

120th COSMETIC INGREDIENT REVIEW EXPERT PANEL
MEETING
MAIN SESSION

Washington, D.C.
Tuesday, September 27, 2011

PARTICIPANTS:

Voting Members:

WILMA F. BERGFELD, M.D., F.A.C.P.
Head of Clinical Research and Dermatopathology
The Cleveland Clinic Foundation

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

CURTIS D. KLAASSEN, Ph.D.
University Distinguished Professor and Chair
Department of Pharmacology, Toxicology, and
Therapeutics
School of Medicine, University of Kansas Medical
Center

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

RONALD A. HILL, Ph.D.
Associate Professor of Medicinal Chemistry
College of Pharmacy
The University of Louisiana at Monroe

JAMES G. MARKS, JR., M.D.
Professor of Dermatology
Chairman, Department of Dermatology
Pennsylvania State University College of
Medicine

RONALD C. SHANK, Ph.D.
Professor and Chair
Department of Community and Environmental
Medicine University of California, Irvine

PARTICIPANTS (CONT'D):

THOMAS J. SLAGA, Ph.D.

Department of Pharmacology

University of Texas Health Science Center

PAUL W. SNYDER, D.V.M., Ph.D.

School of Veterinary Medicine

Department of Veterinary Pathobiology

Perdue University

Liaison Members:

LINDA LORETZ, Ph.D.

Personal Care Products Council

CAROL EISENMANN, M.D.

Personal Care Products Council

JAY ANSELL, Ph.D.

Personal Care Products Council

RACHEL WEINTRAUB

Consumer Federation of America

ROBERT BRONAUGH, Ph.D.

Food and Drug Administration

Staff Members:

F. ALAN ANDERSEN, Ph.D.

Director

LILLIAN C. BECKER

Scientific Analyst

HALYNA P. BRESLAWEC, Ph.D.

Deputy Director

MONICE FIUME

Senior Scientific Analyst

CHRISTINA L. BURNETT

Scientific Analyst

PARTICIPANTS (CONT'D):

IVAN BOYER, Ph.D.
Senior Toxicologist

KEVIN STONE FRIES
Technical Librarian/Editor

BART HELDRETH
Chemist

WILBUR JOHNSON, JR.
Senior Scientific Analyst

Other Attendees:

DR. ROBERT GOLDEN
ToxLogic

DAVID GOLDSTEIN

JANE VERGNESS

* * * * *

P R O C E E D I N G S

(8:00 a.m.)

DR. BERGFELD: I'm going to officially open the 120th CIR Panel Meeting. As you all heard, this is our thirty-fifth year of success. I would like to say success, success, success, and having the perspective of I think the oldest person and the oldest duration on this panel, I can say that the maturation of what we are able to do certainly is beyond my imagination when I first began. I said last night at a wonderful celebration that was hosted by Alan that I thought when I was young and I joined this particular panel that the job would never end and it hasn't. It keeps growing. But you can't do a job of this quality without the help and support of the parent, the local staff including Alan and the specialists that we have on the staff now as well as the newly added CIR Science and Support Committee, and of course the wonderful panel. Everyone gives it their most and they come prepared. They come prepared to do the job. So I wanted to thank all of you officially for a wonderful 35 years and a wonderful outcome of successful products so to speak of wonderful

materials that are peer reviewed journals and are referred to many, many experts and scientists in all fields. Again thank you very much and congratulation, Alan, for a job well done.

DR. ANDERSEN: Thank you.

DR. BERGFELD: We have a very busy time this morning and we had a very busy team meeting. We had 16 contentious ingredients, and I understand that at least one ingredient took 3 hours to discuss which hopefully it will be shorter today. I want to congratulate the staff, particularly because the documents that we're getting today exceed all expectations. They keep getting better and better prepared as well as written, and it certainly makes our jobs a little bit easier.

We had a very interesting presentation because we've been interested in inhalation and respiratory particles yesterday by Dr. Helga Rothe as I think she pronounces her name from Procter & Gamble. We had a long discussion on what we're going to do about inhalable particles or substances and this will probably ongoing for quite a time.

I also before I hand the podium over to Alan want to officially congratulate him. Dr. Marks brought our attention to the fact that this year, 2011, Alan was awarded from Pennsylvania State College one of the most prestigious awards of that college and that is the 2011 Alumni Fellow Award, so congratulations officially.

Now we move on to the business. We need to approve the minutes. Is there a motion to approve the minutes? Second? Is there any discussion regarding the minutes? I'd like to discuss the fact that the minutes as we see them and the dialogue from the teams keep improving as well and they're easier to read, so thank you. So I'll call for the vote. All of those in favor of the minutes please indicate by raising your hands. Thank you. Unanimous approval. Alan, it's up to you, the Director's Report.

DR. ANDERSEN: There are several things I want to update all of you on. The compendium volume that captures all of the abstracts, discussions and conclusions, every safety assessment that this panel has ever done, continues to expand, and for this year's edition

I guess we could say it's special, the Thirty-Fifth Anniversary Edition. What we've done is included everything through June 2011, so we have completed and packaged sandwiched between two electrons because we're not paper versions anymore except for the one that Dr. Bergfeld gets.

DR. BERGFELD: Thank you.

DR. ANDERSEN: But it's one and available and I think is a fitting addition to this thirty-fifth anniversary celebration.

The other thing that either accidentally or on purpose or some combination of those two, we'd thought about show you all this morning the whiz-bang new CIR website, but you'll notice there is no screen and no projector so we're not going to show you the website. But it is just about done and we have it at least a level that we could have shown all of you and shown you how to access that and find every document that you've got in front of you which is now catalogued and presented in the website in a way that is both competently done from the information management standpoint, thank you, Kevin, but it's also intuitive so idiots like me can actually figure

it out. So we have both masters served and I think when we do this as a final launch, you're going to be extraordinarily pleased with the result. It's now in any way, shape or form the old CIR website. It's really nice.

Then the last thing I think I want to mention is that the search for a new CIR Deputy Director is ongoing and hopefully there's wood under this, knock on wood, we'll be able to complete that in time for the new kid on the block to be sitting up at the table for the December meeting. The "International Journal of Toxicology." We've got the manuscript submitted for the final issue. They're all under review, so our commitment to get three published this year looks like it's going to work without any problems whatsoever. I see Kevin in the back choking. There have been a lot of things on everybody's plate this year and I think it's actually extraordinary that Kevin with Julia Linthicum's help has been able to keep not only the important balls juggling in the air, but everything is juggling and as best I can tell, while we may have been a little slower than in past years, nothing

has hit the ground. So nicely done and we'll wrap it up with two meetings this year. This one has eight potential final safety assessments, and again knock on wood, as many of those as possible we can roll out this time because if we don't, we're just going to have to do them again in December. That's it. Thank you.

DR. BERGFELD: For at least printing mine, I'm tired of printing, printing, printing, printing off of the internet for all of these documents cutting down the forest. We're going to move to the first large ingredient and that's formaldehyde and methylene glycol, Dr. Belsito presenting.

DR. BELSITO: When we looked at this last we had come to some tentative safety assessments in June. It's safe when used at minimal effective concentration but not to exceed 0.074 percent formaldehyde equivalence, that there was insufficient data for nail hardeners. In particular we wanted to know the concentration of formaldehyde in one specific product about which there a number of consumer complaints. And that it was unsafe for use in hair-smoothing

products, the use of which involves application of high temperatures. We've gotten if you count the oral presentation yesterday five waves of information on formaldehyde as well as comments from the Personal Care Products Council. And following digestion of all that information, my team decided the following, that formaldehyde and methylene glycol is safe for use in cosmetics when formulated to ensure use at the minimal effective concentration but in no case should formalin at the recommendation of the PCPC with an asterisk indicating that formalin is 30 percent formaldehyde and water as supplied to the industry, so in no case should formalin exceed 0.2 percent (weight, weight) (total formaldehyde and methylene glycol).

Number two, that formaldehyde and methylene glycol are safe for use in nail hardeners and the present practices of us and concentration with instructions to protect the skin either in the discussion or in the conclusion. Then thirdly, in the present practices and concentration of use, formaldehyde and methylene glycol are unsafe for us in hair-smoothing

products.

DR. BERGFELD: Is that a motion or do you have it for discussion?

DR. BELSITO: No, that's a motion.

DR. BERGFELD: A motion. Dr. Marks?

DR. MARKS: So this would be another re-revised tentative amendment?

DR. BELSITO: No. We actually indicated I think the only thing that's changed substantively, not editorially, is that we're now saying that nails are safe and before we said they were insufficient for use concentration which we got. So it's not a change, at least I don't think it's a change, in the conclusion at all. We indicated that if we got the concentration and it was acceptable, it would be fine.

DR. MARKS: I'll let Alan make that decision as to whether going from insufficient to safe is enough to have another review. Probably the only thing in the first portion that you mentioned also from the scientific council, there was the suggestion that methylene glycol level could be established at 0.118 percent, so we might want to include that in that first part. Then the

last part, that's where our team also wrestled with how to deal with the hair-smoothing products fully well knowing that they're going to be used and if we didn't somehow recognize that that it might be used in ways which we were concerned. So we worded it somewhat differently, significantly differently, and we said that they could be used safe in hair-smoothing products when applied by trained professionals using ventilation procedures to prevent irritation to the eyes and respiratory tract. So we were back to establishing a biologic end point for their safety recognizing that it needs to be under controlled conditions of ventilation and also under the use by trained professionals. There was a fair amount of discussion on that. So I think that's where at least our team felt we could handle that and obviously significantly different.

DR. BERGFELD: The Belsito team's response?

DR. BELSITO: In terms of the methylene glycol, and Jay may want to comment, we felt that by putting in formalin and limiting that to 0.2

percent and putting the star in all of the discussion we had had about the equilibrium between formaldehyde and methylene glycol, we covered all bases and really didn't have to put in a concentration limit for formaldehyde or methylene glycol, just .2 percent formalin which will have methylene glycol in it and formaldehyde. So that's the first point.

The second point we also struggled with because we certainly agree that there is scientific evidence that under proper conditions, under very proper conditions, these can be used safely. However, we felt that we have data that showed in the first round that even under apparently proper conditions, levels were being exceeded of formaldehyde in the air. And that in the last go-around there were six salons. We had no idea of how they were selected. And even then if you read all the details of the reports, they're finding out that it depended upon how you position the fans and the ventilation and there was so much going on there that we felt that, yes, scientifically they could be safely used. However, in the present practices and

concentrations of use in some/many instances, they weren't being safely used. And as opposed to certain other chemicals, more specifically, methyl methacrylate, that we said shouldn't be used on nails but is available for us for other reasons and I would encourage you all to go to any nail salon in New York City and you'll probably find that methyl methacrylate will be applied to your nail. This is a product that would be available only if we allowed it for salon use, and if we allowed it for salon use if you're worried about it getting into the underground market, that's how it's going to get in. At least that was I think the consensus of our panel and I'd ask Rachel to comment on this as well.

MS. WEINTRAUB: Yes, I think you stated it very well. I think the concern is that from the evidence we've seen before us, even in what is still unclear to me to be adequate ventilation, it's still unclear to me what a trained professional is given the fact that licensed stylists who took courses given by the manufacturer of the hair-smoothing products, and I've spoken to a few of them who have taken these

courses, still weren't aware of how to use these to minimize exposure to themselves or to their client. So my concern is multifold. First, we don't know what a trained professional means and we don't know what proper ventilation methods are and when those are adequate.

Also we do know as you pointed out that given conditions where it appears that we could argue it's say that there was adequate ventilation, there still have been recorded levels that exceed OSHA limits. So I think that while in pristine, precise conditions there would not be unsafe levels of exposure, those situations are very difficult to achieve in the real world.

I also wanted to point out that in the conclusion Dr. Marks's team recommended, there is no limit on the concentration of use, so I think if you look back on other precedents even when there's a discussion that includes a trained professional and other requirements, there was still a limit and there was no limit given for the level of formaldehyde and methyl methacrylate or formaldehyde for hair-smoothing products. I

think in this case for consumers and for hair stylists there needs to be clear information, there needs to be clarity and consumers and stylists need to be protected from potential high levels of formaldehyde.

DR. BERGFELD: Ron shank?

DR. SHANK: The panel has some precedents in dealing with these kinds of issues, not necessarily with formaldehyde. Some time ago we dealt with a whole long list of glycolates and lactates which if not used properly produced very severe skin reactions, and we concluded that those products are safe when applied by, and this is a quote, "trained professionals using ventilation procedures to prevent irritation to eyes, nose, throat and lungs."

We have often, I shouldn't say often, several times the panel has handed issues like this where products can be used under conditions which would not be safe and we've added caveats to the conclusion. Another example is the diacylglycerol esters where we said that they're safe, and then an important provided that the content of 1,2- diesters is not high enough to

induce epidermal hyperplasia. In neither of these cases was there a number for a concentration given. There was a biological end point given which is probably much more relevant.

With alpha hydroxy acids we had the same problem. If they were used and people went out into the sun, they increased their risk for sun damage. So we said that the alpha hydroxy acids were safe when application is accompanied by directions for daily use of sun protection.

Placental enzymes is another one where we said they were safe, that they should not deliver any metabolic or endocrine activity. The list goes on. I think we should recognize that formaldehyde in hair-smoothing products can be used safely if the professionals are trained properly and ventilation is adequate. Apparently there are conditions today where that's not the case. That means that professionals have not been trained properly and/or the ventilation has not been adequate. And what concentration is important? What concentration is important is that which produces irritation and you don't need a number.

DR. BERGFELD: Could I call on Curt and

then Don?

DR. KLAASSEN: I think we all understand the problems that formaldehyde can cause. We're kind of getting in the in-between area of science and policy here. We know what the effects are so we're not just agreeing about that. What we're talking about is how to protect the people from some of these adverse effects. Our team I think did spend 3 hours on this topic yesterday and so we went back and forth a long time. We came down to the conclusion that at the present time it is not being used safely in many places and that's the reason that we came to the conclusion that we did because it's not being like we usually say for most of our ingredients safe in the present use or practice and it isn't being used today safely. But we did agree as a group that it could be, but it isn't. So that's how we came to our conclusion.

DR. BERGFELD: Don?

SPEAKER: Ron, I appreciate all of the effort you went through looking at the prior reports where we put limitations, but if you review them with the exception of the alpha hydroxy acids where the onus was on the consumer

to use a sun screen or we restricted a pH in a concentration level that could be used by a trained cosmetologist, the onus for all of these other restrictions has been on the manufacturer. Here the onus is on a hairdresser and the cosmetic industry is a very diverse industry. It runs from very upscale branded shops that exist in many cities to little mom-and-pop shops. I welcome you to come up to Columbia University and see the number of beauty salons that stud Amsterdam Avenue where it's one lady in a little storefront. Again as Curt just said, we struggled with this because scientifically, yes, they can be safe as used but our comments have always been in the present practices of use and concentration. In fact, we even got data from the Keratin Council at the last meeting that showed us in the present practices of use in salons that they selected, levels were being exceeded. So we felt that the evidence that we were seeing, the consumer reports that we've been hearing from the U.S. and Canada, would indicate to us that in the present practices of use these products were not being safely used and that to try and control that level

of safety is quite a different level than asking a woman who's shelling out big bucks for alpha hydroxy acids to reduce wrinkles to put on sun screens quite honestly as a dermatologist that's a no-brainer. If they're going that far they are going to use sun screens because they require that the damage is due to sun.

DR. BERGFELD: Dan?

SPEAKER: If I had a high degree of confidence that a trained professional could make sure that this product posed no hazard to either themselves or to their customers, I could easily accept the proposal that your group has suggested. I just in this case have no confidence that that's possible at least under the present circumstances based largely on the data that we've been presented now. Also I think we can't ignore the fact that even though these products are most commonly used in professional circumstances, it's not hard to get ahold of this stuff and use it in ways that are in circumstances that couldn't possibly conform to what we would consider best practices and that this would happen frequently enough that think it would pose a serious hazard.

I can accept the idea in principle but not in practice. It happens frequently enough that think it would pose a serious hazard. I can accept the idea in principle but not in practice.

DR. BERGFELD: Jay?

DR. ANSELL: We faced essentially the same dilemma, that we have here a product which can be used safely but it's unclear that it is being used safely, that we have a higher expectation with professionals in handling these materials, but for cosmetics, they're not used to handling materials with very narrow safety factors that would be particularly amplified if these products found themselves in a home environment. But I think the solution that was proposed to tie it very tightly to current conditions of use is an appropriate solution, that within the context of the report, these materials are not being used safely under the current conditions of use. However, there are expectations that there are ways of using it safely and indeed both OSHA and FDA in their position papers or letters which found the materials deficient cited those specific

deficiencies which will need to be redressed to bring these materials into conformance whether it's conformance under the formaldehyde rule under the OSHA case or why the materials are misbranded and adulterated within the meaning of FDA and I'm sure Linda will amplify on that.

So we fully support the proposed conclusion with the modification that the materials are unsafe under current conditions of use with an understanding that if people do conform with required safety, they may be handled safely.

DR. BERGFELD: Linda, I wonder if you'd respond.

DR. KATZ: I'm listening to the discussion back and forth and with the exception of the conclusions of the two teams, what's being said is virtually the same thing, that the product can be used potentially safely in certain circumstances. As far as the role for this group, it is my understanding that the CIR is supposed to evaluate ingredients on the basis of the data that's presented whether or not the ingredient is safe or not. With regard to how it gets used, that

becomes more of a policy and a regulatory issue. In this case, there is a multifaceted jurisdiction under which formaldehyde or these products would be regulated. It would be OSHA for the salons, the states also regulate the practice of the actual art in the salons and the FDA regulates the products themselves. What I'm hoping as the discussion continues is that the panel itself looks at the issue of the ingredient, whether or not the ingredient in the type of product that is being sold can be used safely, and if the ingredient can be used safely, then to make recommendations as to how it should be used or what you think needs to be there. Then we as regulatory agencies will take that information back to deal with what we need to do to make sure that the products can be used safely if that's what should be done for the public itself.

OSHA went through very carefully and looked at different salons and came out with statements about certain products in certain salons in which the levels of formaldehyde exceeded that which was the expectation. In our warning letter which I'm sure everybody has

looked at, we cited that the product itself for Brazilian Blowout was adulterated under the law and misbranded under the law. It was adulterated since it contained formaldehyde at levels which were deemed to be unsafe which made it adulterated. And it was misbranded because it was claimed to be formaldehyde free and in fact it was not, and material facts were not disclosed on the product labeling which needed to be there. We're still waiting for the opportunity for the company to respond to the warning letter before FDA does anything further at this point in time. Again I think that probably as I'm listening to the discussions, it sounds like probably both sides are not too far off and perhaps more discussion needs to be held to come to some agreement as to what to do about the ingredient itself.

DR. BERGFELD: Thank you. Jim, do you care to respond or give comment?

DR. SHANK: I wanted to clarify, Linda. Did you say then you view our role as the CIR panel to decide whether it can be used safely or not, and if it can be used safely then to elucidate those conditions in which it could be used safely

and therefore defer to the regulatory agents as to enforcing that, so to speak? Did I hear that correctly that if we feel it can be used safely we should declare it as such?

DR. KATZ: That's what I'm saying. The regulatory agencies will take care of the policy and the regulations of what needs to be done, but my understanding unless I'm incorrect about the role of CIR is to review ingredients to make a determination whether or not ingredients are safe.

DR. BERGFELD: Don, do you wish to respond or comment, and then Paul?

DR. BELSITO: I think that our role has been to determine if ingredients are safely used in the present practices and concentration of use and that's how we've always looked at it. I think that at least for myself, again that's why we couch the language as we did in the present practices of use they are not being safely used. If this were a nuclear power plant where there were a limited number of plants in the country that could easily be policed, maybe I might be otherwise persuaded. But I don't know how OSHA

or FDA or any state authority is going to be able to police every cosmetology shop. My concern is that as we all know, professional salon products are sold to clients all the time, either who just walks into the beauty shops to buy them or who are actually sold the products in the shops and I think that by allowing this product out in the marketplace it will be impossible to control the use and to assure that in fact it would be used properly.

DR. BERGFELD: Thank you. Paul?

DR. SNYDER: A couple of comments. I think the first comment I have is that we were presented no data which demonstrated conditions in which it could be safely used like how many air exchanges per hour, whether they need to wear goggles or whether they need to wear a mask. We were presented no data that said under these conditions it can be safely used so we're making a presumption that somebody can figure that out. While FDA and OSHA may want to do that or can do that, I think what we have is the data presented before us so we're making an assumption that it could be done. We have no data that say that it

can be done. As a person who lives in a formaldehyde world being a pathologist and all the tissues that I deal with every day are fixed in formaldehyde, I can tell you after just remodeling one lab that it took multiple visits by our radiological and environmental group to get the air levels appropriate so that my workers could work in there and these are not easy tasks. It was very problematic and cost way more than we thought it was going to cost and I can't imagine a small salon being able to meet the standards that we had to meet to prevent exposure to my workers. So from a personal standpoint, it is very difficult to do.

Maybe the resolution to this could be if we kept the conclusion as our team said that in present practices they're unsafe but in the discussion talk about there is the potential to develop safe environments but those parameters have not yet been construed or figured out.

DR. BERGFELD: Dan?

DR. LIEBLER: I appreciate Linda's reminder to the panel that our role is not regulatory, that our role is advisory on safety

of ingredients, but I think that the safety of ingredients isn't necessarily intrinsic to the stuff in the bottle and that we always have to evaluate these in the context of practices of use and there's the rub for me on this particular ingredient.

DR. BERGFELD: Linda?

DR. KATZ: I appreciate that as well which is part of the reason why I made the other comment, that if there were certain conditions under which one feels that it could be safely used to go ahead and make mention of that in terms of the overall arching opinion. I didn't want it to seem like it's completely black or white because it's really not. This discussion is really somewhere in the gray area as to what should be done with this ingredient from your perspectives even as I'm listening to the discussion.

DR. BERGFELD: I'd like to call on Tom Slaga.

DR. SLAGA: Although I totally agreed with our conclusion, the hardest part that I see how we would discuss what is a trained professional. I don't think we would ever agree

on what a true trained professional would be, and properly ventilated is another. I doubt that this group would ever come together in a discussion with that aspect. That's the hard part for me. I still agree with Ron that this is a solution, but it's a difficult solution.

DR. BERGFELD: Ron?

DR. SHANK: Are you saying that all hair-smoothing products, every one that contains methylene glycol, causes these irritation problems with the eyes, nose and throat, all of them, because you're going to say none of them. What you've just said is none of them are being used properly today. Is that correct? None of them?

DR. BELSITO: I did not say that none of them.

DR. SHANK: Yes, you did. Under current practices of use.

DR. BELSITO: I never did. Yes, because --

DR. SHANK: All of them?

DR. BELSITO: No. But then are you going to define which ones are and under which

conditions they are safe? Rachel made the point if you look at the photographs that we were show, the instructions were to be wearing goggles and masks and in none of the cases were the cosmetologists in those photographs that are supposedly are best-case scenarios were following proper instructions. Clearly there have been a large number of consumer complaints. Clearly in the first iteration in June we were given salon levels that exceeded federal standards for formaldehyde. These you would imagine would be best-case scenarios. Right? When you go to a meeting you present your best cases. You don't present the cases you botched. I'm not saying that it cannot be done and I'm sure that it can be. The question is our approach has always been present practices of use and concentration. We don't know the concentration. We certainly don't know the present practices of use. But we know that in some cases the present practices of use result in release of formaldehyde that exceed acceptable levels.

I'm not saying that these products could never be used. I'm saying currently the

information we have is that when they are used, in cases they exceed acceptable levels.

DR. SHANK: When they are used or when some of them are used?

DR. BELSITO: When some of them are used, but what are they?

DR. SHANK: There's a big difference, sir.

DR. BELSITO: Of course there is and we're not closing the door to the Professional Keratin Council coming back and showing us data that at certain percentage, at a certain lower heat level than 450 degrees Fahrenheit with this type of exhaust system that they could be safely used. But at this point I don't think we have the information that allows us to say that.

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

DR. HILL: Out of character for me I guess, I have nothing to add to what's been said.

DR. BERGFELD: Jim?

DR. MARKS: It's rare when I might particularly after our discussion yesterday be swayed to come to a slightly different conclusion

than Ron Shank, but I must say that if I'm going to err I would prefer to err on the side of consumer safety, and I'm today persuaded that the Belsito team's concerns are enough to sway me to come to a conclusion unsafe but where it's robustly discussed in the discussion about there is the potential of safe use and that if the council, meaning the Keratin Smoothing Council or industry group came back and showed us those things and perhaps better define what professionally trained and good ventilation is that maybe then we could revise our conclusion to have a safe under the current practices.

DR. BERGFELD: Are you seconding the motion?

DR. MARKS: I will second the motion.

DR. BERGFELD: Ron, do you want to have a response?

DR. SHANK: No. I've said what I felt I needed to say.

DR. HILL: In that case, I will say that the science says that it can be done.

DR. BERGFELD: Is there any other discussion regarding the three conclusions?

DR. MARKS: Alan, is this going to be a re-revised or final because there were changes in the nail hardeners and we would have another shot at this again if there were more data from the use in hair salons.

DR. ANDERSEN: I don't think so. I think that the changes to part one of the conclusion that addresses the expanded discussion of formaldehyde equivalence to include what will turn out to be very useful information for manufacturers referring to formalin because that's what they actually add so now we've got that link, all of that is editorial. On the nail hardeners' conclusion, it was contemplated that these data would come in and that if the concentrations were now known and the panel was comfortable, they would put a number and in this case it's understood that the data are consistent so present practices of use is a fine way of characterizing it and that was one of the expected results. And the unsafe for hair smoothers as the motion was made didn't change, so this could be issued as a final safety assessment. The further emphasis that Paul Snyder made and that Jim Marks

is suggesting including an expanded discussion of how it could be used safely in the discussion part is also from my standpoint editorial. So I think this can go final.

DR. BERGFELD: I'd like to make a comment. I would be hopeful that in the discussion you would use the end points that Ron Shank has used as biological end points.

DR. ANDERSEN: Absolutely. Right now that is the only link that we've got to avoid ocular and respiratory tract irrigation is the link.

DR. BERGFELD: Jim, are you going to make a remark? No?

DR. MARKS: No. I agree with all that. Obviously in the past industry has come back and asked us to reevaluate an ingredient and even though we're declaring it unsafe for hair smoothing products and even though we know in certain conditions it can certainly be used safely, we'll put the onus on the industry to come back and prove that it can be.

DR. BERGFELD: Are there any other comments? If not, I'm going to call the question.

All those in favor of Don's conclusion which is a three-parter, please indicate by raising your hands. Voting against are two. It is voted upon and approved with two dissenting.

We're going to move to the next ingredient and that's the benzoic acid group with Dr. Marks presenting.

DR. MARKS: In June of this year the expert panel issues a tentative amended final report with the conclusion that benzyl alcohol, benzoic acid and its salts in benzyl benzoate are safe in the present practices of us in concentration. We're at the point now that I move we issue an amended final report with the conclusion of safe.

DR. BERGFELD: That is a motion?

DR. MARKS: Yes.

DR. BERGFELD: Is there discussion or second?

DR. BELSITO: Second and then discussion.

DR. BERGFELD: It's been seconded. Don, do you wish to discuss?

DR. BELSITO: Yes. On page 1 of the

report and page 14 of the Panel Book, we thought that when we introduce the fact that we've looked at this in 2001 that we should point out that while the data has been summarized in this report that readers wanting specific details of the studies that were discussed in 2001 should go back to that report with a clarification that while we're going to summarize those studies that the details are in the original report and not in this report.

On page 11 and Panel Book 24 where it says that benzyl benzoate is classified as a nonsensitizer at 5 percent and then it says a weak sensitizer at 1 percent, I believe that should be 10 percent. Finally, on page 19 and Panel Book 32, we did appreciate the Personal Care Product Council's comments that part of what allowed the safety was similar metabolism of these compounds. In the first paragraph we said that while the available data on many of the ingredients is sufficient, however, in similarities between structures, structural activity relations and metabolism suggests -- so we just added the word metabolism to point that similar metabolism, but all very editorial.

DR. MARKS: We had one editorial comment. We wanted, Paul, for you to comment on page 32 of the Panel Book, the third paragraph from the top, where it says testicular atrophy was observed in rabbits who received repeated dermal doses. Then in the next sentence it's not classified as a reproductive or developmental toxicant. Actually Rachel pointed out the contradictory nature of that, and as we call on our team, Ron Shank recalled that I think Paul you said that that study that showed testicular atrophy was stress related and not really related to these compounds.

DR. SNYDER: The rabbit studies were repeat dose studies looking for target organs and the testes was identified as a potential target organ. The other studies that are referred to were specifically reproductive and developmental studies in which they looked at reproductive rates and developmental aspects and those were negative. I do have a reference me, I brought it just in case Ron was interested, where there is a nice article by Morton talking about immature rabbits and how sensitive they are to stresses in

regards to their development of the testes because of their immature nature stress related. And there were other parameters in the rabbit study that suggested body weight changes, clinical chemistry changes and hematology changes that clearly indicated that the rabbits were stressed and I was quite comfortable as I stated before that those testicular effects were in fact attributed to stress and not a direct effect of the chemical. So I think that this is not contradictory. I think that there are two different aspects of toxicologic end points that are being measured.

DR. MARKS: Wilbur, would you capture that in the discussion then and I think add that new reference that Paul mentions?

DR. BERGFELD: Don?

DR. BELSITO: Lastly as you'll remember, what held us up was the inhalation toxicity studies so now I think before we proceed with any other reports we probably have to sit back and decide how we want to handle that in the cosmetic use section and in the discussion. In this case it's less important because we have inhalation

toxicity so maybe we don't need to do it with this ingredient, but we're going to have to do it at some point during this meeting. Silylates? So not with this one since we have the tox data.

DR. BERGFELD: I agree that we will not be doing it with this one. Is there any other discussion? Ron Hill?

DR. HILL: Pertinent to the change you suggested that's at the beginning of the discussion section, I have a comment. One is has similarity between structures. I'd like that language stricken because it has no biological meaning. And the other problem with that sentence is it says similarity between structures and structure activity relationships could be read to say similarity between structure activity relationships and that's a meaningless statement. So the statement is unclear as written because it suggests that we're saying similarity between structure activity relationships and there is no way to make such an assessment. I think if it just said if you get rid of similarity between structures and just write and structure activity relationships, period, that it will be very

clear.

DR. BERGFELD: That replaces that read-across statement that we've been using.

DR. HILL: It does in this case, yes.

DR. BERGFELD: I'd like everybody to be reminded of that.

DR. HILL: But of course the metabolism part should be kept. I think that that should stay there definitely.

DR. BERGFELD: Right. Are there any other comments or suggestions? I'll for the question then, the approval of the conclusion as safe. All those in favor? Unanimous. Thank you.

Moving on the next ingredient, Dr. Belsito, the silylates.

DR. BELSITO: In June we looked at this and we issued a tentative safety assessment for the silylates group of four ingredients and our conclusion was safe in the present practice of use and concentration, leave-on and rinse-offs, but insufficient data for use in products that might be inhaled. The issue there was granuloma formation and some inhalation toxicity studies where these particles were sheared down to

dimensions of less than 10 microns that were respirable in order to do the inhalation toxicity studies. However, under the practices of use these are not sheared to those levels and that was very nicely pointed to us as was the fact that under use conditions these particles usually agglomerate and end up with much larger particle sizes that would not be respirable.

Based on that information which of course would need to go into the discussion of the granuloma formations were because of artificial shearing and the agglomeration of these particles in real life we felt that we could conclude that silica silylate, silica dimethyl silylate, trimethylsiloxysilicate and trifluoropropyl dimethyl trimethylsiloxysilicate are safe in the practices of use and concentration described in the safety assessment.

DR. BERGFELD: That's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: Is there discussion or second?

DR. SHANK: There's nothing in your conclusion regarding inhalation and respiration.

DR. BELSITO: Nothing in our conclusion regarding inhalation or respiration, no.

DR. SHANK: Okay.

DR. BERGFELD: Do you want to make a comment, Ron?

DR. SHANK: I think there should be.

DR. BERGFELD: Would you comment on what it should be?

DR. SHANK: We have to decide on what the boilerplate is going to be for airborne materials and I think we came up with a pretty good one. Dr. Marks can read it.

DR. MARKS: What we had as the boilerplate would read when formulated or -- formulated and delivered to be nonirritating to the respiratory tract.

DR. BELSITO: When formulated and delivered to be nonirritating to the respiratory tract, is the formation of lung cancer a nonirritating phenomenon so that if something were delivered to the respiratory tract that didn't irritate it but created cancer, that would be okay?

DR. SLAGA: Lung cancer is irritation.

Chronic irritation has a very strong relationship to lung cancer.

DR. SNYDER: Probably more important is allergic reactions and so I don't think the irritation would also be a prelude to allergic reactions.

MR. JOHNSON: And I'm not sure for a carcinogenic material we would get to the point where we had to add the safety boilerplate.

DR. BELSITO: Irritation does not seem to be the right end point. Do we want respirable, less than 10 microns?

MR. JOHNSON: Inflammation?

DR. BELSITO: I don't know, but irritation to me doesn't seem to --

DR. SLAGA: Isn't that a very sensitive biological response by the respiratory tract?

DR. BELSITO: I'm a dermatologist. I'm not a pulmonologist. I don't know. But the proper term that just seems to me as a dermatologist you could formulate something to be not irritating but it could be highly sensitizing.

DR. MARKS: Certainly to me that seems like if it's a carcinogen it's fairly infrequent

that we deal with agents where we're worrying about an anaphylactic reaction. We could certainly include sensitizing and irritating if you would do that. What we heard yesterday morning clearly shows that just using particle size is not going to be enough, that the way it's delivered whether it's a pump or aerosol and we know that below 10 microns there is still come delivery even though there's a small amount. Then with powders we heard it was solvent that had an impact also. So that's why we phrased it in a way which we thought would address the issues in a more broader way and not just on particle size. That's why we used formulated and delivered. The biologic end point is irritating. If you feel strongly we should put sensitizing in there, that's fine.

DR. BERGFELD: Ron Shank, do you want to respond again?

DR. SHANK: Saying formulated and delivered without irritation or sensitization is fine.

DR. BERGFELD: Paul? Dan? Curt?

DR. SNYDER: The only question is

whether or not the irritation or sensitization are two specific terms, but I can't come up with anything better.

DR. BERGFELD: Alan, do you have something?

DR. KLAASSEN: I think for now this might be appropriate, but I think for many of these compounds there are other things that give us confidence that it's not a major problem in the lung and those definitely should be added as well including the dose. A dose that gets to the alveoli is still extremely small and from what we heard yesterday at the extreme of up to 5 percent. So there are other things that should be added into our discussion or wherever it goes that gives us confidence that this compound is most likely not going to cause problems and not just irritation.

DR. BERGFELD: So you're suggesting that we always put into the discussion some kind of phrase or paragraph regarding why we have said what we have said about inhalation.

DR. BELSITO: There are several aspects of the change in all of the boilerplates that

we've been using. We discussed this also extensively. The first changes in the cosmetic use section when we mention that it's used as an aerosol, previously we had said in practice aerosols should have at least 99 percent of their particle diameters in the 10- to 110-micron range and the mean particle diameter of the typical aerosol spray has been reported to be approximately 38 microns. So we thought that based on what we heard yesterday the standard boilerplate for an aerosol in the cosmetics section would be in practice aerosols have 95 to 99 percent because we heard they could have as much as 5 percent of their particles less than 10 microns, so that have 95 to 99 percent of their particle diameters in the 10- to 110-micron range, period. Therefore most aerosol particles would pause in the nasopharyngeal region and not respirable. That was sort of standard boilerplate in the cosmetic use section.

We thought that in terms of if there's absence of inhalation toxicity data then it really is going to be case by case. Dan and Curt felt very strongly that there are a limited number

of compounds that are known to be respiratory toxicants and obviously if we're dealing with those, that would be one issue. But the other side of the equation would be would inhalation increase the body burden? If it would and then you had significant negative oral tox, et cetera, that we would say that the body of evidence looking at the oral toxicity and the dermal toxicity that the exposure to the lungs would or would not contribute to this and finesse it that way, that it would be very difficult to come up with a boilerplate that would cover inhalation but we have to look at the full range of all other toxicities that we had and that would be our boilerplate, what other tox data do we have, and that's why we didn't need the inhalation.

In the case of the silylates, the bottom line is based on the new we have, they're not respirable so that's why we took that out. Here we have information that the granuloma formation that we're seeing was because these particles were artificially sheared down to 10 microns and forced down the lungs of these animals. That's not what happens. What happens as they showed is

with these aggregates, first of all they're nonrespirable to begin with and then they aggregate to further larger size which is why we felt we did not need to put the caveat on the conclusion.

DR. BERGFELD: Thank you. Ron Hill?

DR. HILL: I'm not sure we have data that says that that aggregation that you're talking about occurs with every silicate, and when you say nonrespirable, I think that's impossible to achieve because you will have some cut, some fraction of particles no matter what that are going to be in that respirable range. In the case of the issues that were identified in that inhalation study, yes, all the data now suggests that it was an overload situation and so what you'd want is some way of ensuring that the load of respirable particles be it .5 percent of what's present or even .1, and in clearly in this case that's almost certainly the case, but we don't control the manufacture, we don't control whether somebody makes a substandard aerosol generator, we don't control any of that. So I think the statements that need to be there need to somehow

ensure that if any of that were to happen that that would be beyond the conditions under which we've established for safe use. So having something about, what did we say, formulation delivery, to ensure that we don't overload. Like I say, the chances seem remote, but I don't think we know in every silylate that these agglomeration -- I've worked with agglomeration and I did agglomeration research for a year or two so I know what that's about. I'm not sure that we can ensure that every silylate that conforms to this category now and in the future that that's in fact true. So if we have some statement in there that says formulated and delivered in such a way that we, effectively what we need to say in this, don't overload the lungs to the point where these kinds of problems could occur, we're good.

DR. ANDERSEN: A couple of comments. One is that this is the first time in quite a while that we've really focused on particles that aren't aerosols so that these are not the nice round aerodynamically pleasing predictable in terms of the data that we heard yesterday. These are asymmetric, these are aggregating, these are

agglomerating so that while we may want to bank on that conceptually, it's just different than what we heard about yesterday. That said, the folks from SASI who have provided the input are extremely confident that their particles would meet the language that Jim suggested, that when formulated and delivered they would be nonirritating to the respiratory tract from their perspective because there won't be significant exposure, but they're comfortable that that's not an impediment to manufacturing these ingredients and supplying them to formulators. So I think because these are, I keep wanting to say powders and that's probably not the right word to use, but these are not aerosol particles from pump sprays or aerosol sprays that we're talking about. This is particles that are of a different sort and putting a little constraint on it I'm not sure hurts and the companies involved feel that that they can meet that.

DR. BERGFELD: Don, it's ingredient, it's your conclusion and Jim has added something to this. Are you going to accept that?

DR. BELSITO: Could you repeat?

DR. MARKS: Instead of the insufficient we would change it to be when formulated and delivered to be in this case change slightly, no irritation and sensitization to the respiratory tract so that we cover irritation and sensitization and the respiratory tract is obviously upper and lower and middle so it covers all that and I think it addresses the sensitization issue although with this chemical that's not an issue.

DR. BELSITO: So safe in the present practice of us and concentration described in the safety assessment when formulated and delivered to --

DR. MARKS: To be no irritation and sensitization to the respiratory tract. That could be wordsmithed.

DR. BERGFELD: Non?

DR. MARKS: Non, yes.

DR. BERGFELD: Nonirritating?

DR. MARKS: You could say nonirritating and nonsensitizing. However you want to word it, that I think is an editorial portion of the conclusion.

DR. BELSITO: Paul had a comment. When formulated and delivered in the final product? Do you want that added?

DR. MARKS: Yes. That's good. Yes. Thank you, Paul. In the discussion I think we could handle it like the hair dye epidemiology that there is a brief paragraph with a link to this very robust discussion. Ivan are you the one who's authoring the aerosol boilerplate that it would go into a great deal of detail in terms of what was presented yesterday morning, et cetera?

DR. BERGFELD: Jay, you wanted to speak?

DR. ANSELL: Yes. I think as boilerplate that's fine, but the boilerplate needs to be applied within the context of this ingredient and there is extensive data showing it's not irritating or sensitizing including rather long-term inhalation data. So do we need the boilerplate specific to this report?

DR. MARKS: I thought the reason we did was because we didn't have the inhalation toxicity, we have the theoretical the way it is, but am I incorrect that we actually have animal studies?

DR. SNYDER: No, I agree. I think that it is part of our basis for our weight of evidence approach to the safety assessment.

DR. BERGFELD: So you would continue to have it included? Is that what you're saying?

DR. SNYDER: Included or reference to a document that talks about the different aerosolization and the different particle size distribution. All of that information that we've learned I think is important because I think that's all part of our knowledge that we're applying on a case-by-case basis to these ingredients.

DR. BERGFELD: But as to the second part of the question, would you have the inhalation statement and the respiratory in the conclusion?

DR. SNYDER: In the absence of inhalation data I would prefer it to be in.

DR. BERGFELD: The question is there an absence.

DR. MARKS: That's what I'm asking, in this particular do we have enough inhalation? That's what Jay's bringing up. Do we have enough inhalation toxicity to say we don't need this

caveat? If we don't then we need to include it.

DR. BERGFELD: Paul?

DR. SNYDER: My opinion differs a little bit from Dr. Hill's opinion in that that was a very robust inhalation study in which they looked at a hydrophilic and hydrophobic situation. Despite the fact that they were sheared, the lesions were minimal related to the silylates and what few lesions there were, they were reversed. In an extreme overload those animals are treated for 6 hours, 5 days a week for 13 weeks. So I have pretty good confidence that these brief intense exposures of a minute or 2-minute duration would not likely result in any significant toxicologic effect on the lungs on a case-by-case basis. Again it might be different if you ask me on the next ingredient.

DR. BERGFELD: Lillian?

MS. BECKER: You also have the additional aerosol studies that we went to you in Wave 2, animal studies.

DR. BELSITO: Then we have all the studies in Table 4.

DR. BERGFELD: Tom, Ron, Ron, do you

have any comment about the caveat to put in the conclusion, whether it should stay or not, whether it should just go into the discussion as a discussant point? Paul, do you want to comment on the animal studies in the second wave of information?

DR. SNYDER: That was the study that I was referring to.

DR. SHANK: We have inhalation data in the report which was not a trivial response. We can explain that but it's still in the report. So I think it should be part of the conclusion. If you don't, you have to make a very strong case or discussion of the inhalation data and why you're not concerned about it.

DR. BERGFELD: Ron Hill?

DR. HILL: Again I say I agree that the studies came up clean but they were using materials that were current sources from current manufacturers and who's to say 15 years from now somebody else doesn't go into that business and come up with a product that ends up in a final product that could cause these kinds of problems? So we put in not only the information in the

discussion but also something in the conclusion that forcefully brings to the attention of anybody who might be interested in doing that to check all this stuff out before they put something out on the market because we don't have any control over they could be manufacturing in a way that will suddenly cause a problem and that would prevent it.

DR. BERGFELD: Curt?

DR. KLAASSEN: I agree it should be in but I think it should be in the discussion and not the conclusion.

DR. HILL: I'd be okay with that.

DR. BERGFELD: Tom and Ron, do you agree with that? Then Jim?

DR. MARKS: I second the motion.

DR. BERGFELD: You second it and you second it as stated by Don without the inclusion of the inhalation statement. Is that correct?

DR. MARKS: That's correct. And then we've already had a really robust discussion and we know that's going to be included in the discussion.

DR. BERGFELD: Yes, we have.

DR. MARKS: Hopefully we've maybe hammered out our boilerplate which is still on the agenda for aerosols.

DR. BERGFELD: Is there any other comment regarding this ingredient and its conclusion of safe? See none, I'll call for the vote. All those approving please indicate by raising your hands. Thank you. It's approved unanimously.

Moving on to the next, the tetraesters, by Dr. Marks.

DR. MARKS: This is the pentaerythrityl tetraisostearate and other esters and will refer to them as PET. The expert panel issued a tentative safety assessment in June 2011 finding these were safe and that report included an ingredient, the PET-cococate which was removed from the tentative safety assessment that was sent out because it chemically was different. It's a monoester and it doesn't fit with the tetraesters. In addition to the removal of that agent which would change the conclusion since it no longer exists in this report, we continued to wait for use and concentration tables and then we

obviously need the inhalation boilerplate. So I would move that we issue a revised tentative safety assessment. We can't move on to the final safety assessment at this point because that ingredient has been removed and we're awaiting the use concentration. So the move is of a revised tentative safety assessment and that these agents are safe.

DR. BERGFELD: Then that's a motion?

DR. MARKS: Yes.

DR. BERGFELD: You need use information?

DR. MARKS: Use information, and the second reason is that we would continue not to move forward to a final safety assessment is because technically we removed an ingredient and that was sent out for public comment.

DR. BELSITO: Which ingredient did you remove?

DR. MARKS: The PET-cocoate. It's under the memorandum from Lillian and it's the second paragraph there.

DR. BERGFELD: It's not on the conclusion list. It's been taken out already.

DR. MARKS: It had been taken out from the document we saw previously and that document was sent out and then subsequently what we had is one item deleted.

DR. BELSITO: I don't understand. It's not in here but what was sent out less than 60 days ago had cocoate in it?

DR. MARKS: Yes.

MS. BECKER: At the June meeting it was still in. We put out a document for comment. Then the council redefined the cocoate as a monoester. So when it came to you we had taken that out.

DR. BELSITO: Were we told that?

DR. BERGFELD: One team was told it yesterday. Maybe yours wasn't.

MS. BECKER: It's in the memo in the documents.

DR. MARKS: It's in the memo. What we questioned and found out was that it was sent out with the cocoate in it. Otherwise that wouldn't have been an issue. The second issue is do we approve a final report before we see the use and concentration table and that could be hazardous.

DR. BELSITO: I think it's six or one

or half- dozen of the other. We weren't aware that the report went out, the initial report at least, with the cocoate data in it and therefore it didn't meet the timeline. We're concerned that we didn't have concentration of use data in aerosols particularly now that we know that we can no longer say that aerosols aren't respirable. So we had said table it for concentration of data in the aerosols, and of course then to change our respiratory boilerplates. But I don't have a problem with reissuing it as insufficient or formally dropping the cocoate and having it come back to us.

DR. BERGFELD: Let's ask Alan how we should proceed.

DR. ANDERSEN: The two issues I think need to be separated. At the June meeting discussion there was no question that the pentaerythrityl cocoate as then defined in the dictionary, and Bart went through the explanation that it's just vague. It doesn't say whether it's a monoester, diester, triester or tetraester so you guys left it in on the off chance that it could be a tetraester. The council has come back and

resolved the issue. They changed the definition so that it's a monoester. I don't think that needs to go out again for comment. It's just that the definition has been changed so you take it out.

The second question at least to get specific, we've got a pentaerythrityl tetraethylhexanoate that as captured has a potential inhalation exposure, inhalation sprays, with a concentration range that goes up to 50 percent and that's the red flag about which the concern exists. That may not be a spray, but right now you don't know and you want that to be clarified and I think that's a perfectly reasonable question to ask and to expect an answer, and either putting it on hold or whatever we do to await the answer to that question is a just fine idea.

DR. BERGFELD: Dr. Marks, do you want to make a motion to table?

DR. MARKS: Yes. I will withdraw my former motion and make a motion that we table this ingredient.

DR. BERGFELD: Is there a second to table?

DR. BELSITO: Second.

DR. BERGFELD: Second. Is there any other discussion? There is no discussion on the table. Excuse me. All those in favor to table? There is no discussion on the table.

DR. BELSITO: Before we move on to the next ingredient, can we have a respiratory discussion?

DR. BERGFELD: I need a vote. Yes. All those in favor to table this particular ingredient please indicate by raising your hands. Thank you. It's tabled. Don, what do you have to say?

DR. BELSITO: I think that while we all appreciate the ease with which we can assess concentration ranges in leave-ons and in rise-offs and in mucus membranes, the issue becomes particularly with underarm deodorants since we heard that those tend to have the lowest particle size yesterday and also with anything that could be sprayed, what we would like to see in the future would be deodorants, aerosol, nonaerosol -- what were the words? Not aerosol.

DR. SNYDER: Nonspray.

DR. BELSITO: Spray, nonspray, and then under spray, pump aerosol. So if we could begin to get that kind of information which would give us a little bit more specifics about, one, because a deodorant could be a roll-on. There is no respiratory component. Or it could be a spray or it could be -- use it to spray, not a pump, but hairs could be sprays or pumps. We now know that the mean diameter of a spray is smaller than the mean diameter of a pump. It would give us some idea of what kind of respiratory toxicity we're looking for, so we would like that change in future reports.

I think the other area for discussion that came up in our group and we may not want to go there now is what do we do with all these reports of the past 5 years where we just blew off the lack of inhalation toxicity because we assumed that they were not respirable based on the information we had yesterday? At some meeting do we need a list of those and a decision as to whether based upon our combined wisdom we need to go back and readdress some or do we say that was done and that was done?

DR. BERGFELD: I'd like to take the prerogative of the chair and say that we will make that an agenda item for a later meeting and discuss how we will handle that. In the meantime, Alan can get the list up for us.

DR. ANDERSEN: Message received.

DR. BERGFELD: Jay, did you want to make a comment on how you're going to be able to accommodate Dr. Belsito's requests?

DR. ANSELL: I think what come up yesterday and during our meeting is that the potential for inhalation is going to require some significant discussion and I think that's appropriate. I do think that we came to the conclusion that we can address these through looking at systemic toxicity and irritation potential. But I also wanted to make a point which I have the microphone that yesterday's discussion was intended to focus on the potential for inhalation exposure, not that inhalation exposure should be ignored. We did some back-of-the-envelope calculations overnight and I still think we end up coming to the conclusion that this is not a significant route of exposure,

that based on the data we saw, based on average applications, uses rates, depending on the assumptions for the breathing zone in the room, we come up with exposures in the order of 50 nanograms to a microgram for percent used in the product. I think this is important and should be assessed, but I do think we need to keep the dose in these considerations.

To the specific request, I think I'll have to turn to Carol and see how we can address that and provide the type of data. Perhaps it would be valuable to look at it once and it might not be necessary then to go back and look at it every single time in every single product, but I don't think until we've had a chance to consult with the CSSC we could respond.

DR. BERGFELD: Thank you. Alan?

DR. ANDERSEN: I think in many of the discussions yesterday, a problem came into very specific focus and I want to at least acknowledge it. It's not easy gathering these use concentration data and getting the information on whether a chemical used in a deodorant is used in a spray or a stick or whatever. A very thorough

job has been done to try and gather those data, but as we get more pushy about what it is we want to receive, I think appropriately so, it's just going to make it that much harder. I don't want to suggest that this is a wrong direction to go. I think maybe for CIR staff it has a message that maybe some more time needs to be provided in order to gather sufficiently accurate data to resolve some of these questions. We're going to be increasingly sensitive to that issue and at the same time, Jay clearly appreciates that the panel is putting an additional burden to get more data, more characterization and we'll see if we can work together to give you what you need when you get a report. But getting a report that has missing information, that the survey is underway and you haven't got the data yet, doesn't accomplish a whole heck of a lot. We need to make sure that this process isn't moving too fast.

DR. BERGFELD: Paul?

DR. SNYDER: Alan, I had a question regarding the gathering of that information. The act that we're developing these large ingredient safety assessments, does that hinder do you think

the process of getting that data? Because we're getting a lot more things on not reported and it's not reported because there are huge groups and it is difficult to get people to report the use? Do you think that impacts that?

DR. ANDERSEN: There are so many factors involved, I'm not sure I'd argue that you can end point one or the other. Every time the panel changes the ingredients on a list whether for good reason or not, that leaves the council hanging a little bit having asked for data, or when the panel adds an ingredient, it's fiddlesticks. We didn't ask for that one. Now we're missing data. So I think it's a combination of things. I would not want to suggest that it's the inherent size of these groups that's the problem. You're asking more questions of more suppliers. It's going to be harder to pull teeth. But it's not a fundamental flaw.

DR. SNYDER: From our side, yes.

DR. BERGFELD: Ron Hill?

DR. HILL: I'm not a toxicologist by training, but I've worked with toxicologists for some number of years now and as a medicinal

chemist I'm heavily focused on biochemical pharmacology and increasingly mechanistic toxicity. One of the fundamental tenets of toxicity is the dose is really the key piece of information upon which you base a decision of safe or unsafe. Lacking that information and the route of delivery, you're trying to make a decision without adequate information. I wasn't around when the reporting became voluntary.

DR. BERGFELD: Thank you for all your discussion and your questions.

Let's go to the DEA group and Dr. Belsito.

DR. BELSITO: As to DEA, in June we issued a revised tentative safety amendment for DEA and 17 DEA salts with a conclusion based upon insufficient data for the lauraminopropionate. We had previously looked at that and found it to be insufficient for a number of reasons. So that made 16 safe as used and one insufficient. We looked at this and we felt that the lauraminopropionate belongs to be moved out into a class where it's looked at. It's not being used and probably didn't really belong in this group

since it was more lauraminopropionate wagging the tail than the DEA. We thought this was editorial to eliminate the DEA-lauraminopropionate from this group and put it into a lauraminopropionate group at some point if we ever get there and rule that the remaining ingredients were safe as used. We also did agree with the PCPC that the current language that was being used suggested that products could be made to form nitrosamines, so changing somewhat our conclusion to state that the DEA and its related salts -- safe use in cosmetics when formulated to be nonirritating. Were there ingredients in future use -- the expert panel cautions that the ingredients should be formulated in products to avoid formation of nitroso amines.

DR. BERGFELD: That's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: Is there a second or discussion?

DR. MARKS: Both. I think we don't have problem with removing the DEA lauraminopropionate either. We had a little bit of a different take in terms of the last sentence

concerning the N-nitroso compounds and we felt the only change that needed to be made in that sentence was after N-nitroso compounds can be formed. We feel that the ingredient should not be used in cosmetic products in which N-nitroso compounds can be formed. Ron, I'll ask you. You felt strongly that it should be N-nitroso and not saying nitroso amines.

DR. SHANK: Yes. There are carcinogens in N- nitroso compounds other than just the nitroso amines.

DR. MARKS: So for it was very small. Instead of having R, we substitute can be formed.

DR. BERGFELD: Dr. Belsito, do you want to comment?

DR. BELSITO: Paul reminded me that in this conclusion it's a little bit deviating from our standard boilerplate now which is safe for use in cosmetics in the current practices and concentrations of use as outlined in this report when formulated to be nonirritating, so the standard boilerplate. I'm fine with the language about nitroso compounds rather than nitroso amines.

DR. MARKS: I assume based on our previous discussion that removing the DEA-lauraminopropionate would editorial, Alan, and not require a 60-day reissue. Is that correct?

DR. ANDERSEN: I think there is no reason we couldn't proceed that way. It would improve our sanity.

DR. BERGFELD: Is there any other discussion or comment? Seeing none, I'll call for the vote on DEA safe in this conclusion. All those in favor? Unanimous. Thank you.

Moving on to Dr. Marks and DEA amides.

DR. MARKS: At the June meeting the expert panel issued a tentative amended safety assessment that concluded that the DEA amines were safe when formulated to be nonirritating. We also had the N-nitroso compounds caveat in there. So I move that we issue a final amended safety assessment that reads that DEA amides are safe when formulated to be irritating and that they should not be used in cosmetic products in which N-nitroso compounds can be formed. Did I say nonirritating? Thank you, Tom. Move.

Nonirritating.

DR. BERGFELD: Don?

DR. BELSITO: Again in the current concentration and practice of use, it was pointed out to us though that in some cases, particularly cocoamide DEA could contain up to 18 percent free DEA and that would exceed the -- in the carcinogenicity studies, probably an effect on choline, there were positive results across the board. So we had a slightly different take and that was safe as used in current concentrations and practices of use when formulated to be nonirritating and when the levels of free DEA do not exceed those considered safe by the panel as discussed in the current DEA report, linking back the levels of free DEA and these DEA amides that we had approved in the DEA report.

DR. MARKS: I think that's fine. I would amend my motion and conclusion to include that.

DR. BERGFELD: That will be a first that you've put in a conclusion a reference back to another ingredient. Are you sure that you want to put it there?

DR. BELSITO: Yes, because we felt that

again the major ingredient that we were looking at of concern here was DEA and if information were to change on DEA, it would affect this report. However, if we link this report to DEA and in the future had to change information on DEA based on new findings, we would not have to reopen this report that changes to DEA would be reflected in this report. That was the thinking behind that linkage.

DR. BERGFELD: Is that acceptable to Dr. Marks's team?

DR. SHANK: Why don't you just repeat the conclusion from the DEA report, when formulated to be nonirritating?

DR. BELSITO: When formulated to be nonirritating, but also we linked it to levels of free DEA.

DR. SHANK: That's what the DEA report says, to be nonirritating. That was the conclusion.

DR. HILL: But it also captures present concentrations of use which concentration sort of implicitly. If you don't mention that in this particular case, I don't think you capture that

information do you?

DR. LIEBLER: That was the purpose. We wanted to capture the .64-percent limit that we were saying was safe as used in the present practices in the DEA report.

DR. SHANK: We didn't say -- formulated to be nonirritating.

DR. BELSITO: No, in the current practices and concentrations of use. In the current concentrations of use the highest is .64.

DR. BERGFELD: And you've decided not to put the .64 into this conclusion?

DR. BELSITO: We decided not to put the .64 because again we've gone through many iterations in the almost 20 years that I've been here. At one point we would set limits based upon the highest limit of the study we have, and now our approach has been current practices of use we have the data that it's safe. I don't know that .64 is the limit. It could be .8. It's just used at .8. I don't have data on .8. I'm not going to approve it at .8. But if someone wanted to use it at .8 in the future and we had data that it was fine, in 15 years when we look at it if it's being used at .9,

then we don't necessarily have to open the DEA amide report, we have that data. Right now its current concentration and practice of use, the highest one there is .64, .67, whatever. That was our thinking.

DR. BERGFELD: Jim?

DR. MARKS: I guess as you can see I thought it was a clever way of covering that in the conclusion. Ron, I guess your concern would be should it be handled in the discussion versus the conclusion since this may be a bit precedent setting.

DR. BERGFELD: Ron, do you want to comment on that?

DR. SHANK: No. I don't think it's necessary in the conclusion on DEA amides to refer the reader back to a different report. We can handle it in the conclusion as we did with DEA itself.

DR. LIEBLER: I would point out that in the discussion right above the conclusion on Panel Book page 44, report page 19, there's a paragraph, for reasons described above, the panel stated that the amount of free DEA available in

DEA amides must be limited to no more than that considered safe by the panel as described in the current CIR report on DEA, so that essentially says what we were going to put into the conclusion right above it. That could suffice I suppose rather than having the conclusion be more lengthy and having that statement right there in the conclusion.

DR. BERGFELD: Paul or Curt, do you have a comment on that?

DR. SNYDER: My opinion was that it should be as Don stated because it's problematic. It's a unique situation where these two documents are linked and that if there is such re-review at some point in time that the potential for a disconnect there, I thought we could alleviate that by the conclusion stated the way we presented it.

DR. BERGFELD: Curt?

DR. KLAASSEN: We discussed this in quite some detail yesterday. I like this way that we've summarized it and prefer to leave it that way.

DR. BERGFELD: Don, do you have any

further comment?

DR. BELSITO: I've said it all.

DR. BERGFELD: Ron Hill, do you have any comment?

DR. HILL: Although I agree with what was said about the statement in the discussion, the way it's written there infers that the current report right now doesn't seem to make allowances for any further possible changes or alterations, so if you put it in the conclusion in the way that Don stated it, it would refer to whatever was in force if we now had a new document, and I like that better, so I really like the way that Don stated it personally.

DR. BERGFELD: Tom?

DR. SLAGA: I think it's fine in the conclusion.

DR. BERGFELD: Jim? Fine? Ron?

DR. SHANK: I'll go along with it.

DR. BERGFELD: Dr. Marks, will you please state the conclusion, and I gather it's been seconded.

DR. MARKS: Don, was that inhalation --

DR. BELSITO: Yes.

DR. MARKS: The question I would have again, Alan, we're doing a lot of this, do you consider this an editorial change in the conclusion so that we would have to go back out or can we just move forward with issuing a final amended safety assessment?

DR. ANDERSEN: It's editorial. You've simply recaptured the language of present practices of use and concentration which is additional clarifying words, so it's editorial. You're taking language that was already in the discussion three paragraphs above and putting it into the conclusion. It's an editorial change.

DR. BERGFELD: I gather we've seconded it. I'm hopeful. We're going to call for the vote now. All those in favor of this conclusion please indicate by raising your hands. Thank you. Unanimous.

We're moving on then to the TEA group and Dr. Belsito.

DR. BELSITO: In June we agreed on a final list of 31 ingredients for which the available data were sufficient to support safety and we issued a tentative amended report. Again,

the major comment from the council was the wording on the nitroso compounds. Otherwise we really didn't get much in the way of comments. So we'd go ahead and say that the 32 TEA and related TEA ingredients listed in the report are safe in the present practice of use and concentration described in the safety assessment when formulated to be nonirritating, the usual about the ingredients not in current use. As to the boilerplate for the formation of nitroso compounds, the expert panel cautions that the products containing this ingredient should be formulated to avoid the formation of nitroso compounds.

DR. MARKS: N-nitroso.

DR. BELSITO: Ni-nitroso compounds.

DR. MARKS: Correct. Second.

DR. BERGFELD: Are there any other comments or discussion? I'll call for the vote. All those in favor please indicate by raising your hands. Thank you. Unanimous.

Going on to the next blue final which is the crosslinked acrylates. Dr. Marks?

DR. MARKS: At the March meeting of this

year we were concerned about the possibility of residual benzene in these cosmetic ingredients, and with that in mind we have before us a draft final safety assessment on crosslinked alkyl acrylates with the conclusion that the ingredients listed below are safe in the present practices use and concentration described in this safety assessment except when they are polymerized in benzene and that the available data are insufficient to make a determination of safety for these ingredients when polymerized in benzene and then the caveat about if they were not in use. So I've move that this conclusion as stated in this memorandum be a final safety assessment.

DR. BELSITO: Second.

DR. BERGFELD: Second. Are there any comments or other discussion?

DR. BELSITO: Just to discuss why they're insufficient. I'll let Paul speak to it further, but the issue was whose safety assessment on benzene do you accept? We received several different ones, one with a borderline safe margin, the other with a margin that clearly

was unsafe. It was unclear to us how much benzene one might expect in a trade product and therefore how much one might expect to get into a finished product. I think that was why we felt this was insufficient. We just didn't have that data or that level of confidence in terms of doing risk analysis for a carcinogenic end point.

DR. BERGFELD: Paul?

DR. SNYDER: I'd second Don's comments. We felt that the uncertainty factors are very complex and there was not unanimous agreement on that which led our team to not have very confidence in the risk assessments and which one to pick or how to approach that.

DR. BERGFELD: Ron Shank and then Tom?

DR. SHANK: I would like to suggest changing in the discussion, replacing the last two sentences in the fourth paragraph, the sentences that begin if residual benzene were present and then all those numbers. Dr. Heldreth had made a very good statement which I think could replace that, and that statement was since it cannot be predicted with certainty what quantity of benzene would be volatilized or leached from

the cross-polymers during manufacture, formulation or product use, the panel determined that the data are insufficient are to conclude that cross-polymers polymerized in benzene are safe.

DR. BERGFELD: Thank you. Tom?

DR. SLAGA: I agree.

DR. BERGFELD: Ron Hill? Dan?

DR. LIEBLER: I'm fine with that.

DR. BERGFELD: Curt?

DR. KLAASSEN: Yes.

DR. BERGFELD: Don?

DR. BELSITO: Then we need to do what is the respiratory boilerplate for this one.

DR. BERGFELD: Do you have a suggestion?

DR. ANDERSEN: I think certainly as of now we are offering the blanket comfort that they're nonrespirable and that clearly needs to change.

DR. BELSITO: Right.

DR. ANDERSEN: We talked yesterday about what the full presentation of an argument on the safety of ingredients that are used in products that may be aerosolized. Jay expanded

a short while ago on one aspect of that which is sprays enter a breathing zone, don't enter a breathing zone and there are issues of how much gets in that are independent of what's the particle size. A small percentage of particles can get in but there is not that much material. I guess you parlay those two pieces of information into an argument that it's unlikely that inhalation is going to be a significant route of exposure for systemic toxicity so I think that gets captured.

Then it's a matter of looking at the individual chemicals to see what's the use concentration and that's another factor that deserves mentioning. If that's low, it's another factor in the right direction that there is no concern. In the document if there are oral systemic repeated dose toxicity data that are say it's simply clean and in particular no evidence of lung damage, that's a further factor. If there is reproductive and developmental tox data that are negative, that's another factor, genotox, right down through while they're not inhalation toxicity end points, they add to that picture of

what do we know about the particular ingredient.

Paul commented yesterday that over the long term those are all things that we've looked at every single time anyway. Now we would potentially be putting them into a way of capturing that for the reader now to see in the discussion. So instead of that one lonesome little sentence that says don't worry about it, it becomes a more expanded and I think robust discussion, but it must be tailored to each individual ingredient. I'd like to think that there's a boilerplate but I think it's a way of presenting the data and if they're there, we include it, if they're not, we don't include it.

DR. BERGFELD: What are you proposing for this ingredient?

DR. ANDERSEN: I think for this ingredient that single sentence that says don't worry about inhalation because particles won't be inhaled gets replaced with a paragraph that goes through those factors.

DR. BELSITO: The same with TA.

DR. ANDERSEN: I think so.

DR. BERGFELD: Is this going to come

back to us to look at or is this going to be automatically placed and this sent out? What is the procedure here?

DR. ANDERSEN: I think if the panel is comfortable with the pattern -- which one are we talking about?

DR. BERGFELD: We're talking about crosslinked.

DR. ANDERSEN: Alkyl acrylates. This is something that since I'd rather have this issued as a final, I think we can develop that discussion language and run it by the chair and the two team leaders and proceed.

DR. BERGFELD: Is that acceptable?

DR. MARKS: Alan, I would suggest since it's easy, the electrons, run it by all the panel members and not just the chair, just the team leaders.

DR. ANDERSEN: Can do.

DR. BERGFELD: We'll have an email signoff of the inhalation statement in the discussion. We've had a motion made and seconded to go forward with safe with some caveats here at the N-nitroso. I think that is in this one too.

Yes.

DR. HILL: So if the minutes could reflect that we're going to do that and then when we approve the minutes next time that will say we did it.

DR. BERGFELD: Yes. The minutes on these are being taken as we speak. Can we move the question now or is there further discussion? Move the question. All those in favor then of this conclusion please raise your hands. Unanimous.

We've come to 10 o'clock. Is there a need for a 10-minute break? Ten minutes then.

(Recess)

DR. BERGFELD: As you're all being seated, I want to thank you for the robust as Jim Marks likes to say discussion for the Blue Books. I'd like to also say that we've never had such a group of blue final reports that had to have so much discussion, so this has been an interesting morning. But we do have a number of reports advancing to the next level and we're going to move on and Dr. Belsito is going to present on the glucoside group.

DR. BELSITO: In June we issued an

insufficient data announcement for this group of 17 alkyl glucosides, one of which is decyl, and we wanted further classification on the actual use concentration of the active ingredient for decyl glucoside or sensitization data at the level of 11 percent that appeared to be the highest concentration of the active ingredient. Since then we've gotten clarification that in fact it wasn't 11 percent decyl glucoside, it was 11 percent of the commercial product which represents only 0.5 percent decyl glucoside. Based on that information and Carol's ongoing attempts when getting concentration of use to assure that its active ingredient, the only comment I would make is please put that on the tables that it is active ingredient.

DR. EISENMANN: To clarify, it was in the wrong product category. It's a rinse-off product and the 11 percent is still there but it's in a rinse-off.

DR. BELSITO: Right.

DR. EISENMANN: It was active, but it was in the wrong product category.

DR. BELSITO: Based on that, we found

that the alkyl glucosides were safe as used when formulated to being nonirritating as our conclusion. We need the usual respiratory issues inserted into the use section and the discussion section. It is a penetration enhancer and that would need to be in the discussion section as well.

DR. BERGFELD: That's a motion?

DR. BELSITO: That's a motion.

DR. MARKS: Second.

DR. BERGFELD: Jim, second. Is there any other discussion that's worthy of being discussed this morning here?

DR. SHANK: I would like to add the reference that Dr. Snyder has on stress and male reproductive toxicity in rabbits as it applies to this one as well.

DR. BERGFELD: Thank you for that reminder. Is there anything else? Seeing no one wanting to discuss this particular ingredient, I'll call for the question. All those in favor indicate by raising your hands. Unanimous.

Moving on to the next item, this is a green item, the MEA group, Dr. Marks?

DR. MARKS: This is the first time we've seen this split-out in which now we have the MEA group or what will be known, a/k/a, as the ethanolamine group. First when we looked at this we wanted to decide which actual add-on. This is an add-on. This would be an amended report so we're dealing with the rules that we set up for add-ons. If we go to Panel Book page 12, the add-ons from the 21 ingredients there we felt could be done easily, the inorganic acid salts and the organic acid salts. We had concerns about the proteins in the protein sales that we could easily deal with them, so we wanted those to be removed. And the organic substituted inorganic acid salts, we wanted the last one of those, the stearyl phosphate, the phosphate removed. Then all the ingredients in the alkyl substituted, ethanol removed so that we had a more limited list of ingredients that would be included.

If we go to page 25 of the CIR Panel Book there was the second part of this report with the ethanol amides and we decided that we would separate this report out, table a discussion on these and not include it in this particular report

since again we felt it would take more than just no-brainers to include those. So we would move then that the ingredients that I had mentioned on page 12, we would proceed forward, that they are safe as long as formulated to be nonirritating. That's a motion for a tentative amended safety assessment of the ethanol amines.

DR. BERGFELD: Dr. Belsito?

DR. BELSITO: I have a couple of issues. Believe it or not, we agree on the ingredients to be included in the ethanolamine report, but I would point out that previously we had said that these were safe for use only in rinse-off products. So now we have some leave-on uses and perhaps because we were doing this at the last report age 5:15, we took it upon ourselves to assume that what we're being asked us do we want to split the reports into MEA salts and MEA amides and we said, yes, two reports. The ethanolamine report ingredients as agreed upon just now. The ethanolamide report, we felt that all the ingredients listed there could be included in that report and that we would be going forward with two new reports, p.s., when you look at the

ethanolamine realize that the last go-around we had said rinse-offs only, so do we have data to support leave-ons? And p.s., when we did some of the ethanolamides before, we were setting concentration limits I think because of irritation. I think the approach we've now used is that you can predict irritation, so when formulated to be nonirritating. But we wanted both reports reopened under separate categories, the ingredients in the ethanolamine report as listed, the ingredients in the ethanolamide report as listed on page 14 or 25 of the Panel Book, and that's all we are prepared to do today and not issue any safety assessments.

DR. BERGFELD: Jim?

DR. MARKS: That's fine. So essentially table it with the suggestions we've made.

DR. BELSITO: This is a new report, not tabling it, just agreeing on the ingredients to go forward.

DR. BERGFELD: I don't think we have to table.

DR. MARKS: Okay.

DR. BERGFELD: So it is a consensus

agreement to separate this report into two group entities and to throw it back to CIF staff.

DR. BELSITO: Right.

DR. BERGFELD: Good. I see everyone shaking their heads so I'll assume that's a straw vote to move on so we will.

Let's go on then to the citric acid group with Dr. Belsito presenting.

DR. BELSITO: This is the first time we're looking at this group and we've gotten a lot of data on it, much of it unpublished data. It's pretty comprehensive. Citric acid as you know is a grass substance. We felt that we could go ahead with a safe as used in the current practices and concentration of use. We had a little bit of debate as to the issue of irritation and whether we should put the caveat when formulated not to be irritating. The data would suggest that as to the use concentrations at least listed in book there were not issues with irritation. It was Dan's feeling in particular with which I agreed that we don't want to keep throwing this in when it's unnecessary, that we go with a safe as used in the current practices of use and

concentration.

DR. BERGFELD: That's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: Jim?

DR. MARKS: We came to a different conclusion. We wanted to issue an insufficient data notice, and if you go to page 16, we agree that all the ingredients that are listed there, these 46 ingredients, be included in the report. However, for the ingredients in the inorganic salts and the alkyl mono di triesters, we wanted some inhalation data. Then I also felt that it would be worthwhile to see an HRIPT of citric acid up to 35 percent since I wasn't totally sanguine that it couldn't be a sensitizer. For those below in the glycol mono di- and triesters, we felt again insufficient data and that there was very little toxicologic data on these compounds so we wanted to see what the absorption is, and clearly if the absorption is minimal then it wouldn't pose a systemic risk, plus we wanted to see irritation and sensitization data on those. Then Ron Hill had a recommendation that the triesters, the glycol ones, two of those compounds, the

propylene and the tripropylene be categorized as alkyl-PEG.

DR. HILL: It's the other way around, that all of those in that category are alkyl-PEG except those two. The only true glycol esters are the propylene glycol citrate and tripropylene glycol citrate. Those are the two that are glycols. The others are alkyl-PEG and it's just the categorization in the report. That's all that was.

DR. MARKS: So you can see who the chemist is on our team.

DR. BERGFELD: Is there a comment by the Belsito team about the suggested chemical reorganization?

DR. LIEBLER: I don't object.

DR. BERGFELD: Don, regarding the request for insufficient?

DR. BELSITO: There has been no motion to remove any of the ingredients but simply to call instead of glycol mono di- and triesters, alkyl-PEG esters. Is that what you're calling that group?

DR. HILL: That's my recommendation

except for the two that are glycols.

DR. BELSITO: So then there would be four groups, alkyl-PEG esters and then glycol esters?

DR. HILL: You could say glycol mono and tri. There are no di. But, yes, four categories.

DR. BELSITO: I'm sorry, I wasn't following all the insufficient. I have 35 percent sensitization with HRIPT with citric acid.

DR. MARKS: That's correct. And then inhalation data for those inorganic sales, the alkyl mono di triesters. And then for the glycol and the alkyl-PEGs, absorption data and irritation and sensitization data for them.

DR. BELSITO: If you get data on citric acid at percent, why do you need data on the alkyl-PEG esters since we've already found alkyl-PEG esters to be okay? You'd only be concerned about the citric acid component wouldn't you? Do you really need sensitization and irritation on that if you have 35 percent citric acid?

DR. BERGFELD: Ron Hill, do you want to address that?

DR. HILL: We have a whole category here of compounds with no data of any kind. I think everything is based on the read-across for extrapolation is probably the better word in this case for laureth-7 citrate which is the only thing we have data on and I was uncomfortable with that. There's a lot more structural variegation I think than is captured, but I think I also said yesterday perhaps that maybe Dan would like to look at and comment or not.

DR. LIEBLER: Ron, you're saying that the data for laureth-7 citrate is the main thing we have to go on and that's inadequate for you?

DR. HILL: That's the only thing we to go on, I guess, is that we've just got --

DR. SHANK: Ames sensitization in the eye.

DR. HILL: Yes. We've got Ames human dermal and eye and no tox of any kind.

DR. BELSITO: You have the four-generation study in rats that were fed a diet of distearyl citrate.

DR. HILL: Diisostearyl, not laureth-7, not any of the alkyl-PEGs. That's the point.

DR. BERGFELD: Dan?

DR. HILL: And I would say that none of those are in use other than laureth-7, so they would remain insufficient and I guess if somebody wanted to use them at some point they would have to come in with some data. That's what I was thinking.

DR. BERGFELD: Ron Shank, do you have a comment?

DR. SHANK: You could just eliminate the PEG glycol citrates and handle it that way.

DR. LIEBLER: Ron Hill, are you concerned about the longer PEG citrates?

DR. HILL: I honestly doubt that there would be any problem.

DR. LIEBLER: Yes, but nevertheless I'm concerned. The reason I'm hesitating here is because I'm trying to get an idea what chemical space you want more data on and what the rationale would be.

DR. HILL: Let me remind myself of the exact structure of laureth.

DR. LIEBLER: So it's just the citrate mono ester? It's on Report page 18, Panel Book

33.

DR. HILL: I think the problem is that laureth-7 citrate was a monoester and that others were triesters.

DR. LIEBLER: So my feeling with the triesters, for the fundamental chemistry is similar, these are going to be bigger, more hydrophobic, less likely to penetrate, but other than that, I wouldn't anticipate any significant differences in metabolism or biological effects and that's probably why my alarm bells didn't go off about those.

DR. HILL: Here's a sort of operative question, Alan. When we have a conclusion that says in the current practices of use but in those particular ingredients we have no concentrations of us, no idea whether they would be administered in a way where we're only talking about dermal exposure or some other possible routes, how does that shake out if we essentially approve their safety, I don't know if that's the right word, but we affirm their safety along with other ingredients that are used in all of these other ways?

DR. ANDERSEN: It's a long-standing conundrum and the way in which the panel has handled it is to argue that these represent a category of ingredients almost always with the same functions. So when an ingredient is not currently used and the use is called safe in the present practices of use, that that ingredient that wasn't in use would only be used in the same categories of products so that if it was in leave-ons it would be used in leave-ons or if it was only in rinse-offs it would be used only in rinse-offs and at concentrations of use similar to the other ingredients in that group so that it adds some boundaries to the lack of information on use because there are no current uses. If we found that an ingredient that had not previously been used was being used in products, I'm trying to think of a good example, let's say the present practices of use was for rinse-offs and we found leave-on uses for an ingredient that hadn't been used. That would be a red flag and we'd raise that for the panel. If we found that the present practices of use and concentration were 10 percent in leave-ons and we found somebody using

it at 75 percent, that would be a red flag. That wouldn't be consistent with the rest of the ingredients in the group.

DR. LIEBLER: There are definitely ingredients in this group where there is at least incidental inhalation by sprays. We don't know what the parameters are for that. Probably suntan sprays, for example, the tri-C14-15 alkyl citrate of which we have no inhalation or any data of that nature. So if you look at the compounds that we do have data on, any long-term toxicology or inhalation data, they're a lot different than these alkyl-PEGs. I agree with that if it's strictly dermal exposure I wouldn't really anticipate any safety problems. They're really up to fairly high concentrations and I think these are probably useful ingredients but they're not being used right now, at least reported uses.

DR. BERGFELD: Ron Shank and then Paul?

DR. SHANK: My feeling is to take that group now called glycol mono-, di- and triesters and remove it from the report.

DR. BERGFELD: Paul?

DR. SNYDER: I wanted to make a note that

the introduction has a listing of eight of these ingredients including the parent compound or raw substances for direct food additives. Generally we don't include all of that data, but there would be a wealth of data that could be captured if we needed to. So I wasn't concerned about the absence of significant amounts of data and also the reference to the alpha hydroxy data group. Did you consider those in your consideration?

DR. HILL: Sure, but all the GRAS substances are salts. We don't have any information about the metabolism sufficient enough to know if that's even pertinent. I don't consider any of the citrates to be alpha hydroxy acids in the same way that those are categories. Biologically they're just a lot different.

DR. SNYDER: One is triethyl citrate so that there is one of those.

DR. HILL: Yes. You mean in terms of the GRAS substance? Sure, but those are short-chain esters. I wouldn't necessarily expect that the biohandling of those longer ones would be different. I doubt there are safety issues, but again we're making an affirmation on

essentially no science.

DR. SNYDER: Going back to your provision of insufficiency, you said on absorption but you didn't qualify dermal absorption or do you want a dermal study?

DR. HILL: I wanted to see dermal penetration.

DR. BELSITO: For which?

DR. MARKS: For the alkyl-PEG and glycol.

DR. HILL: Something in that category.

DR. MARKS: Yes. So that's a little bit different than what Ron just suggested. We have an insufficient in that group, we have an insufficient data notice is how would proceed and get inhalation data, the HRIPT and then for the ones down below, the absorption. Ron Shank now has suggested potentially one way to handle is just eliminate the glycol and alkyl-PEGs. I'm not sure that's necessary. I'll defer that to you.

DR. BELSITO: That was before we started discussing all the data needs I guess asking Ron why he wants to do that and asking Dan and Ron to comment. Ron Shank to state why and Ron Hill.

DR. SHANK: For the glycol mono-, di- and triesters, we have no toxicology data on any of those except laureth-7 citrate. On that compound we have one Ames test, the sensitization test, and an eye-irritation test. There's nothing on any of the others, most of which are PEGs. Most of them are not used. The laureth-7 citrate has one single use at no reported concentration in a rinse-off. The tripropylene glycol citrate has one reported use in a leave-on at no reported concentration. We don't have very much data and I would not hold up all of the rest of these compounds just because of those. None of the compounds in that last category are GRAS agents so we can't reply on GRAS data. So I think it makes it much simpler to remove those from this document.

DR. BERGFELD: Is there agreement to remove those from this document?

DR. BELSITO: I'd like to hear from Dan.

DR. LIEBLER: I concur.

DR. BERGFELD: The straw vote says they're removed. Then we are left with what request, Jim?

DR. MARKS: Inhalation data and HRIPT for citric acid. When you look at it, citric acid has 6,800 uses so it's got to exist.

DR. BELSITO: Inhalation data for citric acid?

DR. MARKS: No, for something up here.

DR. SNYDER: Any inorganic salt.

DR. MARKS: Right.

DR. BERGFELD: So the proposal and motion right now is, to clarify?

DR. MARKS: Don had the motion. You've been modifying it, so can I have your motion? I guess Don has to.

DR. BELSITO: I'll withdraw mine and we'll listen to Jim's for a moment.

DR. MARKS: An insufficient data notice for those two needs.

DR. BELSITO: What are you concerned about in terms of the inhalation toxicity?

DR. MARKS: Rons?

DR. BELSITO: If we get rid of the alkyl-PEG ethers and the glycol, what inhalation toxicity are you worried about from citric acid or citric acid esters?

DR. SHANK: Citric acid and some of it is in organic salts and are used in sprays and powders.

DR. BELSITO: I understand that, but we've been dealing with reports all morning where we had no inhalation toxicity.

DR. SHANK: We haven't asked for it yet. This is a new report. We haven't asked for it yet.

DR. BELSITO: And if we don't get it?

DR. SHANK: Then we'll deal with that with some kind of consideration of respiration.

DR. BELSITO: I guess my point is that if we really want industry to respond to data that we need to make safety reports, we should ask for data that we really need. If you have some respiratory concern then let's ask for it and make sure we get it and if we don't get it then it's not going to be safe. If we have data to finesse the lack of respiratory inhalation toxicity, then I don't think we should be asking for it because then industry is going to say they come up with these wish lists and what do they really need from this wish list and what don't they need? And these studies are not inexpensive. So if we really need,

if you think we really need it, let's ask for it and then therefore it would be insufficient if we don't get it. If we can finesse the lack of respiratory data, then I would prefer that we not ask for it so that industry understands that when we ask for things, we want them and if we don't get them it's done.

DR. BERGFELD: Go ahead, Alan.

DR. ANDERSEN: I think that positioning of the panel is a very good one. It's incontrovertible though that were there inhalation tox data available, we'd love to have them. So I think we could ask for those data in using that if available.

DR. BELSITO: Okay.

DR. ANDERSEN: We would like available inhalation tox data. We don't want you to go out and do any new studies.

DR. BERGFELD: Jay?

DR. ANSELL: Yes, I would agree with Alan's statement. It's very concerning that looking at the end- use products we would not do an inhalation study for a variety of reasons, but most specifically for materials which are

nonrespirable. So what we'd up having to do is to artificially manipulate the material to induce exposure and then have a report which might not address the concern. Ultimately we've seen a lot of these studies today as they do them by installation because the inhalation exposures are so complicated to control. So it's certainly at the green stage. I think what Alan said is less expressive of concern and an interest but not establish some obligation which might provide data which would be uninterpretable in terms of its use as a cosmetic ingredient.

DR. BERGFELD: As I see what is being requested for sure is the HRIPT, the repeat insult patch test, for citric acid at 35 percent.

DR. BELSITO: And if available, inhalation data.

DR. BERGFELD: Inhalation, right, but specifically we want the HRIPT. Is that agreeable?

DR. BELSITO: That's fine.

DR. BERGFELD: We've had a motion made and withdrawn, another motion and a second. Is there any further discussion? Ron Hill?

DR. HILL: Looking at the citric acid salts, my biggest concern would be with copper and possibly manganese where the water solubility would be extremely low, so maybe there would be some issue with that, otherwise, not.

DR. BERGFELD: Thank you. I'll call for the question then. All those in favor of this conclusion indicate by raising your hands. Thank you. It's going out as insufficient data.

DR. ANDERSEN: Before we move on I want to thank Monice. If you look down the agenda, she's been sitting here for quite some time. We've got quite a few M.F.s here in getting these things moved through the system. Nicely done.

MS. FIUME: Thank you.

DR. BERGFELD: I agree. Thank you. Moving on, Dr. Marks, sulfosuccinates.

DR. MARKS: This is the first time we've seen this draft report on the sulfosuccinates and I'll refer you to Panel Book page 7 and that list of the ingredients that were recommended for this review and we concurred with all of those ingredients so we did not change that list at all, but we did conclude that we would recommend or

move that an insufficient data announcement be issued. The needs were, one, dermal absorption and obviously if there is absorption, reproductive and developmental toxicity. Two, mammalian genotoxicity. Three, we were concerned about what impact trisodium sulfosuccinate would have on the citric acid cycle which is a critical cycle. And then, four, we're back to inhalation again, that controversial topic that we've dealt with today, so that we wanted to see inhalation data also.

DR. BERGFELD: Are you asking on a specific ingredient or all of the ingredients?

DR. MARKS: Any inhalation data.

DR. BERGFELD: Any inhalation.

DR. MARKS: But again I guess one could use the caveat that we just talked about that if we didn't have the inhalation data we'd use the boilerplate. So I don't know that inhalation data would prevent us from moving forward, but if it exists we would like to see it.

DR. BERGFELD: If available?

DR. MARKS: If available, yes.

DR. BERGFELD: Does the Belsito team

have a response?

DR. BELSITO: We didn't come to anywhere near the same conclusion. First of all, it was Dan's feeling that trisodium sulfosuccinate be removed from this group, and I'll let him comment on that before going any further.

DR. LIEBLER: In terms of its physical properties, it's quite different from all of the rest of them and I felt that it really didn't belong in this group.

DR. BERGFELD: Ron Hill, do you want to comment? Keep or get rid of?

DR. HILL: At a level I don't care either way. I assumed that it was in here primarily as a possible metabolite of any of the others words. In other words, that it's not necessarily disodium, but the sulfosuccinate moiety was there primarily as a metabolite in case it's generated from any of the rest.

DR. LIEBLER: That wouldn't be about being an ingredient then.

DR. HILL: Correct.

DR. LIEBLER: It's something we could consider if it were a metabolite, but the issue

would be whether it's an ingredient and whether we should consider it in this group of ingredients.

DR. HILL: As an ingredient I would concur that it ought to be removed.

DR. BERGFELD: So it's removed. Next?

DR. BELSITO: Then we were asked by the council to consider adding disodium disodium lauryl sulfosuccinate which we declined to add.

DR. MARKS: We did too. That's why it's not on the list.

DR. BELSITO: Then we felt with the deletion of trisodium sulfosuccinate, the decision not to add disodium lauryl sulfosuccinate, that these were safe as used in present practices and concentration of use when formulated to be nonirritating.

DR. BERGFELD: Do you have a comment, Jim?

DR. MARKS: I think we have to comment about the concern about reproductive and developmental toxicity and mammalian genotoxicity so I'll defer to my team members, Tom, about the mammalian geno and, Ron Shank, about the

reproductive and developmental.

DR. SLAGA: We have bacterial mutagenesis, but there is really nothing related to mammalian, and to be consistent with the past it would nice to have both.

DR. BERGFELD: Do you have a comment, Curt?

DR. KLAASSEN: I doubt if it will be mutagenic and that's why I didn't ask if it was necessary, but you are right, we often for many things ask for both the Ames test as well as the mammalian.

DR. BERGFELD: Do you concur then? Ron Shank?

DR. SHANK: Apparently these compounds have bactericidal activity, so an Ames assay is inappropriate for doing a mutagenicity assay, and we don't have any dermal absorption/penetration data.

DR. BERGFELD: Paul?

DR. SNYDER: I'd like to clarify that we would like dermal absorption data and if absorbed then we may want a reproductive study. The other issue was related to on page 78 of the

document in the MSDS sheet, there appears to be some inhalation data, at least they describe inhalation effects, with the Lubrizol product so we've asked to see if we can get additional data from that supplier to glean some information regarding inhalation effects.

DR. BERGFELD: Are there any other comments? Ron Hill?

DR. HILL: I think in terms of the dermal penetration or dermal absorption that the only chronic tox studies that we could rely on and we only have it for one ingredient is oral. And I'll repeat my assertion that the problem with oral toxicology studies is that if you have a situation where we're relying on rodent toxicology and we don't do something to at least characterize whether we've got essentially 100-percent first pass loss which is possible with rodents, that everything gets kicked out in -- and we get significant absorption and unless we have some indication that there is absorption that oral toxicology data may not reflect what might occur if you have dermal penetration and some other means of systemic availability based on that. The

thing is that oral tox is not necessarily indicative.

DR. BERGFELD: Paul?

DR. SNYDER: The acute oral studies would suggest that this is a very low toxicant. It's very, very high LD50. So I wouldn't predict that even with dermal absorption you're going to see much.

DR. HILL: But acute isn't chronic.

DR. BERGFELD: Don, do you want to respond to your position versus the Marks's team's position?

DR. BELSITO: I think what's being brought out is not a cutaneous issue, it's genotox and its potential systemic tox issue so I would defer to Paul, Dan and Curt.

DR. BERGFELD: With deferring, I did hear that Curt agreed. Paul and Dan, do you agree to go for the genotox data?

DR. SNYDER: Would you restate, please?

DR. MARKS: First of all again I would say issuing an insufficient data announcement is not a big issue in my mind as an alternative step as we're early on with this. But there are three

things, dermal absorption, two, mammalian genotox and, three, inhalation if available, and I underline if. So it's getting more data and we're early on.

DR. BELSITO: The inhalation should be available.

DR. MARKS: Right.

DR. BELSITO: As Paul said, there's an MSDS from Lubrizol that indicates that there should be some data there some place.

DR. BERGFELD: As to dermal absorption, if absorbed then we have the others. That's understood. So it looks like we have agreement on the Belsito team with the Marks's motion. Is that correct?

DR. BELSITO: That's fine.

DR. BERGFELD: Is anyone going to second it?

DR. KLAASSEN: I'll second it.

DR. BERGFELD: Thank you. Is there any further discussion? Seeing none, I'm going to call for the vote as going out as insufficient. Unanimous. Thank you.

Then we're moving on to the next

ingredient, the glyceryl ethers. Dr. Belsito?

DR. BELSITO: This is green under ethylhexylglycerin. This is the first time that we're seeing this report. We've got quite a bit of information on it. Our team looked at all of this and we felt that we could come to the conclusion that these were safe as used in the current concentrations and practices of us.

DR. BERGFELD: That's a motion?

DR. BELSITO: That's a motion.

DR. MARKS: Second.

DR. BERGFELD: And that's a second.

DR. MARKS: There will be discussion, let me tell you.

DR. BERGFELD: How about some discussion?

DR. MARKS: Ron Hill, do you want to present your position, because it wasn't unanimous by our team.

DR. HILL: Again we've got a situation where there is essentially no chronic tox data for any of these except an oral study with ethylhexylglycerin. There is no real alert with the ethylhexylglycerin data, but then there's a

big difference in structure. What we've really got if you look at this is a reduced monoglyceride, and what we do have on the chimyl alcohol and the batyl alcohol suggests incorporation into phospholipids which in turn suggest that there could be biological effects that haven't been captured because we don't have anything chronic at all other than the oral chronic study with ethylhexylglycerin. With the acknowledgement that that looks pretty clean because only at the very highest doses do we see anything and that seems to be mainly fatty accumulation types of effects, it's an oral study. So because there are glycerides and there is a lot of data in here to suggest that there is extensive intestinal metabolism prior to absorption, that means that the oral tox data in my mind are invalidated in terms of any type of chronic tox.

DR. BERGFELD: Paul, do you want to respond?

DR. SNYDER: We have data on percutaneous absorption that is very, very low.

DR. HILL: No. For ethylhexylglycerol it's high. It's not low. It's high. Am I

mistaking something here?

DR. SNYDER: At .025 percent.

DR. HILL: How much?

DR. SNYDER: On page 5, .025 percent.

DR. HILL: Wait a minute. I'm looking at 44 percent, 47 percent and 55 percent on the top of page 6 which is Panel Book 12, and that's human skin.

DR. SNYDER: I stand corrected. I was looking at the rabbit study in which it was only .025 percent.

DR. HILL: The rabbit one was done with which compound? Also ethylhexyl?

DR. SNYDER: Correct.

DR. BERGFELD: Dan?

DR. LIEBLER: Why would it be more in human than in rabbit skin?

DR. SHANK: The human one is in vitro.

DR. LIEBLER: Yes, I know.

DR. HILL: And it depends highly on how that's done.

DR. LIEBLER: So the rabbit skin, correct me somebody if I'm wrong, it's easier to penetrate rabbit skin than human skin?

DR. SHANK: Easier but not like amounts.

DR. LIEBLER: Yes. I'm wondering if that human in vitro data really represents what might be expected for penetration. That rang an alarm bell for me.

DR. HILL: The only concern I have, and I have to look at the applied dose here really carefully, is if we know it's being incorporated into phospholipids, it could be that it's getting into the skin and actually incorporated there and therefore not getting through the skin so that if that in vitro study was done with not viable skin, and I'm assuming that it was viable skin, we should know that for sure. I didn't notice this until yesterday sufficiently to have looked up reference 21 so that that would probably be the key piece of data. That's unpublished data from the Personal Care Products Council. Is there anybody here familiar with exactly how that was generated as to what the nature of the skin was?

DR. BERGFELD: Jay? Carol?

DR. HILL: I'm trying to find it now.

DR. BERGFELD: Can you summarize what Carol said, please, Ron Hill?

DR. BELSITO: It should be in the back of the book if it's unpublished data.

DR. BERGFELD: Thank you.

DR. HILL: I've looked through the back of the book and I have a lot of highlights here, and I thought I came to the same conclusion as I did when I made the notation in the main report which was, yes, this stuff could be absorbed so I can't count for what's going on with the rabbit data other than perhaps the applied dose is being captured in skin and isn't getting through skin which is fine. That means we're going to minimize any systemic toxicity and then we have to be concerned about what's going on on the skin. Could we promote the growth of nascent melanomas, for example?

DR. MARKS: For me and the Belsito team, our other team members took this and still decided that we felt it was safe as you moved, safe as used. The reason I brought this up is, one, to allow Ron Hill to express his concerns and see whether this brought alerts for your team.

DR. LIEBLER: No, I don't think so. I think that their data on incorporation of label

into phospholipids in one case, it's suggested that it's been due to metabolism to palminic acid which -- incorporated in the other. It looks like some of the label might be in the head group here. I think the question of whether it's incorporated into phospholipids is one thing and that may be indeed true, but I think making the leap to significant adverse effects based on that is too much of a leap for me. We've had a similar discussion in previous meetings and I don't go that far. I don't think that the available information will allow us to make that jump.

DR. BERGFELD: Paul or Curt, do you have any other comment before Don comments? Don? No?

DR. BELSITO: I have no comment.

DR. BERGFELD: Is there any other comment, Ron, before we call the question or Jim?

DR. MARKS: Yes. And Wilbur, you heard my comments yesterday. On page 16 I thought the title for this section, "Skin Depigmentation," should be changed to "Skin Tanning."

DR. BELSITO: Page 16, Panel Book or page 16 report?

DR. MARKS: Panel Book. You'll see that

it's in bold at the bottom of the page. With skin depigmentation we would get into the issues now of are you going to depigment the skin and such.

DR. BELSITO: It's a sunscreen.

DR. MARKS: Yes. Essentially either that title should be removed or changed to skin tanning. It's pretty interesting the effect it has, but I'm not worried that it's a toxic effect and you could apply this and get depigmentation of the skin. That's editorial.

DR. BERGFELD: Wilbur?

MR. JOHNSON: Do you have any specific statements that you would like to be included in the discussion?

DR. MARKS: Concerning the tanning?

MR. JOHNSON: Anything.

DR. MARKS: I'll defer to the panel members.

DR. BERGFELD: Ron Shank?

DR. SHANK: I think the discussion should include the absorption through skin and we're using the rabbit data. We have oral reproduction and developmental toxicity data which are negative. We have mutagenicity data

which are negative so that we don't require carcinogenicity data. I think that should be in the discussion.

DR. BERGFELD: Is there anything else to be added?

DR. BELSITO: Sensitization and irritation data is fine. We're not concerned about those issues. It is a penetration enhancer, yes.

DR. HILL: If we're going forward with safe, at least in the data section of the book which was part of the unpublished data, their paper makes reference to these alkoxy lipids are widely distributed in human and animal tissue. Differentiation is made between neutral and ionic alkoxy lipids. What I made a note of here is could we capture a summary about that? In other words, there's a statement but there are no references here, but given the fact that that information is stated, I'm guessing there are references and if we could capture what's known about the biology of those alkoxy lipids at least briefly.

DR. ANDERSEN: What page is it, Ron?

DR. HILL: It's not given in the Panel

Book page, but it's the third page of the data section. It's the report about Sc 50 Sensiva. Right under origin it says these alkoxy lipids, because if we get the right information, that certainly may increase my confidence that we've got no problem here.

DR. BERGFELD: Thank you. Is there any other discussion?

DR. BELSITO: Have you heard, Wilbur, the penetration enhancer in the discussion?

MR. JOHNSON: Yes.

DR. BERGFELD: Are there any other additions to the discussion? Seeing none, I call for the question then. Those who are in favor of the conclusion please indicate by raising your hands. Did you vote, Dr. Hill?

DR. HILL: I'm going to abstain in this case.

DR. BERGFELD: Thank you. One abstaining. Moving on to the next ingredient with Dr. Marks, gluteral.

DR. MARKS: I move that we close this report.

DR. BELSITO: Second.

DR. BERGFELD: Is there any discussion?
I call for the question. All those in favor?
Closed. Safe. The next ingredient, Dr. Belsito?

DR. MARKS: It's a re-review, so the two
things that are really important in the
discussion are that the small amount of gluteral
which is present is an impurity in leave-ons and
is not a safety hazard and that we do the
inhalation business.

DR. BERGFELD: Thank you.

DR. MARKS: I couldn't leave it just
with two words. That was a surprise. I thought
we would have a disagreement on that one.

DR. BERGFELD: Dr. Belsito, the anisole
ingredient?

DR. BELSITO: This is the first time
that we're looking at this report. It is a hair
dye so subject to all the usual issues with hair
dyes that as long as it's labeled to be tested,
the sensitization and irritation issues aren't
there. Having looked at this, safe as used when
formulated to avoid the formation of N-nitroso
compounds.

DR. BERGFELD: Motion?

DR. MARKS: Second.

DR. BERGFELD: Second. Is there any discussion? I'll call for the vote. All those in favor? Ron's got his hand up early. Let's go for it. Are there any discussant points that have to go in or comments that need to be made or editorials? Seeing none, we'll move on.

DR. MARKS: Obviously hair epidemiology. I'm not sure that Don mentioned that. The other thing that came in our team meeting which I think we need to address are reactive products so that in the discussion we should talk about and there was a reference to a paper that already exists on that.

DR. HILL: What I was bothered by was that if you look at the structure of the dye substance that's proposed to be formed, there doesn't seem in this case to be anything that would prevent dermal absorption. In a lot of cases we'll see the dyes and there will be more than charge or charge groups. This is small molecular weight, nothing that's sufficiently basic or acidic to suggest that it would be highly charged and I can't see any reason why it wouldn't

get into the scalp. Julie Skare was with us yesterday and she made comment that it was formed in a small amount and if only a small percentage gets converted to that dye, that means the rest of it is available for absorption so then I had a question about the toxicology of the parent substance. We got into a sort of circular argument about, yes, it's supplied as a hair dye but it's being reacted and heavily converted to a dye substance and I said the dye could get in but we have no toxicology on that dye substance. Then the statement was made only a small percentage of it gets converted to the dye substance and that would mean we have a high amount of the unreacted parent substance and we don't have I think much in the way of toxicology on that so that I was troubled by this.

I went back and looked at the presentation that I missed last meeting that included some chemistry about the dyes, but the upshot of the discussion was that at a future meeting we would have a more in-depth discussion of these kinds of compounds because epidemiology is epidemiology. It has its limitations and I was

going back through her presentation and there was a lot about what those limitations were there. I think we have a long way to go before we can use epidemiology to draw real firm conclusions.

DR. ANDERSEN: I think that happy juxtaposition of this going out as a tentative safety assessment, comments, come back in December. I've asked Julie to come back in December to really focus on the chemistry part that we short-changed at the June meeting and we'll put all of these issues on the table as this one's being readied to go final in December.

DR. BERGFELD: It's timely to do that. We've said we'd do that at least every 2 years or more often especially when the question arises. Thank you very much for bringing that to our attention again. We're going to move on to the last item that falls under reports advancing to the next level with Dr. Marks presenting on sodium lauriminodipropionate.

DR. MARKS: This is the eye compounds, salts and acids, and as you'll recall, in 1997 we had an insufficient conclusion. Then at the June meeting we reopened this safety assessment and

particularly looked at the amino, the dipropionate and added the acids and salts. We felt that it's safe. We split out the amino, the A compound, because it's a different chemical, and we were prepared to move that we issue a tentative amended safety report with a safe conclusion, but then we don't have the concentration of uses table so the question is do we issue a tentative amended without that? Could there be a concentration or use that might affect our conclusion? So we ended up with tabling to get that last piece of data. I guess it's how confident do we feel that we could move forward without it.

DR. BERGFELD: Before a motion to table, can I give a Belsito response?

DR. BELSITO: We went through the same iterations and whether to go with insufficient for concentration of use in dermal leave-ons since it's a pink and we fully expect that Carol would be able to get it for us and then we would be able to go with a final in December and boost our numbers or table it in which case we wouldn't be able to get a final because we'd have to go out

again. We also wanted some information on the impurities on the dipropionate. Is that correct or not?

DR. BERGFELD: Dan? Paul? Curt? Yes? No?

DR. SNYDER: That was the 1997 report and part of the insufficient data announcement was based on impurities.

DR. BELSITO: For the amino. Someone asked for impurities on laurimino.

DR. LIEBLER: Laurimino, the impurity being the lauramino.

DR. BELSITO: Actually because it said that one of the manufacturers had lauramino in their trade-name product. Do you remember this discussion?

DR. SNYDER: We have a memo from John Bailey that says that it does not contain sodium lauriminodipropionate.

DR. BELSITO: That's right. On page 14 of the Panel Book under impurities under sodium laurimino, it says the commercial product that is approximately 30-percent solids contains about 25 percent sodium laurimino and 5 percent amino,

we're being told that would not be considered in this report so that should be deleted from the report. We were toying with either tabling for concentration of use data. I felt why not go insufficient and move it head, we'll get it and we'll be done with it, but I could go either way.

DR. MARKS: Procedurally, Alan, can you go from an insufficient with a final without putting a tentative out?

DR. BERGFELD: A tentative final.

DR. ANDERSEN: If this is issued as a tentative safety assessment with an insufficient data finding and the only insufficiency is the concentrations of use, when you get those concentrations of use and arguably you'll have them in December, you can issue it as a final. Yes, it is more expeditious if we're looking to knock it out this year to issue it as insufficient data without prejudice because it's not like the council really had time to get those data in. They just didn't.

DR. ANSELL: Yes, we have to express our concern. There was never any expectation that these data could be available for this report.

The idea that the report got advanced absent the data which we knew would not be available seems to me to be somewhat inconsistent with procedures and fair process. Otherwise we might as well just go tentative final on everything and that will accelerate things enormously.

DR. BERGFELD: A little sarcastic there.

DR. MARKS: Jay, you would feel that it would be better to table it?

DR. ANSELL: We would suggest that reports in this state do not come onto the agenda at all, that the panel should not have seen this at this time and it puts us in a very awkward position to have advanced reports without any expectation that the data could have been complete.

DR. BERGFELD: What is your suggestion? I'm not quite sure where your suggestion is going.

DR. ANSELL: We suggest tabling it.

DR. BERGFELD: Thank you.

DR. BELSITO: I appreciate where you're coming from and I fully agree particularly at a meeting like this where we were inundated with

information. However, in a way you should be thrilled that the only thing we're asking for is something that you should simply be able to provide us and that is concentration of use data. I would assume that since the next meeting is 2-1/2 months away that you could get it in that timeframe.

DR. EISENMANN: These ingredients went out in the July survey, yes, but normally it takes about 4 months.

DR. BELSITO: I understand. My only question is I don't want to embarrass you because I fully agree and understand Jay's point. However, if you think that you can reasonably get the one little piece of information we're asking for by the December meeting -- in the future we understand that it should have never come to the table, but it did, and the only data we need are concentration of use. It went out in July and it usually takes 4 months and that's November. We don't meet until December. Why don't we go insufficient, hopefully we'll have it in December and we'll be done with the whole thing?

DR. BERGFELD: Alan?

DR. ANDERSEN: On the matter of principle I can assure you that we've gotten the message. The practical matter here might be to take advantage of the error.

DR. SNYDER: This is just a one-of circumstance, that it in no way sets a precedent that we'll proceed this way.

DR. BERGFELD: Jay?

DR. ANDERSEN: We of course serve at your pleasure.

DR. BERGFELD: Thank you.

DR. MARKS: I withdraw my motion to table it and, Don, I concur with your motion to move on as insufficient and in the minutes make it clear that this is not precedent setting as Dr. Snyder has suggested.

DR. BERGFELD: But done for efficiency. Do you want to second that?

DR. BELSITO: Second.

DR. BERGFELD: Is there any further discussion? Seeing none, I call for the vote. Those in favor please raise your hands. Thank you. Unanimous. Moving on to the re-reviews, Dr. Belsito?

DR. BELSITO: This is 4-chlororesorcinol. It was reviewed in 1996. It's a hair dye. Its uses have jumped tremendously from 33 in 1996 to 210 currently. The maximum concentration range though has remained the same. We're told that the SECS has looked at it and has no concerns in concentrations up to 2.5 percent which is the concentration; we're told it's now used up to 2 percent and there was no additional data here that for a hair dye caused any significant concerns and we elected not to reopen it.

DR. MARKS: I second that motion.

DR. BERGFELD: Is there any other discussion? Seeing none, I call for the question. All those in favor raise your hands. Thank you. Unanimous. We have really done a lot of work here. Thank you so much everyone. I'd like to know if we have to discuss the aerosol precedent. We've been discussing it all morning.

DR. ANDERSEN: I don't think any further discussion is needed. We have a couple of homework assignments clearly related to a couple of these documents and I think that will advance

the discussion. I have no doubt that we'll be revisiting this at future meetings, but for now I think let's not waste our time.

DR. BERGFELD: Then we'll move on to the priority list. Bart?

DR. HELDRETH: This is hopefully a final chance for the panel to look at the priority list for 2012. Primarily what's posed for you is the list that's on CIR Panel Book page 16. There are additional pages that are provided for informational purposes only, so what's before you to approve is the list on page 16.

DR. BERGFELD: I'd like to ask the panel members if you've looked at this and you have comments to make about any of the ingredients. Jim?

DR. MARKS: Yes and no.

DR. BERGFELD: Yes and no? Interesting.

DR. MARKS: Yes, we looked at it and, no, we don't have any comments.

DR. BERGFELD: Don?

DR. BELSITO: Our major comments were directed to the issues of the botanicals and that when they do come to the plate it's really

critical that we go to -- or whatever we need to do to get the ingredients, the specific composition of these different botanical groups, issues as to are we going to do the amino acids all as one big amino acid group? Have we decided that? We had knocked that around at one point.

DR. ANDERSEN: The answer is, yes, we are, it's underway and we'll form the foundation for the ones that are on the list that will be undertaken after that next year.

DR. BERGFELD: Jay?

DR. ANSELL: We had a comment in terms of the footnote and the three materials which were placed on the priority list with a footnote suggesting they're not actually going to be worked on. We'd like to have Alan reaffirm that the three items on hold are in fact not on hold, they've just been prioritized and will be on the 2012 priority list.

DR. ANDERSEN: I think as a matter of practicality it was flagged for panel discussion, but now that we have a strategy for moving forward, those asterisks disappear so that they are not on hold any longer.

DR. ANSELL: We would not like to see materials on the 2012 priority in which there was no expectation that they would be worked on. We also looked at the hydrolyzed protein group and will make further comments later, but we do believe that wheat should be pulled out from that.

DR. BERGFELD: I'm sorry. You're going to want that withdrawn?

DR. ANSELL: No. We think that it should not be grouped with soy and silk. There are a lot of materials in there, but that will be a recommendation.

DR. BERGFELD: We'll need a motion to approve the priority list.

DR. BELSITO: I'm not clear since we're going to make a motion to approve the priority list as to why you want wheat pulled out of soy and silk. Are you concerned about gluten?

DR. ANSELL: Yes, we think it may present some issues, but we will submit it to the CSSC and come back with a more precise discussion in terms of the grouping.

DR. BELSITO: So at this point as to the priority list, we're going with hydrolyzed

proteins and then the council will come back and perhaps suggest we yank wheat as an ingredient in that? Is that what we're doing?

DR. ANSELL: The priority list talks about hydrolyzed proteins and pulls out soy and silk specifically. But if you look at the next page and the further discussion, you'll see that the group is actually very much larger than those two ingredients, so we would like to reserve the right to comment on the appropriateness.

DR. ANDERSEN: I think that the procedures are exactly designed to give the industry that option and that information is being sought and I think that input would be really excellent and appreciated so that there is no question. By doing this early definition, one of the goals has always been to let everybody know what's going to be worked on and if you got input, it gives you the opportunity to get in early and often and that's exactly what we want to hear.

DR. BERGFELD: Ron Hill?

DR. HILL: I made the comment yesterday that I thought every protein ought to be looked at by and large individually because as soon as

you hydrolyze, unless we're hydrolyzing all the way down to amino acids then we've got distinct peptide mixtures that are present in each and every protein that will be different and if you ungroup them you don't face that problem.

DR. BERGFELD: This is large task, but our task right now is to approve this list. May I have a motion?

DR. BELSITO: So moved. Second. All those in favor indicate by raising your hands. Thank you. Unanimously approved and we'll wait for discussion from the scientific support group. Rachel?

MS. WEINTRAUB: In one of the groups that I participated in, I don't remember which one because I went back and forth, there was a brief discussion but I thought it was useful to talk a little bit more about the criteria in this document in the future that is looked at to make these decisions. All that's included is similar criteria to 2011, primarily frequency-of-use data. But if there are any other factors and I believe there are, including that in this type of document in the future would be useful.

DR. BERGFELD: Thank you. Many of us who have been on the panel a long time understand that, but I agree it should be in the document. We have done away with all of the very biologically active ingredients and we're now into frequency of use and volume of use. We'll make that correction. We've come to the last item and that is the HC red No. 1 and Dr. Andersen is supposed to lead this conversation.

DR. ANDERSEN: We talked about it at each team yesterday in terms of the fundamentals of presenting re- review summaries where the decision is to not reopen. There were a couple of pieces of input that I think are good in terms of ongoing improvement. It must help the reader for example as Paul Snyder suggested if in the first sentence we identify the year of publication of the original report. It just gives it some more context and it's in the reference, and if you go to the reference you'll see it, but it sure doesn't hurt to include it. As we go along I think we tweak these to better communicate to the reader and any and all editorial changes that we have from the panel will be used. I think we

also since we have updated the epidemiology boilerplate and I'm comfortable now that what's on the website is updated, we can now refer the reader to that as well. I think it's good to look at these and to constantly reaffirm that we're communicating adequately.

DR. BERGFELD: We've come to the end of a very long morning and a very arduous amount of work that everyone has done. I again want to thank not only the panel members but the support staff who have made this possible. I think that I'd like to also thank you for the wonderful discussion which will be recorded in the minutes because it's been very enlightening and probing. At this time I wish to adjourn and look forward to seeing you on December 12.

(Whereupon, at 11:19 a.m., the
PROCEEDINGS were adjourned.)

* * * * *

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.

Notary Public, in and for the District of Columbia

My Commission Expires: January 14, 2013