids technically could be called a protein even though it's commonly called a peptide. But there's not a molecular weight cutoff or a number of amino acids. It's clear --

DR. SNYDER: Well, the FDA has a cutoff. There's documentation here the FDA says that the 40 amino acid is a cutoff. That anything less than that is considered a peptide.

DR. LIEBLER: I didn't see that..

DR. SNYDER: And over is 40. That's what ping-ed me on it, because we have these reports that specify amino acids, and we have reports that go all the way to protein. But then.

DR. BELSITO: Well, and the uses are not trivial. I mean, we're talking about, you know, probably 2,000 -- well, I mean, there is over 1,000 just for hydrolyzed wheat protein, that's the biggie. And hydrolyzed soy is also huge, no?

DR. LIEBLER: So what's the question, Paul? What's the -- could you sort of re-state

your concern?

DR. SNYDER: Well, it was -- just made me aware of something to think about and was going to what Don raised about these smaller size proteins, having these activities --

DR. LIEBLER: Okay, so this all hangs on this one Reference 21, which I just tried to look up on my Papers app on my iPad and I couldn't -- it didn't find it. The journal looks fairly obscure, so I don't know if you can provide me a copy, Christina, of Reference 21 so we could take a quick peek at it.

Depending on how that story was done, I mean, they might have -- you know, if they just hydrolyzed soy protein, purified some fractions, and then incubated them with some types of in-vitro, you know, model systems or proteins or enzymes and looked at inhibition then I would say, big deal. If they actually used some type of a model system that was more relevant, particularly to the kinds of exposures that we would be talking about here, then I would say we need to look at this more carefully.

But I suspect this is some kind of a,

you know -- take some peptides from soy hydrolysate, stir it in with some simple other in-vitro biochemicals, and record some result, and that's why it went into such an obscure journal. But I'd like to see paper.

MS. BURNETT: I'll pull it up for you right now.

DR. LIEBLER: Great, thank you. So there really might not be anything there to be concerned about. It would be good to take a look at the paper.

In general, I think with these protein hydrolyses here you are -- you've got proteins that differ -- all the amino acid -- all the peptide bonds and the proteins differ in their intrinsic susceptibility to hydrolysis, either by HCL or by enzymes. And so, you're going to get a mixture of the most easily-cleaved peptides and the least easily-cleaved peptides, which will be the longer ones. And depending on the purification system used, either the longer ones or the shorter ones are going to get discarded because usually there's an ultra-filtration step, particularly when they use a protease to do the

prep, there's an ultra-filtration step used to get rid of the protease. So basically, the big stuff won't go through the filter and the smaller pieces go through the filter.

Carol, am I on the right track?

DR. EISENMANN: Yes, and what the industry is concerned about is Type 1 allergy.

MS. BRESLAWEC: Type 1.

DR. EISENMANN: Type 1, immediate contact sensitization. And one approach industry has been taking is trying to look at the size of the proteins and I guess the theory is that if it's below a certain size it cannot bind in the (Ig)E antibody. And we tried to provide -- we'd like you to look more in-depth and more theoretical references on this issue, because it is an issue of concern..

And I don't know if you're aware of -- there was an issue in Japan, and that's part of the -- I put a memo out this morning that describes they've been looking at this for a while, and they have a special committee in their -- it's the Japanese Society of -- I want to say "allergies", it's easier than the word they're

using. But they're planning to continue to look at this issue for a couple more years.

I found a recent abstract -- it's in this instance, they had like 400 or some cases of people reacting to soap that contained a hydrolyzed protein, and I found an abstract this morning that's just a high molecular weight protein.

I don't know -- I only found the abstract today, so I don't know the details.

DR. BELSITO: I mean, I guess that's what bothers me about this report, is that we don't even have a Dr. Duke's Phytochemical and Ethnobiologic Dictionary to look at and tell us, okay, when we partially hydrolyze soy protein, how many amino acids are we looking at? And I have this obscure knowledge that oligopeptides can have all of these biological activities. Now, chances are they don't penetrate the skin and have biological activities internally, but what kind of biological triggers do they sense in the skin? Not just contact sensitization. I mean, most proteins really aren't contact sensitizers. You know, but do they trigger, you know, receptors

that make you more or less likely to develop sun- induced skin cancers or melanoma, you know? I don't know. I just don't know what's in this report.

I don't know what I'm reviewing, and that's what at the end of the day bothers me.

DR. SNYDER: Yeah, the size issue is complicated because many things that people are allergic to are actually heptynes so they don't bind directly, they only bind when they're complex with commonly-present proteins in the skin.

DR. BELSITO: Right.

DR. SNYDER: And so that -- I don't buy that argument, certainly not from a hypersensitivity point of view.

DR. BELSITO: Rachael?

MS. WEINTRAUB: This is also one of the reports that I tagged where carcinogenicity is not mentioned. There's not one of the bullets that says "no carcinogenicity data was found", there's just no mention.

So, you know, it's one of those two where, you know, if there was none found but

there's other data that was found, that leads to that conclusion, that needs to be mentioned.

DR. KLASSEN: I thought also here where we summarize the data in the table -- this is CIR Panel Book Page 11 -- you know, where we say it's just at Table 5 or it's just in Table 4 or Table 6, Table 7, I think we should give at least a sentence or two saying that, you know, in essence what does Table 6 say?

DR. BELSITO: I mean, but even then, you know, I mean we can summarize it but -- okay, so there are two studies here on hydrolyzed silk protein. One where, you know, they're doing an LLNA and the other a guinea pig maximization test. But what the heck is that hydrolyzed silk protein? How many amino acids was it? Is it the same hydrolyzed silk protein that is going to be used in a consumer product? I mean, again, my whole issue -- and I don't know how I personally can resolve this -- is even hydrolyzed silk protein is not one ingredient..

DR. EISENMANN: Well, that's one reason at the beginning we suggested that you focus on one protein and to try to look into this complex

issue and then maybe consider the rest of them. Because it is true, each different manufacturer's hydrolyzed protein might be a little bit different, especially when you're talking about wheat. I mean, silk is a loose -- it's -- I think it's a couple proteins but it's, you know, not -- I don't know. Wheat protein is -- there's a lot of different wheat proteins.

DR. BELSITO: It's not even that, Carol. It's where it's cleaved. How many amino acids, you know, and which point in the molecule. I mean, hydrolyzed wheat protein could be several thousand different chemical structures.

DR. KLASSEN: It will be.

DR. BELSITO: And I don't know how to wrap my arms around it, never mind my brain. I just -- you know, particularly since we know that oligopeptides can have biologic function.

DR. LIEBLER: I think these really have to be looked at in the same way we look at extracts, like plant extracts for example. Where we know that it's a complex mixture, we know what the major components of it are, but we know that there's variation from batch to batch between the

exact percentages of all the components. There are a lot of minor components and to be able to define this would require protein by protein analysis of each preparation. That's something that's way beyond anything that industry would ever provide us, and it's probably way beyond anything we need to evaluate the safety of these.

Because you're really talking about the -- these mixtures are going to contain individual amino acids and they're going to contain peptides, and those peptides are the part that's going to be the most variable. And the mixture of cleavages depends upon how the products are prepared. In some cases, you do a partial acid hydrolysis, which is going to be less selective. In some cases it's an enzymatic hydrolysis which is going to be more selective. Again, that's going to depend on the protein, its sequence, and how it folds.

So I think we have to look at these as extracts with sort of net overall similarity in the components, but variations in the individual contributions of each peptide to the composition of the whole mixture.

For first approximation, all of these molecules are identical in properties. That's what I would say.

DR. SNYDER: So are we -- I guess to me, there should be a plethora of oral studies on these, right? Again, going back to the argument used on the last one, the wording saying the oral studies would not think that the skin would present any different toxicities.

DR. BELSITO: I don't know that there's a lot of oral studies on these.

DR. EISENMANN: Well, and oral really doesn't -- in the cut, it's all broken down to amino acids before it's absorbed, rather than on your skin. I don't know that they'd be absorbed.

DR. SNYDER: The point I was going to go to was that are we really only interested in irritation and sensitization? Or are we concerned about absorption and systemic toxicity?

DR. EISENMANN: I think you should be concerned with the immediate type sensitization reactions.

DR. BERGFELD: Well in my opinion,

clinically if an individual who uses something with this extract who is allergic to wheat or some food product, they're going to react.

And so it seems to me we could come at this and individuals who have known sensitivities should not be buying these products.

DR. EISENMANN: Not if the proteins are hydrolyzed to be small enough that they might not see it the same way as if -- I mean, it depends on what they're reacting to.

DR. LIEBLER: It's like maybe, maybe not.

DR. EISENMANN: Right.

DR. LIEBLER: I mean, you really don't know if -- let's just accept the proposition that somebody who has a food allergy to a wheat protein would develop a skin reaction. Then the question is, if their food allergies to the intact wheat protein in some wheat product that they eat, is that same epitope present in the skin in a way that would trigger a reaction? And it's maybe, maybe not and it's just protein by protein. It depends on maybe batch by batch, it depends.

DR. BERGFELD: You're probably never

going to run that study.

DR. LIEBLER: No, never.

DR. KLASSEN: This is actually the same problem that we've had on genetically-modified grains; corn, wheat, you name it. Everything we eat now, basically, is genetically modified. People don't realize it, but it is.

And you know, this is the question. Do you have allergies to these new things? And basically, it's turning out that it's not a problem and I guess my feeling is the likelihood of these -- of hydrolyzed proteins on your skin causing major problems other than potentially -- definitely getting absorbed. I mean, there's no question that polypeptides -- I mean, a lot of our hormones in our body are polypeptides. So polypeptides can have many biological effects, very specific polypeptides.

But the likelihood of any of these products on your skin causing those problems, I think, are rare. I mean, we eat these proteins where we get -- you know, basically gallons of it a year compared to micrograms on the skin. And we don't have our hypothalamus reacting

differently when we eat this, compared to that, so I don't think --

DR. BELSITO: But don't we digest down to the amino acids? I mean, are we absorbing oligopeptides?

DR. KLASSEN: Not very much. We don't absorb them. They are broken down to polypeptides because peptides won't go across biological membranes. Not only the GI mucosa, but even more so the skin.

DR. BELSITO: Right.

DR. KLASSEN: So I think we're protected, first of all, because they don't go across the skin. And so the only potential problem I see is some irritation and local effects, and that is highly unlikely.

DR. BELSITO: But I mean, I guess you know -- I mean, it's a good point. If we could show that they don't, you know, show us a trimer and a tetramer and do an absorption on pig skin and show me that it doesn't get across the stratum corneum, and then to the epidermis, then I'm not concerned. But if it does, then I'm still concerned that those oligopeptides could trigger

receptors on epidermal cells that might have biological effects that aren't apparent in feeding studies. And that's my whole point.

My point is, I don't know what the heck is in these things, and to address what you said, Dan, I don't think it's the same as a botanical because we don't have Dr. Duke's Phytobiological book to give us a range of what to expect. You know, this could be a trimer and it could be a 50-mer. I don't know what sizes and what parts of the protein we're looking at.

You know, hydrolyzed wheat protein could be 3,000 different amino acid chemical structures.

DR. SNYDER: I think we can make the assumption, though, that wheat-based, soy-based, milk-based are going to probably potentially be allergens. We know that, right? Potentially.

DR. BELSITO: Could be, depending upon size and epitope.

DR. BERGFELD: And concentration..

DR. LIEBLER: So, do we know -- oh, I'm sorry. Go ahead.

MS. WEINTRAUB: Well, my question was

just a big threshold question depending on what stage we viewed this as. I mean, if adding hydrolyzed proteins as a category, this whole concept of what we've been doing recently is supposed to be a no-brainer. So, we're adding these ingredients that make sense to add together, so is this one of those instances that because of the huge variety and the implications for that variation that it just doesn't make sense?

DR. BELSITO: I don't think it's the grouping of the ingredients that doesn't make sense.

MS. WEINTRAUB: Oh, okay.

DR. BELSITO: I think the problem is that we don't -- you know, it's like I think if you chop up milk and you chop up wheat you can probably end up with the same oligopeptides from both of them. So I don't think it's a grouping issue. For me, it's an issue that I don't know what I'm looking at.

MS. WEINTRAUB: Okay.

DR. BELSITO: You know? When you tell me it's hydrolyzed wheat protein, you know, what is the size? I mean, you know, maybe we need to

table this or, you know, insufficient for, you know, what size ranges does industry --

DR. EISENMANN: I've tried to collect as much as possible and provided some of that -- I mean, and that's what --

MS. BRESLAWEC: We've struggled with this grouping, frankly, and you know the assessment of this as a category. And what we had proposed, I guess, a while ago was in order to maybe minimize some of the factors that confounded, to limit it to one source and maybe looking at it one source would eliminate some of the confusion -- I don't know if that's the best report or not.

DR. BELSITO: I don't have a problem. I'm very confused right now, so if you want to come back to me with hydrolyzed wheat, which is the highest volume, and get all the information you can for hydrolyzed wheat, that would be very nice. And then, you know, we can, you know, make a decision whether that is helpful in assessing safety. But I personally, you know, would either abstain or vote against the safe as used conclusion for this because I don't even know what

I'm voting for.

MS. BRESLAWEC: Again, I think that's a question that CIR needs to answer or to deal with this. What issues are important to the Panel to be able to characterize so that you can make the assessment? And whatever information we find that's available, we will certainly provide.

DR. BERGFELD: Alan had a memo on his desk this morning that he showed me regarding the conversation via e- mail with the Japanese who care to work with us.

MS. BRESLAWEC: We've raised this issue over the past several years that the Japanese are particularly concerned because there have been reported up to, you know, almost 500 cases of wheat allergy in cosmetic-type products --

DR. EISENMANN: In a soap.

MS. BRESLAWEC: In a soap. And the concern there was that the soap was being used in a shower and then the shower -- that the wheat proteins being aerosolized and causing hypersensitivity or maybe even Type 1 allergic reactions.

DR. BELSITO: Salute. Kurt's having one

right now.

MS. BRESLAWEC: He's having one right now. And so we think it's a very valid concern that, you know, needs to be addressed. We know the Japanese are spending quite a bit of effort addressing it and we would like that body of work to be incorporated into this review.

DR. BELSITO: Okay. I mean, then I am certainly in favor of, you know, going back to what, you know, Rachael suggested, maybe. And that is, let's carve out an ingredient, let's go for the major one, let's look at wheat, try and get us to -- up to speed. Explain to manufacturers what they mean by hydrolyzed wheat protein. Maybe -- I don't know how many U.S. Manufacturers -- major manufacturers -- there are, ask them to give us their spec sheets. What is it, what's in it, so we can get some idea of variability from
manufacturer- to-manufacturer..

DR. EISENMANN: What questions do you want to ask?

DR. BELSITO: I would like to know method of manufacture. I would like to know what

kind of specs they've put out on it. These are, you know -- this is the amino acid structure, this is whatever. You know, I would like information on, you know, sensitization and irritation, and information -- you know, when you do that you could miss sort of carryover reactions, you know, contact due to carry out- type of issues.

But I think the biggest issue I'd like to know, you know, is what is it? Give me some idea of molecular structure. I mean, how many amino acids are strung together? Are you looking at certain aspects of the wheat protein that you're interested in extracting? So, I would like that data from several different manufacturers to get a sense as to how variable, you know, whether -- you know, a rose is a rose is a rose or you know, they're all completely different.

DR. LIEBLER: So, the analytical method that would be most suited to characterize these is mass spectrometry.

DR. BELSITO: Okay.

DR. LIEBLER: This is essentially proteomics. We're talking about --

DR. KLASSEN: No kidding.

DR. LIEBLER: Peptidomics.

DR. KLASSEN: By definition.

DR. LIEBLER: So meaning what actually would be useful -- the best chemical characterization would be what is the median molecular weight of the peptides that are produced by these, and what's the range of molecular weights? You know, what's the distribution like and how consistent is that distribution?

DR. KLASSEN: I'd like to mention --

DR. LIEBLER: One more. Okay, yeah. Yeah, sure.

DR. KLASSEN: Excuse me for interrupting. This is Curt Klassen, for you recorders. But you know, on Page -- Panel Book 17 and 18, we do have some information about "how big" these hydrolyzed -- doesn't have wheat, it has hazelnut, soy protein, and milk proteins. You know, it gives you some idea of the size of these.

DR. LIEBLER: Just to give you an idea, 5-10 to 1,000. That's less than -- that's nine amino acids or less in a row. So, they're small peptides.

DR. KLASSEN: Right.

DR. LIEBLER: So, this does -- one of the things that I'm sort of hearing between the words that Don's talking is the fear that you've got some highly-bioactive peptide accidentally produced by hydrolysis of a protein that triggers, you know, an interaction with the right receptor to produce an adverse effect.

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah. And I think that's sort of the idea behind this Gibbs paper. If I can get a copy of it, I'll look at it more carefully. And I just -- I think that that's likely to be a very chance event, and keep in mind that many of the allergic reactions that are associated with proteins have to do with post-translational modifications on the proteins like glycosylations, for example. Other things that would also be affected by the hydrolysis process, particularly acid hydrolysis or alkaline hydrolysis.

DR. BELSITO: So then, you know, I mean I guess if you're asking where we're going, you know, I would say let's break one protein, let's

look at wheat protein, let's get as much information as we can on method of manufacture or what the molecular weights are.

You know, I still worry that, you know, these oligopeptides could have structural effects on skin. Maybe a 28-day dermal, if there is any out there and some sensitization and irritation. You know, I think with a human repeat insult patch testing you would see the carry-over reactions coming up, which would be a much better system than just a patch test where they could be masked, since they would come and go before the patch would be removed. So you know, repeat insult patch testing data on some of these.

I mean, just personally give me a sense of what's going on, as much chemical characterization as possible.

DR. LIEBLER: So is wheat allergy pretty common?

DR. BELSITO: Yeah.

DR. LIEBLER: So this would be -- so it's a high- use and a high-propensity for high -- relatively high incidence of allergy. So if you did the patch test with wheat protein

extract --

DR. BELSITO: Well, there are --

DR. LIEBLER: Hydrolyzed wheat proteins.

DR. BELSITO: There are allergens that are more common than wheat. I mean, if you really wanted to go with the biggies in kids, you know, it would be milk and soy and egg and peanut. But you know, gluten sensitivity is pretty -- not rare. So --

DR. LIEBLER: I'm just wondering what to ask for in terms of the sensitivity testing.

DR. BELSITO: I think that, you know, you want to ask to be tested on an at-risk population.

DR. LIEBLER: I didn't even think of that.

DR. BERGFELD: The rest as to --

DR. LIEBLER: I am thinking of what products to test -- what ingredients to test.

DR. BELSITO: Oh.

DR. SNYDER: So, maybe if I could -- if we could back off a minute. So I think Alan will want a better path forward. So if we look at

Page -- CIR Panel Book 19 through 26, I believe it is. I mean, the different types of proteins are all over the map. There's plant proteins, there's yeast proteins, there's animal proteins -- not just animal, but also fish proteins. So, and then there's wheat protein and then there's wheat gluten and protein. So, is there a way that we could logically maybe -- this is one that's not a no- brainer, is lumping these all together in a path forward. Can we sub-group these to plant-derived as opposed to animal -- or some better path? Because if I think we look at wheat, I think we're going to do the wheat thing and then we'll be right back to square one, because how is that going to translate to yeast?

There's one even in here, conchiolin. I have no idea where that comes from. Is that conch? I mean, I don't --

MS. BRESLAWEC: My recollection is that -- Christina, please correct me -- is that wheat protein is the one with the most uses.

DR. BELSITO: It is.

DR. KLASSEN: Yeah, it is.

MS. BRESLAWEC: That's the one with the

most ingredient.

DR. BELSITO: That's why I suggest that, you know, we can always go back and add them back in, but at least for my comfort zone I would like to have the staff spend as much time and for Carol to wield as big a stick on wheat and find out what we can find out. See really what's out there.

I mean, because I personally am having a hard time with the entire group. I just am.

DR. KLASSEN: I guess another question where we might get some idea is in this whole area peanuts has probably been looked at scientifically the most. And I guess, you know, what happens with the peanut allergen when you hydrolyze it? Does it go away or does it become worse? I mean, are these -- you know, as far as allergenicity is concerned, which is different than absorption and causing some other type effect..

But in regard to allergenicity, which is one of our concerns here, is what is known about one of these -- you know, the most well-studied compounds, the peanut allergen, and what happens with it when you hydrolyze it under these

procedures? Because it is also used.

DR. SNYDER: No, but I would -- my judgment would be that it would not go away, because basically if you orally intake peanuts you have a systemic reaction and you've hydrolyzed it in the gut. So, I mean, I would suspect that that's the case and people that have peanut butter and other things that have been highly processed still have significant allergies. So I would assume that the modification is not going to decrease the antigenicity.

DR. LIEBLER: You know, and as far as the bioactive peptide idea, sort of the Manchurian peptide, if you will, that's waiting to be activated in your wheat mixture -- so that's actually a pretty straightforward bio-informatic exercise that, in fact, one that might even make a good test problem for my proteomics class in the Spring. Which would be, to take the sequences of the wheat proteins that would go into this, you can actually do this computationally. You could compute -- you could determine, first of all, with a database of all known human bioactive

peptides -- because I think that's pretty well-understood. What are the sequences of the bioactive peptide mediators in human biology? And then ask, how often -- where do those sequences appear in any of the wheat proteins? I would expect it relatively rare, if at all, but that can be computed.

And then you could actually do something that's similar to a quantitative risk assessment. If you assume that there's a sort of random cleavage of the proteins, what is the likely percentage of any of these bioactive sequences in a mixture? You know, it involves assumptions but none of them are any worse than in a typical quantitative risk assessment.

You could actually do a proteomic quantitative risk assessment for bioactive peptide generation. Manchurian peptide generation.

It would actually -- it even could be a cool little communication to write, publish.

DR. KLASSEN: Has wheat been cloned -- sequenced, the whole thing?

DR. LIEBLER: Oh, I'm sure that genome

is done so I'm sure the sequences are there.

DR. KLASSEN: I know that rice has, I don't know if wheat has but probably it has.

DR. LIEBLER: Yeah.

DR. KLASSEN: Okay, yeah. No, that's clever. That could be done.

DR. BELSITO: Let's do it.

DR. LIEBLER: There's a colleague of mine at Vanderbilt called Dave Tab I could talk to about this.

DR. BELSITO: We charged Dan with doing it.

DR. LIEBLER: And I will sometime.

DR. BELSITO: We're looking for that Manchurian candidate.

DR. LIEBLER: I just hope that makes it into the final report, the Manchurian peptide.

DR. BELSITO: Yeah. Okay, so we are tabling this to take out wheat and specifics, and use that as an example of what kind of information we can get for manufacturers in terms of manufacturing, in terms of what's in it, in terms of the range of molecular size, in terms of repeat -- human repeat insult patch testing, in

terms of inverted carry-over reactions, as much information as we can. And if CIR, PCPC, or Vanderbilt wants to run some bio-computational program to see what kind of cleavage of wheat there could be that might result in the generation of biologically-active endopeptides, that would be super. And if not, we'll have to deal with it at the next time we see this.

That fair summary? But we're taking spinal cord -- we'll never see.

DR. SNYDER: In the wheat, are you including wheat protein and wheat gluten protein?

DR. BELSITO: Well, I think at this point probably. I mean, I don't really understand -- I mean, wheat gluten protein is taking gluten and breaking it down, and wheat protein includes gluten and glyadine and everything else, right?

DR. EISENMANN: Well, I will ask suppliers of wheat -- hydrolyzed wheat protein if they include gluten when they hydrolyze. See if I can get a response. My guess is, yes, but --

DR. LIEBLER: Could we -- is there any sub-protein extract of wheat that's used as the

starting protein mixture that gets hydrolyzed? So in other words, are all possible wheat gene products on the list or is there, you know, a soluble extract that's pulled out and used to do the hydrolysis?

DR. EISENMANN: One other -- I wonder if it would be good if you -- if the Panel or instead of me reaching out to what's going on in Japan, if it would be helpful if the Panel or staff would also reach out to them, because I think you might find their work very -- I really wish they would publish a little bit more in English. That would be helpful.

DR. BELSITO: I don't read Japanese.

DR. EISENMANN: Interim reports and we thought, well maybe --

DR. BELSITO: Matsunaka is involved with it.

DR. EISENMANN: Is that the guy?

DR. BELSITO: I don't -- where is that thing? Matsunaka? I can shoot an e-mail.

DR. EISENMANN: I mean, there's this abstract that just came out from another group, I think it's about high molecular weight. There's

the high molecular weight fraction that caused a problem, but it would be good to know --

DR. KLASSEN: What is the definition of high molecular weight?

DR. EISENMANN: Right, right. But I don't get that from the abstract.

DR. KLASSEN: But you know, I think these papers -- you could easily have someone translate them if there's just a few little papers. It might be useful for us, there's a lot of people who know Japanese.

DR. BELSITO: But, Matsunaka is very fluent in English. Have you tried writing?

DR. EISENMANN: He said that they would be putting something up on their website in a couple of days, but that was a few days -- that was a while ago, so I hope eventually they will do something in English.

MS. BRESLAWEC: Yeah, this is an issue that Carol has been pursuing for probably over a year in terms of trying to get additional information on this, because we knew this issue was coming up or these ingredients have been coming up. This has been a concern in Japan, an

so she's been following up pretty systematically for a while, trying to get information.

DR. BELSITO: So, I guess that's it, right? So manufacturer -- the range of the endopeptides, what they are, HRIPT if they have a 28-day dermal, that would be very nice and give us some idea of whether there's bioactive peptides. And if anyone wants to do computer modeling for the Manchurian Candidate, that would be sweet but I don't think that's going to happen.

Okay. Conflict of interest, no? Okay. So, moving off of hydrolyzed source proteins, we now move to 6- hydroxyindol. This is also a first-timer for us, and so this is again coal tar exemption hair dye ingredient, and so I guess the first thing that I had was that 5 percent. This seemed to be a photosensitizer, and is this covered by the exclusion to patch test? Because you wouldn't pick up a photosensitizer with our instructions for patch testing. 5 percent, right?

MS. BURNETT: Dr. Breslawec. It's Page -- you're looking at Panel Book Page 15 for the photo-toxicity. It's used up to.5 percent.

DR. BELSITO: And it says, irradiated and treated animals received 0 or 5 percent. So, it was determined that 5 percent 6-hydroxyindole and paraffin was the photosensitizer. That's what I said, no?

MS. BURNETT: Yes. There was confusion because I think she was thinking it's used only up to.5 percent in hair dyes.

DR. BELSITO: Right, but we don't know that that's not a photosensitizer. We know 5 percent is --

MS. BURNETT: Right.

DR. BELSITO: I guess, number one -- and since we've never addressed this before, in the fragrance industry it's a photosensitizer at any concentration. It's automatically just banned because of concerns about persistent light reactors. So, number one I don't know if that's a mantra that's followed in the cosmetic industry, number one. Number two, I've never dealt and I don't believe the panel has with a hair dye ingredient that's possibly a photosensitizer. Because in this case, the requirement for patch testing is irrelevant because the patch test is

going to be negative unless you expose it to light, which is not the instructions we give..

DR. SNYDER: This one is complicated because it's both a contact sensitizer in addition to being a photosensitizer.

DR. BELSITO: Right. So that was my first issue, as a dermatologist. And it is a strong sensitizer in the local lymph node assay at.5 percent, which is concentration of use.

DR. SNYDER: 2 percent.

MS. BRESLAWEC: If you look at the third study that is summarized there, you have a 2 percent --

DR. BELSITO: What page are you on?

MS. BRESLAWEC: I'm sorry. CIR Panel Book Page 16. You have a third dermal photo tox and photogenicity.

DR. BELSITO: Right.

MS. BRESLAWEC: 2 percent was not photo-toxic or sensitive -- photosensitizing.

DR. BELSITO: Yeah. No, that's what I said. My point was that you know, with fragrances it's the approach of IFRA that if it's a photosensitizer it doesn't matter at what dose

you can get it not to be a photosensitizer. The ingredient is just banned because of concerns about, you know, persistent light reactivity, just like muscanbret was banned. They never asked that these be done to show at what concentration it no longer is a photosensitizer. Boom, it was just banned.

So I don't know if the cosmetic industry has that same kind of regulation.

MS. BRESLAWEC: This hair dye is approved for use in Europe -- in the EU.

DR. BELSITO: Yeah.

DR. EISENMANN: It's an oxidated hair dye, so the form that it's in eventually will be in the form -- it will be bound to something else inside the hair.

DR. BELSITO: I'm just, you know, raising issues, trying to sort through what I'm being asked to do here.

Okay. So, yeah, I agree. 2 percent, it's not -- we're using it at.5 as maximum concentration. It's a sensitizer, but we already know that that's absolved by the FDA as long as there's warning to patch test.

And then I had a question for Paul, Dan, and Curt if they were okay with the geno-tox and carcinogenicity data on this.

DR. SNYDER: There was geno-tox data that was positive in-vitro, but we didn't have any. And then carcinogenicity data we had a NOAEL of 100 milligrams per kilogram. So again, I'd probably defer to Tom's assessment of that geno-tox data because it was all in-vitro that was positive, what I noted.

DR. LIEBLER: I hadn't flagged anything with this. I mean, it was mixed in-vitro geno-tox positive results. Then the carcinogenicity was at relatively -- I'm trying to think -- relatively higher doses in the last study. That's what Paul just referred to, the NOAEL.

I think that when we consider this compound we do need to consider the way it's used in the product. I mean, this is basically mixed with an oxidant. It's going to be consumed almost completely in the preparation of the hair dye when it's applied to the hair. And I think this is -- could be a little bit like hydroquinone in the nail polishes, you know. Hydroquinone is

consumed during the polymerization reaction.

I don't know that that's document-ably true with this. That's data that I'd like to see if it's available, on whether or not the preparation or the use of the 6- hydroxyindole in the oxidative hair dye actually results in quantitative consumption of this material or not, or how much it's consumed.

MS. BRESLAWEC: If I recall correctly, I think that CIR has a boilerplate -- some boilerplate language on exactly that. On --

MS. BURNETT: On couplers and --

MS. BRESLAWEC: On a hair dye being consumed in the process of mixing a hair dye. I'm pretty sure there is.

MS. BURNETT: I was talking to Dr. Hill this morning. We had -- last December we finalized the report on 2-amino 4-hydroxyanisol -- the anisols, and that's the report that has the information that Dr. Scary had presented. So, I can do a copy-paste if --

DR. SNYDER: I just think it's important for --

MS. BURNETT: -- I think I have it pulled

up on my laptop right now if you want to see it.

DR. SNYDER: It would be important for our discussion, at least, because there's no way that if even at the highest use concentration, .5 percent, that when this product is applied to the hair that .5 percent 6-hydroxyindol is going on to somebody's hair. It's probably much, much lower, but how much lower?

MS. BRESLAWEC: In the boilerplate that I was referring to, Christina, goes way back. It goes way further back than last year. I mean, it's been on the books for a while.

DR. BELSITO: I guess the other thing is under the risk assessment we give this risk assessment for the SCCP. I mean, it's certainly fine, 638. And it was based upon an NOAEL for oral rat of 60 mgs/kg, but then we give an NOAEL of 50 milligrams as the lowest, I thought. At least that's what I wrote down.

MS. BRESLAWEC: (OFF MIC)

DR. BELSITO: Yeah, here on Page 11, the first full paragraph down. The maternal NOAEL was 150 milligrams per kilogram body weight and the fetal was 50 milligrams per kilogram. So I mean,

it doesn't really change that much your calculations, so it comes out to 500-and something as a margin of safety, but it just sort of looked funny to me that we're putting in this calculation that the Europeans did when we have the data to do our own calculation.

MS. BRESLAWEC: I think this is the same data that they based it on, so they obviously must have made a determination not to use that 50 and to use 100. Because all of this data that was submitted was part of the SCCS submission industry made and the basis for the SCCS decision -- SCCP at that point.

DR. BELSITO: Well then I will -- I just -- you know, I think it just begs the question, you know, why do we use an SCCP-derived and we're reporting -- it's not going to change the safety, it just to me seems logical that we would do our own margin of safety and use 50 milligrams per kilogram, which is what we have here in a rat study and come up with a margin of safety of 500-and some odd and say, we're happy with that. It's just, you know -- it's like, okay. CIR was too dumb to calculate their own margin of safety so we took

the European one. And by the way, we took the European one that had had different NOAEL than the one we quoted in our study. I just -- it looks sloppy to me.

DR. SNYDER: Well, it may be because the basis for the 50 milligram NOAEL is a slight reduced ossification and some people don't consider that adverse. So, that may be.

DR. BELSITO: Well then we should explain that someplace. I just -- it just looks sloppy to me. You know, I just finished reading 50 mgs/kg and then I see a calculation done by some other body and it's using 60 mgs/kg and no explanation.

Okay, I guess we're going ahead safe as used? Is this where we're at with this one? Discussion about photosensitization at 5 but not at 2? Margin of safety, decide how you want to do it? Admit that it's a strong sensitizer at.5 but it comes with instructions to use test? Or, to test -- and that we're okay with the geno-toxicity and carcinogenicity data. And, Paul, you're okay with that because?

DR. SNYDER: The --

DR. BELSITO: Doses --

DR. SNYDER: Yeah, the doses were relatively high, yeah. It was 25 milligrams per kilogram, and 100 milligrams per kilogram, NOEL.

DR. BELSITO: Okay. Anything else in the discussion? If not --

DR. BERGFELD: Weren't you going to do a risk- assessment?

DR. BELSITO: I said, you know --

DR. BERGFELD: In there?

DR. BELSITO: Pointing it out, I would recommend we do our own. And if we continue to use the SCCP, we need to put some statement somewhere why we think, you know, that we agree with their use of 60 mgs/kg as an NOAEL because the 50 milligrams was based upon ossification and that's not considered --

DR. SNYDER: Well, do they have access to this other study? I didn't see the basis for their calculation.

DR. BELSITO: I'm being told by Halyna that all their studies came from their report.

DR. SNYDER: Because that 60 milligrams per kilogram was a NOEL and the subsequent

study --

DR. BELSITO: Right.

DR. SNYDER: The generous thing, they interpreted to say that even though the pre-implantation was different than the control, it was not considered toxicologically relevant because it was lower than the control group. So, I'm confused even why they came up with a 60 milligram. So we'd have to see that data for the basis of that.

MS. BRESLAWEC: This data was submitted to the EU as part of the same process that we were discussing earlier, where on phenylenediamine the industry decided not to supply data in support of a different ingredient. Here, this data were supplied to EU and that forms the basis both for their decision and it's the same data that are being submitted here for your decision.

DR. BELSITO: Right.

MS. BRESLAWEC: So, the data are the same. There's no difference in what was submitted.

DR. BELSITO: Okay. I mean, I don't -- it's safe regardless how you do it, in

terms of that endpoint. My big --

DR. SNYDER: Because the margin of safety is going to go up, because that even if we use the 50 milligram -- which is not considered an adverse finding -- that's going to be the lowest --

DR. BELSITO: Right, it would be the lowest and it's still -- the margin of safety is over 500. So you know, I mean, I think it's fine. I just like to be consistent and not look like we're depending upon the Europeans too much and have an explanation why we would put a NOAEL on the page before 50 and then assume to go with the Europeans for 60. So if we don't do our own and we don't use 50, I think we need to at least make mention somewhere why we chose not to do that.

Anything else? Okay. Let's see. Oh, we still have a whole bunch more to go. Nylon. Okay.

So we wanted irritation and sensitization at use concentration and we got it. Other relevant tox data including geno-tox. We got an AMES test that was negative. Do we need a mammalian here? I leave that to my comrades to

decide.

MS. BRESLAWEC: I think you got a mammalian on this, didn't you?

DR. BELSITO: No, we got an AMES.

DR. EISENMANN: There's now an HPV report on the monomer. Doesn't that --

DR. BELSITO: Yeah, but they're (inaudible). That was only an AMES test.

DR. EISENMANN: No, I think it includes more than that. Here's the -- I have it.

DR. BELSITO: I got it here, too. Nylon 12 at use concentration a leave-on cosmetic was negative, and the HPV testing was human health and it was an in-vitro geno-tox study.

DR. EISENMANN: The "chrome ab" --

DR. BELSITO: Oh, I missed that..

DR. EISENMANN: -- on both the sites.

DR. BELSITO: Oh, okay. See, I printed this out wrong because -- anyway. It's backwards, okay.

So, in-vitro geno-tox HRIPT testing, chromosome elaboration test in human lymphocytes. Yes, I apologize. Missed it. Okay.

So, it looks like we pretty much got

everything we asked for, right?

DR. SNYDER: The HRIPT data was up to 6 percent but is used up to 35 percent.

DR. BELSITO: No, we got an HRIPT of 35 percent in a leave-on product.

DR. SNYDER: Oh, we did?

DR. BELSITO: Wave 2.

DR. SNYDER: Oh, okay.

DR. BELSITO: You missed that wave. You're a bad surfer. (Laughter)

DR. SNYDER: That Wave 2 gets you every time.

(Laughter)

DR. BELSITO: Yeah. So I mean, safe as used.

DR. LIEBLER: I agree.

DR. BELSITO: Okay.

MS. BURNETT: Would you care to elaborate on the discussion for me?

DR. BELSITO: It's nylon. (Laughter) You know, the --

MS. BURNETT: I can wing it off of that, I suppose.

DR. BELSITO: You know, I didn't really

have a lot of issues to begin with it. You know, I think the -- I think it was the Mark's team had the real issues about this. I think we're ready to go safe as used at the last panel meeting, so I don't know that there's a lot to be discussed, other than, you know, if there is a lot of un-reactive monomer it's not showing at 35 percent in an HRIPT. So --

DR. LIEBLER: That's correct. And the chemically- reactive nature of the monomers. It's not highly-reactive. It's not like we're talking about an acrylate here, for example, an acrylate polymer, you know. These lactins are pretty biologically non-reactive.

DR. BERGFELD: Is it true that they're also high molecular weights? No penetration?

DR. LIEBLER: They nylon is, the monomers are not --

DR. BELSITO: The monomer is not.

DR. BERGFELD: Okay.

DR. LIEBLER: And we also stated that there is not the expectation that any monomer would release once the polymerization occurs.

DR. BERGFELD: So isn't that a

discussion point?

DR. BELSITO: We need to have a discussion.

DR. BERGFELD: We have to keep the inhalation, do you not?

DR. BELSITO: Yeah.

DR. BERGFELD: And so this would be your second point to elaborate.

DR. BELSITO: Yeah.

MS. BURNETT: Thank you.

DR. BELSITO: Okay. So nylon is done. PEGylated oils, that's a Blue Book. So, you know, we went final with this the last time. Did anyone have any problems with the final report that we're now being asked to okay? I didn't. Paul? Any Paul-smithing need to be done here?

DR. SNYDER: I had a couple issues.

DR. BELSITO: Anything substantive? Or just a few?

DR. SNYDER: Well, one issue was just in some things probably to be consistent. Under the reproductive and developmental toxicity and carcinogenicity toxicity, the way that the language -- it appears to be there are studies in

those tables. But in fact, those are summary statements from previous CIR reports and so I think it's a little misleading that those aren't actually individual studies that are given in those tables. And so, I think we need to make it very clear that those are summary statements.

DR. BELSITO: Okay.

DR. SNYDER: And then in the discussion --

DR. BELSITO: So that's Page what of the Panel Book?

DR. SNYDER: Page 18. And then in discussion, I don't like the language at the end of the first sentence; Because of this unique chemistry, the Panel determined the data available in previous safety assessments, PEG and plant derived fatty acids -- and I wanted to strike out -- I think we shouldn't use "strongly". I think we should just say "support the safety", not "strongly supported".

That was it.

DR. BELSITO: Okay. Pretty easy.

DR. BERGFELD: Did you want to add on Panel Page 18 carcinogenicity not available?

Because you don't have it here.

Rachel's comment. PP Yeah, I ping-ed that also. I said, how do we decide to include more than a summary statement under each heading? For example, in this Book carcinogenicity and reproductive developmental -- there were just summary statements referring to tables. That same thing with the geno-tox and irritation sensitization, which has a summary statement table reference and some details. And so, how do we -- I think we need to be a little more consistent about when we give some details as opposed to when we give absolutely no details. Or in some instances, even worst-case scenario, no sub-heading.

DR. BELSITO: We give some details when we have the actual ingredients we're looking at, and we give summarized details when we're basing it on components, but I mean, we have absolutely no carcinogenicity and geno-toxicity on any of the PEGylated oils. We have it on components. So I think we have --

DR. LIEBLER: We have one. The PEG-60 hydrogenated castor oil --

DR. BELSITO: Right. And then you describe it. But what my point is, when you're summarizing -- when you're relying on data from the components. I think it's fine to say they're available on this component and this component and see the table, because you're not going to give details when they're available on the actual ingredient we're looking at, then some of the details I think are helpful. That's my own personal viewpoint.

DR. SNYDER: I agree with that, as long as it's shared by the writers who are drafting them. That's the assumption they're making.

DR. LIEBLER: So just to clarify -- and since Rachael is here, she can speak to this, perhaps. When we say there are no carcinogenicity data but we have a reason not to be concerned, that goes in the discussion, right? Yeah. And I'm just scanning the discussion to see if that's said anywhere because basically there are no structural alerts in the geno-tox that we have for the precursors, which are summarized in the tables, is clean. And the geno-tox for the one compound we have is also clean. So, that's all

consistent with a picture of not concerned about carcinogenicity.

MS. WEINTRAUB: But this one actually didn't fit when I reviewed it through this lens. It does say the carcinogenicity data was available for some of these things --

DR. LIEBLER: For one of them, yeah.

MS. WEINTRAUB: Yes.

DR. LIEBLER: Okay, so it's not exactly the same as your concern --

MS. WEINTRAUB: Exactly. There is a mention -- I mean, in terms of the pros, its scant detail but there is --

DR. LIEBLER: Close, but not quite.

MS. WEINTRAUB: Exactly.

DR. BELSITO: Okay. So, modified terephthalate polymers used in an eyeshadow up to 46 percent, but we got product use testing on these and despite concerns that somehow these might be fishhooks getting into the cogent tide and ripping it apart, there don't seem to be issues and there certainly haven't been issues with a lot of consumer complaints to the FDA. This time of year, women tend to love them, as my suits

attest to when you come back from glitter all over your shoulder. A nice hug, okay?

So, I mean, I thought they were fine. I thought they were safe as used. I didn't see any issues with them.

DR. LIEBLER: Right. My only comment was that we didn't have use concentrations but that's in Wave 2 so we're good on that.

MS. BECKER: Yes, it is. Just to cover everything we have, we were -- in 1985 there was a recall of glitter by the FDA that with no real reason why, other than (inaudible).

MS. BRESLAWEC: On that particular issue, we've not been able to ascertain why those particular products were recalled. But I do think there are a couple of mentions in the report about the mechanical structure of this component, and we believe that that issue really needs to be addressed and discussed in this context..

We also feel that it's important to base the discussion and conclusion on data and documented references. We appreciate that the people coming forth with opinions are accredited. Their opinions are valuable, but in fact they are

opinions and I think you need to -- we all need to make sure that the decisions are based on data, not --

DR. BELSITO: We have the data.

MS. BRESLAWEC: I'm not disagreeing with it, I'm talking about specifically the references in the report to conversations and notes from people --

DR. BELSITO: Well, I think that should all go away.

MS. BRESLAWEC: But again, that's an issue that we believe needs to be addressed and supported. The Panel decision supported by data, not opinion.

DR. BELSITO: And as we, you know, read a lot of these reports it's quite clear that, you know, when they go in submission to The Journal, you know, that a final report. There's oftentimes a lot of editorial anecdotal comment about where the Panel is thinking and what they're doing, and you know, with the final report that should all disappear.

So, yeah. I mean, it's the same thing as what Dan was saying about I forget what,

so-and-so --

DR. LIEBLER: Talc and asbestos, yeah.

DR. BELSITO: Yeah, so-and-so in his letter to so- and-so said, gee, I think there's asbestos in talc. And so- and-so responded, well, gosh. Maybe there is. So, yeah, I think that type of reporting should disappear.

Okay. So, safe as used. We'll see a final version coming up, get rid of a little bit of the editorial writing. I'm sure that the PCPC Scientific Council will do a good job in submitting comments and making sure that this is cleaned up in an appropriate way.

DR. KLASSEN: All that glitters is not gold.

(Laughter)

DR. BELSITO: I was waiting for that, but I thought it would come from Dan.

Okay, so.

MS. BECKER: Do you have anything else you want put in the discussion?

DR. BELSITO: No.

DR. BERGFELD: Excuse me. I thought you were going to put some statement regarding

mechanical irritation and not observed in the studies.

DR. BELSITO: Yeah, I mean that's -- you know, use testing at concentrations of use were negative.

Why did you leave botanicals as the last two things we had to look at? Lord.

Okay, so the next one is --

MR. ANDERSEN: A little St. John's Wort will help that.

DR. BELSITO: Yeah, right. The next one is hypericum perforatum-derived ingredients. So, we looked at some new data in June and agreed that it likely addressed some of the insufficiencies in 2001 and we're going to go ahead and open this up and add in all the hypericum people that were out there. So, a total of eight ingredients.

And so, here we are. So, we have some issues here. Hypericum is a photosensitizer. Kersatin is an impurity and we'll probably want to eventually as we get around to dealing with this deal with it in some way.

Sensitization and irritation at concentration of use -- I guess, here's where I

ran into problems. And I had e- mailed Alan at one point about this, because it's the old issue where these are not 100 percent. They're available as 2 to 25 percent of active ingredient, and then are the percentages -- Carol, giving us.2 of 2 percent, or is it.2 percent?

DR. EISENMANN: They are supposed to be giving me the concentration of name to ingredients. So it's not just supposed to be the hypericum perforatum part and not the solvent part.

DR. BELSITO: Okay, so when -- let me --

DR. EISENMANN: That's what I tell them to give me.

DR. BELSITO: -- confirm this. When they say that they're using.2 percent hypericum it's.2 percent hypericum that's in there and not.2 percent of a 2 percent extract.

DR. EISENMANN: That's what they're supposed to be telling me.

DR. BELSITO: That's what they're supposed to.

DR. EISENMANN: Yes.

DR. BELSITO: So this is actual

concentration of the actual ingredient.

DR. EISENMANN: Yes.

DR. BELSITO: Thank you. So, I don't know that we have sensitization and irritation data to cover the maximum use. We have.03 as the highest, right?

MS. BRESLAWEC: Dr. Belsito, the new use information had a maximum concentration of.07 percent which is down from the 5 percent maximum listed in the draft report.

DR. BELSITO: Okay.

DR. LIEBLER: Is that Wave 2?

MS. BRESLAWEC: Yes, Wave 2.

DR. BELSITO: How did I miss Wave 2?

DR. LIEBLER: I missed part of the wave.

DR. SNYDER: I didn't miss that part of the wave.

DR. BELSITO: Well, Paul, you're exonerated there. Okay, so.007 is --

MS. BRESLAWEC: .07.

DR. BELSITO: .07 is the max. And the max -- and clearly hypericum is not going to be present in levels of 1 percent in an extract of.07 of hypericum as a whole. And a 1.1 percent extract

of hypericum was not photosensitizing, and that's in there.

Yeah, I've got Wave 2 printed out, I just failed to note it in my notes because I did the botanicals first and then I had to go back and re-look at them when I got Wave 2 with concentrations, and just missed that.

So, I -- you know --

MR. ANDERSEN: Don, you've also got photosensitization data in which the extract was tested at 1.1 percent.

DR. BELSITO: No, no, no.

MR. ANDERSEN: It was not photosensitizing, so --

DR. BELSITO: Right, yeah. I mean.

MR. ANDERSEN: It's also not sensitizing.

DR. BELSITO: Right, yeah. No. I'm happy with that.

And I guess probably the likelihood that any other botanical would have sufficient amounts of hypericum that it would throw it over when mixed together would be small. In the past, when we're concerned about, I think it was thujone

we mentioned that when mixed with other botanicals that could contain this, they should remain under a certain limit. So if we're concerned about kersatin, we should say that.

I also queried Ann-Marie Appie about this and if in the case of hypericum I don't think it's important because it really doesn't contain a lot of essential oils. But as we look at botanicals, some of which will contain essential oils like eugenol and IC-eugenol, apparently the IFRA regulations on concentrations of use would pertain to total in a cosmetic ingredient, not just a fine fragrance -- assuming that the manufacturer was actually using it as a fragrance ingredient.

However, if they weren't using it as a fragrance ingredient -- if they were using it as an emollient or some other thing, a solvent, then even though it contained a fragrance material like eugenol it would not count, which I thought was sort of interesting.

And I wish there were some way that -- and that's an IFRA issue, I don't think it's a RIFM issue. But I just wanted to point that

out to you that, you know -- and it's very funny because I just actually saw a product that contained lavender, lovengila, and it was listed as fragrance- free. I swear to god. And you smelled this thing and it quite clearly smelled like lavender but obviously the lovengila was added by the manufacturer for purposes other than the fact that it had an odor.

DR. LIEBLER: Maybe they meant no extra cost, so the fragrance part is free. (Laughter)

DR. BELSITO: But I just thought I'd point that out. So anyway, you know, yeah. Sure. Let's go ahead safe as used.

DR. LIEBLER: I think the hypericum content in the mixture is low enough that at the maximum use concentration for the mixture that hypericum content is way below the photosensitization level. So, I think we're okay there.

DR. BELSITO: Well, needs to be part of the discussion.

DR. LIEBLER: Correct.

DR. BELSITO: That 1 percent was not a photosensitizer, not a sensitizer of the

hypericum.

DR. LIEBLER: Right, but.1 percent was.

DR. BELSITO: Yeah, and that, you know -- kersatin will be low, given the low concentration of use below threshold of toxicologic concern I think is how we phrased it. But when formulated with other botanicals that may contain kersatin, manufacturers should be aware of it to keep it as low as possible.

I don't know what else in the discussion. I mean there aren't, again, a lot of essential oils so I don't think that was an issue for this one.

MR. ANDERSEN: Well, I would expect we'd go through each of the previous data insufficiencies and now note that we have those data.

DR. BELSITO: Right.

MR. ANDERSEN: Just for the record.

DR. BELSITO: Okay.

MS. BECKER: In the Council comments they suggested that the callus culture extract is not appropriate here. It's got a different extraction method and doesn't -- it's not the same

as the others, and they're suggesting that it be removed and we have no argument.

DR. BELSITO: That's sort of callous of them, though.

It's fine. It's okay, I don't care.

DR. LIEBLER: Dr. Belsito will be charged one time-out. (Laughter)

DR. BELSITO: I'm fine removing it. So, we're going to remove the callus extract. Safe as used, discussion, on photosensitization on hypericum but it's going to be low in the actual cosmetic product. Kersatin will be even lower, caution when combining with other botanicals that may contain kersatin, and address all the other data insufficiencies and how they work -- how they were satisfied for us.

Anything else?

DR. SNYDER: Page 4, that's not a carcinogenicity study, so --

DR. BELSITO: Pardon?

DR. SNYDER: That Page 4.

DR. BELSITO: Oh, I didn't realize (inaudible) -- Page 4.

DR. SNYDER: Page 4 under

"Carcinogenicity". That's not a carcinogenicity study, so we need to --

DR. BELSITO: Panel Book 12, Page 4?

DR. SNYDER: It's actually -- yeah. Panel Book would be correct. Oh, I'm sorry. Page 6.

DR. BELSITO: Panel Book 14 Page 6.

DR. SNYDER: Yes, correct.

MR. ANDERSEN: So, what is it?

DR. BELSITO: It's an anti-carcinogenicity study.

DR. SNYDER: No, it's just a modulation of a pathway, a PKC pathway. It deals with anti-inflammatory, anti-tumor. It's not really a carcinogenicity study.

DR. LIEBLER: I don't think it belongs there at all.

DR. BELSITO: So what would you do? Pharmacologic effects, or?

DR. SNYDER: That would be fine.

MS. BECKER: Okay.

DR. SNYDER: Or, just under other studies, something.

MR. ANDERSEN: We're trying to remove

that heading.

DR. BELSITO: What, "Other"?

MR. ANDERSEN: Yes.

DR. BELSITO: Pharmacologic effects.

MR. ANDERSEN: Yeah, that sounds much better.

DR. BELSITO: Anything else, Paul?

DR. SNYDER: No.

DR. BELSITO: Okay. Any other comments? Okie-doke. So, moving down to the last one. Achillea millefolium, a.k.a. yarrow, right? So, in June we again agreed that new data would likely address our data insufficiencies of 2001. And so, we re-opened the safety assessment. And so, the use concentration is to 0.04 percent, is that the?

MS. BRESLAWEC: Sorry, could you repeat that?

DR. BELSITO: The current use concentration -- you know, again --

MS. BRESLAWEC: .03.

DR. BELSITO: .03. Okay, I had.04. In this report it was tested at.01 but in the old report we had.1 percent of a 2 percent extract, which was.002. So, this is one where I didn't see

that it was tested at concentration of use.

And then, thujone comes into play here, but we deal with that with low use, et cetera. Which just brought up the fact that, you know, granted when we're -- these have been reported and reported as insufficient, but gosh, it would have been so much easier for me when I was reviewing it if there was a summary of the data that we had looked at before in terms of sensitization and irritation so I wouldn't have to go back and open up the old report and look at it if it were just in the new report. Just as an FYI.

I just found it, you know -- this is a waste of time when you're going back and forth. You know, so it would be a nice summary. Previously looked at it, at concentrations of this, this, and this and found to be negative or, you know -- I don't know. I know it's an issue with the publishers that were recycling old data, but you know maybe it could be put in and then deleted when we publish it or done in some way that it just makes it easier when we're re-reviewing.

MR. ANDERSEN: I think we get it.

DR. BELSITO: Yeah. But anyway, I

didn't see that there was any testing at concentration of use. Maybe I missed it?

DR. EISENMANN: You do have a local lymph node assay, to 100 percent of that aqueous extract.

DR. BELSITO: Yeah. You know, we've dealt with -- you know, local lymph node assays of mixtures in the RIFM panel, and they can be a little bit unreliable. Yeah, there have been cases where we've looked at, you know, assays of individual constituents and then assays of the mixture itself, and you would think that they don't come out together, necessarily, all the time. So if you read review articles and critiques of local lymph node assays, they will say that there are issues with assessing mixture toxicity. So, I don't know that a local lymph node assay satisfies me in terms of a mixture. I mean, it's just -- and maybe it's just me. Maybe other people have different opinions.

I would like to see an HRIPT. It would make me feel a little bit more comfortable.

MR. ANDERSEN: Don, is there -- from the testing that you do have, is there concentration

at which you were comfortable? Like, .01 percent you said was the highest?

DR. BELSITO: No, it's.001.

MR. ANDERSEN: Okay.

DR. BELSITO: Oh, .002 in the old report. It was .1 percent of a 2 percent extract, and then in this report the highest was .001 percent. Correct?

MR. ANDERSEN: Yes.

MS. BECKER: Yeah, correct.

MR. ANDERSEN: Why couldn't you pick the highest of those available data and set a concentration limit?

DR. BELSITO: I mean, I could and then ask industry to come back and support -- I wrote down.04, but maybe my writing was wrong. So, it's.03 is the highest leave-on?

MS. BECKER: Leave-on I got.04.

DR. BELSITO: Yeah, that's what I have. But someone down there said.03.

DR. EISENMANN: Are you looking at the new --

MS. BECKER: Yes, let me pull up the data and I can double-check the source..

DR. BELSITO: No, it's -- yeah, I think you're right.

Well, it's.04 in Table 3.

DR. SNYDER: It's Wave 2.

DR. BELSITO: It's Wave 2 is also.04.

MS. BECKER: Yes.

DR. BELSITO: Okay. Yes.

MR. ANDERSEN: Well, again regardless of --

DR. BELSITO: Body and hand cream, lotion, and spray.

MR. ANDERSEN: If you have data at.002, that's where you can set the limit. We've done it before.

DR. BELSITO: You know, then we don't say safe as used. Safe up to.002 and provide us the data at.04 if you want to go there.

It's just that these botanicals are so, so difficult to deal with as a dermatologist. And this is one, I should point out, that is going to have fragrance oils like linalool that can oxidize and create issues. The leaf has up to 4,000 parts per million of linalool. It has limonene and it has a good number of terpenes that

can be issues for contact sensitization, which is why I'm not comfortable signing off on something that they don't have data at their use concentration.

DR. LIEBLER: We also asked for UV absorption, and there's a spectrum on Panel Book Page 32 that plainly shows UVB absorption.

DR. BELSITO: Panel Book 32. It tells us so much.

DR. LIEBLER: You got -- it's always misleading when they show the -- you know, the band that's 190 because it makes everything look small. But you know, there are two bands there. There's one at about 280 -- that's not the UVB, but there's another one at about 280 and another one at around 320, 330. Anyway, there's --

DR. BELSITO: Yeah, I mean --

DR. LIEBLER: UVB-absorbing stuff in this mixture.

DR. BELSITO: Of course.

DR. LIEBLER: So the question I had was, what is our trigger for then -- given data like this, what's our trigger for asking for photo-tox or photosensitization? You know, historically?

Has there been any kind of?

DR. BERGFELD: It's the peak. There's basically where the peaks were.

MR. ANDERSEN: I don't think there's ever been a number that has ever been linked to it, but where the panel has been comfortable is where that keeps going down and there's no shoulder.

DR. LIEBLER: I see two shoulders.

MR. ANDERSEN: Me, too.

DR. BELSITO: Yeah, and the second one certainly is way out in the UVA range, and when you're worried about photo- toxicity it's usually UVA you're worried about, not UVB. You know?

We certainly can ask for it at concentration of use. I mean, I guess looking at the --

DR. LIEBLER: If you put a botanical extract in a cuvette, I would be willing to bet you the house payment this is what you get every time, something that looks like this.

DR. BELSITO: Yeah.

DR. LIEBLER: So, I guess the short answer is there's been no clear-cut trigger,

historically, based on a UV spectrum for requesting photosensitization or photo-tox data.

DR. BELSITO: No.

MR. ANDERSEN: But in this case, those data were part of the original insufficiency. And at this point, you have a couple of things you can legitimately do. One is to wonder what the significance of that absorption spectrum is and ask for either more clarification, or real photo-tox data to back it up. And you do that by tabling it and asking for that.

Or, you could make a judgement that you still don't have sufficient photo-tox data or UV absorption, and declare it to still be insufficient.

DR. BELSITO: Well in the spirit of moving it on, why don't we declare it insufficient both for concentration, for lack of sensitization and irritation data up to.04, and for photosensitization data, and let industry know that right now we're comfortable with a.002 for sensitization and maybe they can finesse the absorption spectrum in ways that will make us less concerned about photosensitization.

But I mean, go ahead without because someone's using it at.04, and hopefully they have some data that will tell us that it's okay to be used there.

It's just that, you know -- I mean, now we're getting really high into the terpenoid ingredients here and you know, linalool, a lot of things that get oxidized -- limonene -- and make them much more allergenic. So I think we need to take a little more, greater caution than we did with St. John's Wort.

MR. ANDERSEN: Okay -- go ahead.

MS. BECKER: I just want to point out that the limonene and the linalool -- I'm not sure how to say it.

DR. BELSITO: Linalool.

MS. BECKER: Yeah. That they're both in the leaf but not in other plant parts. And of your ingredients, only one of them has the leaf and it's a flower/leaf/stem extract. So we're talking about it's not even part of the whole extract, it's a smaller part. Just to throw that in the hopper.

DR. BELSITO: Right. The whole thing

is in the hopper.

MR. ANDERSEN: The -- proceeding from here gives me a little bit of pause. Where we were before September is that this ingredient was insufficient. So, if you decide to just not do anything further, it's already insufficient.

DR. BELSITO: So we need to table it and ask for the data, is what you're saying?

MR. ANDERSEN: Well, if you want to really stimulate interest and say that this isn't a lost cause, tabling it might be the right message to send.

DR. BELSITO: That's fine.

MR. ANDERSEN: I think -- Halyna can opine as far as what the industry reaction is going to be to whatever we do. Your discussion sends some pretty clear signals, so maybe we don't have to label it anything.

DR. BELSITO: So, you know, I guess I agree with you. Thinking about it, we already said it was insufficient. It's still insufficient. When that happens, the whole thing goes away until industry re-submits another thing to us. So, I don't have a problem with saying

table it. You know, industry is on alert that we, you know, may re-look at the UV data and find out we don't need photosensitization but right now we'd like to see if there's any photosensitization data out there and any data that would support leave-on use up to.04 percent.

Okay?

MR. ANDERSEN: You get to move it tomorrow. So --

DR. BELSITO: Wow.

MR. ANDERSEN: See what happens..

DR. BELSITO: Good. Anything else before we break? So, Alan, are we meeting in the lobby at 6 or we're at the restaurant at 6?

MR. ANDERSEN: We ought to meet in the lobby at quarter to 6 after the panel for dinner.

DR. BELSITO: Okay.

MR. ANDERSEN: And be at the restaurant at 6 for MSN.

DR. BELSITO: And so for those people who usually meet you for apres-meeting/pre-dinner?

MR. ANDERSEN: Further conversation.

DR. BELSITO: Further conversation.

MR. ANDERSEN: 5 o'clock or so. Maybe a little earlier. Alcohol kills germs, doesn't it?

DR. BELSITO: Yes.

(Whereupon, at 3:19 p.m., the PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

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

(Signature and Seal on File)

Notary Public, in and for the District of Columbia

My Commission Expires: January 14, 2013