118th COSMETIC INGREDIENT REVIEW EXPERT PANEL
MEETING

Washington, D.C.
Wednesday, March 4, 2011
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Voting Members:

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Other Attendees:

GEORGE HAZELTON
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DR. BERGFELD: I want to welcome everyone again to the 118th CIR meeting and our 35th year. And as Alan told us yesterday, 2,200 ingredients thus far and adding another 351 today to that large group.

I want to again compliment the team, the CIR team and staff, for the evolution of a wonderful group of documents. They keep getting better and better and we are very appreciative of that.

The meetings yesterday were very informative, and we are pleased to have had so many guests participate with us. So I wanted to thank you all as well. It's certainly with all of the participation makes the outcome much improved. So, thank you.

So, we're going to approve the minutes. May I have a motion to approve the minutes?

DR. BELSITO: So moved.

DR. BERGFELD: Second?
DR. ANDERSEN: Second.

DR. BERGFELD: Second. All those in
favor indicate by raising your hands? Thank you.
The minutes are approved. We're going to move on
to Alan's report.

DR. ANDERSEN: Okay, thank you. Good
morning, all. I want to just give you an update
briefly on some things that are happening at CIR.
First, a very positive step that is being taken is
that the council has approved the addition of
another technical writer to the CIR staff. So, if
you thought you were getting lots of material for
these meetings, we're going to have added capacity
to put things in front of you to try and continue
the effort to increasing the throughput.

Also wanted to highlight something that
you as a panel don't see, the public doesn't see
it. But it has become an integral part of our
efforts to produce safety assessments. This is
what we call a CIR pre-production pack. And it's
even now gotten its own shorthand of pre-pro
pack. I like to think of it by the other three
In this document, which happens to be the one for cross-linked acrylates, which you looked at, the writers' efforts are essentially supported by a chemistry look. All of the structures that are potentially going to be included in the report have already been captured and credentialed. The information that exists -- the mass of information in the International Cosmetic Ingredient Dictionary and Handbook -- has already been pulled and is here for the writer to work with, yadda, yadda, yadda.

It's just, at this stage we had not yet incorporated the toxicology overview, but that is indeed the next step. So that an entire outline of what's relevant from a first-blush viewpoint for this particular group of chemicals has already been captured, and the technical writers are off to a running start.

So, it's internally a huge effort.

Kevin Frees from the library science side of it has been able to capture likely search approaches
that will ferret out the rest of the information
that is going to be needed. It's just -- it's
also consistent with our current view of life that
it takes a team to raise a report. And in this
case, it's chemistry, it's searching, and
summarizing information. It's toxicology, and
it's working.

So, thanks to all of the staff who have
been developing this approach. And we look
forward to seeing more and more of this as we move
on into the future.

And then finally, I just wanted to
comment. The CIR science and support committee
was gracious to invite Halyna and I to participate
for an hour or so in the last meeting that they
held. We took Bart Heldreth and Ivan Boyer along
with us, and we talked about the CIR philosophy on
creating groups. You've probably noticed that if
left to my own devices, I will create very large
groups.

And one of the issues that was on the
table is that just generally speaking, a good
strategy. I think the conversation came away with
the result, yeah. It is, as a first step. With
the understanding that it may be perfectly
reasonable to remove ingredients either smaller
groups of ingredients or specific ingredients if
there is a good reason to do so. So, it's -- I
think it was a good credentialing of the
philosophy that is in place and, you know,
yesterday's team discussions appeared to be an
excellent second step on, okay, now we have this
huge group. Are there any that maybe don't
belong? And for what reason?

So, I think, again, the strategy is
working. You can expect to continue to see as
expansive a grouping as we can do tempered by the
panel's sense of, whoa. And I think that's
perfectly reasonable.

I think that -- Halyna, are there any
additional things that I should have said that you
can think of? The end of my report.

DR. BRESLAWEC: Well, thank you very
much. Excuse me. We as a panel certainly have
appreciated this team effort. The better you are, the better we are. And we all like looking good and doing our best.

So, we're going to move on, then, to the final reports or the reports going to the next level. And the first report, plant derived fatty acid oils, Dr. Belsito will be reporting.

DR. BELSITO: Yes. In December, we issued a tentative report on 244 plant-derived oils. And we found that 234 were safe as used, and there were 10 that were missing ingredients.

Prior to this meeting, we received the ingredient concentration on additional seven, and then at the meeting got concentrations on fragaria chiloensis, which is strawberry seed oil. And what we were missing, the remaining two were fragaria vesca and fragaria virginiana, both strawberry seed oils.

And we looked and compared the information we received on the chiloensis to the ananassa, which we had previously had and noted that the predominant fatty acid composition of
both of them (inaudible) and linolenic acid. And we felt comfortable that it would be fairly certain that the vesca and virginiana would follow along the same lines.

So at this point, we found the entire group of plant-derived oils as listed. I will not read them all --

DR. BERGFELD: I guess not.

DR. BELSITO: -- to be safe as used.

DR. BERGFELD: Oh, why not. Thank you.

Is that a motion, then?

DR. BELSITO: It's a motion.

DR. BERGFELD: Second?

SPEAKER: Second.

DR. BERGFELD: Any further discussion?

DR. BELSITO: Yes.

DR. BERGFELD: Okay. Don?

DR. BELSITO: On page 1 of the report it indicated that the -- all of the ingredients in the report -- in the introduction, the fourth line, it's says, all of the ingredients in this report are mixtures of triglycerides containing
fatty acids and fatty acid derivatives. Well, there are on some unsaponifiables in there. So we changed that wording to "most" of the ingredients in this.

And then in the discussion, also brought in the idea that most of the ingredients were triglyceride-derived, but there were some unsaponifiables. And wanted to mention that we had previously reviewed the safety of corn and sesame seed oil on unsaponifiable in the discussion part.

And those were the major additions. And I can't remember if it was Dan or Paul that had some wordsmithing on the arachidonic acid in the discussion.

DR. LIEBLER: I did. On page 8 of the report, the new language that has the vertical lines indicating it. The initial sentence there was kind of a whopper, and I thought it would be better to just divide out the expert panel, discuss the fact that arachidonic acid is an ingredient of the -- or is a fatty acid in these
oils. And then add a sentence -- although the
previously published CIR evaluation concluded that
insufficient data exists to support the safety of
arachidonic acid in cosmetic products, the panel
was of the opinion, blah, blah, blah.

So it just tried to make it a little bit
more clear.

DR. BERGFELD: And Paul? Any comment?

Dr. Marks' team? Any comment?

DR. MARKS: No.

DR. BERGFELD: I'd just like to draw
your attention to the fact that the actual text of
this particular ingredient document is basically
11 pages, but the whole document is over 90 pages.
And that includes the addition of all these tables
-- or table-ized informational pieces, which makes
this document readable.

So, this group is to be congratulated on
this format.

DR. BELSITO: And quickly

understandable, as well.

DR. BERGFELD: And quickly
understandable. So, all those -- I'll call for
the motion and vote now. All those in favor,
please indicate by raising your hand. Unanimous,
thank you.

All right. Then moving to the next
item, which is Dr. Marks' presentation of the
alkalide benzoate group.

DR. MARKS: In December the CIR issued a
tentative report that came to the conclusion that
C12-15 alkyl benzoates and related alkyl benzoates
were safe as used in cosmetics. I move that we
make this a final report with that conclusion.

DR. BERGFELD: Is there a second?

DR. BELSITO: Second.

DR. BERGFELD: Second. And discussion,
then?

DR. BELSITO: Yes. Again --

DR. BERGFELD: Okay, Don?

DR. BELSITO: Dan had some editorial
changes that he wants to share with us,
particularly on page 23.

DR. LIEBLER: Yes. On one of the things
that I noticed in the report is that it seems to highlight what is portrayed as a contradiction in some of the data regarding the octanol water partition coefficients, and the experimental penetration data in pig skin in vitro. And I felt that the text as it was written -- and actually in two places. On page 4 of the report, the fifth paragraph, Panel Book 27, the sentence says, "Actual test data indicated a different picture." I don't think that this is really that contradictory. So I suggested deleting that sentence.

And then the second change I had was at the very beginning of the discussion. Excuse me -- at the very beginning of the discussion on Panel Book page 46, discussion page 23, first paragraph, replacing the third and fourth sentences with the following text: Alkyl benzoates, which have octanol water partition coefficient values above 8 were not expected to leave the stratum corneum and reach the epidermis. However, 5 to 8 percent of C12-15 alkyl benzoate
applied in 3 different product formulations was reported to penetrate epidermis of pig skin in vitro.

And then the second paragraph, to change the first sentence to: The panel reasoned that the data indicating modest penetration of alkyl benzoates into the epidermis suggested the need for a conservative approach that would consider the potential for systemic exposure.

So, it just tries to sort of sand down the rough edges of this suggested contradiction because I don't think the data are really contradictory.

DR. BERGFELD: Dr. Hill is shaking his head in agreement. Any other comments? Dr. Shank?

DR. MARKS: Yes. Dr. Shank had a number of editorial comments in the discussion. Lillian has captured those. It really doesn't change the conclusion.

The only other editorial comment I wanted to make is Dr. Ron Hill yesterday noted
that in the summary, that on Panel Book page 45, next to the last line from the bottom, the isostearyl alcohol at 5 percent was sensitizing. So that raised an alert for him in the isostearyl benzoate, which is one of the ingredients in this group that we reviewed. And the butyloctyl benzoate and hexyldecyl benzoate, there was really not data in terms of its sensitization. But we felt we could handle that in the discussion. And again, would not change the conclusion.

Did I capture that correctly, Ron Hill?

DR. HILL: Yes, that's fine.

DR. BERGFELD: Any other comments? Don, do you want to respond, then?

DR. BELSITO: No. I mean, the isostearyl alcohol is not a very commonly seen contact allergen. So I'm not that concerned. My only other comment was that since we're going with boilerplates, the next to the last paragraph of the discussion, we should use the boilerplate for highly refined plant-derived materials as indicated in page 5 of the
boilerplate document.

DR. BERGFELD: Any other substantial comments, other than editorial?

Seeing none, then I'll call for the vote. All those in favor, please raise your hand.

Thank you, unanimous.

So, moving onto the third ingredient, which is in a green book. And that is Dr. Belsito reporting on silylates.

DR. BELSITO: Okay, the silylates. This is really the first time that we're looking at this group. And it turns out that there are two major forms to this family. There are what are called grafted and the co-—condensed. And we thought that the data were insufficient for the physical and chemical properties of the co-condensed group. The grafted group we felt was fine.

And then the only other comment that we had was that, given the inhalation data that we have from Panel Book page 9, would we need a boilerplate when we get around to this for
respiratory and inhalation? But at this point we
want to go ahead with insufficient for additional
data on the physical and chemical properties of
the co--condensed.

DR. BERGFELD: That's a motion. Dr.

Marks?

DR. MARKS: Second that motion.

DR. BERGFELD: Second.

DR. MARKS: But we would add another
insufficient data in the
trifluoropropyldimethyl/siloxysilicate. There were
fluorine impurities, and we wanted to know what
those -- whether there would be fluorine compound
impurities. And also, the stability of that
compound.

DR. BELSITO: Yes, but that's a
cocondense --

DR. MARKS: Right.

DR. BELSITO: So it's basically what
we're asking for.

DR. MARKS: Okay.

DR. BERGFELD: Any other discussion? So
-- yes, Ron.

DR. HILL: I had raised a question about the particular product called antifoam A, which is a mixture, and the fact that there was organic silicone -- anyway, the result is that in urine and in, I think, some areas of the lymphatic system silicone was showing up and my concern is not the presence of those silicone-containing compounds, but that there might be these organic impurities in antifoam A. And so I was asking specifically if that product was used, what the nature of those are because there are certain things in there that could be very deleterious if they actually were in there as impurities.

DR. BERGFELD: So that's your request for information?

DR. HILL: I guess that's a request for information, probably, from the industry side. And I know we don't evaluate products, but if there are others that are out there consistent with the same process of manufacture, that's the question.
DR. BERGFELD: John? Do you want to comment on that?

DR. BAILEY: We can look into it and see, get some more information on impurities.

DR. BERGFELD: So the motion has been made and seconded to go safe on a portion of this and insufficient for other. Are there any other comments? And this will go out as a tentative final. Insufficient? How is it going to go out?

DR. ANDERSEN: No, this will be an insufficient data announcement, which alerts all interested parties that unless additional data are provided, there is a risk that the data will be determined insufficient. So, it's a heads-up opportunity to provide the information and get back on track. Otherwise, the panel may have no alternative other than to find the data insufficient.

DR. BERGFELD: All right. The understanding it will go out as an insufficient data announcement. Although -- yes, Dan?

DR. LIEBLER: I just want to note the
one nice thing that appeared in this report, and
another report that I'd want to acknowledge that
the chemist for is a representation of these
structures -- in addition to this sort of standard
2-D representation, is a sort of ball diagram that
kind of represents what the structures present to
surrounding biological systems. And it's a nice
representation, and I encourage its use in the
future when applicable.

DR. BERGFE LD: Ron Hill?

DR. HILL: One other general comment,
and this is just because all of the staff members
are here to hear it. I don't remember whether it
was this document or the acrylates, but at the
beginning -- and it was just information to us.
It was stated that a PubMed search was done, but
then when I asked clarification -- I don't
remember who I asked clarification, it actually
did include chemical abstracts. And that was, you
know, the -- some of the reports have shown at the
beginning which databases were searched, along
with the search strategy. If you just tell me
PubMed and you don't indicate these other databases, then I -- it raises questions in my mind whether the search was done properly. So, just needs to be sure that we state where the searches were actually conducted, because that's important.

And also, quite a bit of money is being expended getting those searches done. So, we want to make sure everybody knows that.

DR. BERGFELD: All right, thank you. Call for the vote then. All those in favor?

Unanimous, thank you. Moving on to the second Green Book, which is formaldehyde. Dr. Marks?

DR. MARKS: Formaldehyde may have been the thinnest book we had, and it was inversely related to the length of the discussion about this ingredient. So, in December, the panel agreed to reopen the assessment of formaldehyde because of three reasons. There was new safety data, its use in hair-smoothing products, which had created significant amount of salon user adverse events.
And then lastly, to include methylene glycol, since that had not been in the original report, which was published in 1984. Which came to the conclusion that formaldehyde was safe in cosmetics if free formaldehyde was minimized, but in no case greater than .2 percent.

And in the second sentence sort of equivocal in that conclusion, the panel also said it can’t be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized. This was actually re-reviewed in 2003 by the panel, finding the same conclusion valid. And that was published in 2006.

So, in light of these new developments at the end of last year, we reopened it, as I said earlier, and considered the new data, the use in hair smoothing products, and the elucidated chemistry of free formaldehyde, formalin, and methylene glycol, and the chemistry and bounce going between these chemicals.

When we re-looked at the original report, it seemed like the conclusion was based on
0.2 percent formalin in skin irritation and sensitization studies, or repeat insult patch test. And that the amount of free formaldehyde was actually 0.074 percent. So that -- we had some difficulty in terms of deciding, well, what really is the level of free formaldehyde that would be safe.

And then dealing with a second sentence in the conclusion. First of all, aerosolized it may be better to use the word "vapor" instead of aerosolized. And then we really didn't have enough data to decide on the respiratory route of toxicology, that being cancer and reproductive and development, and wanted to arrive at a conclusion of insufficient versus unsafe for the vaporized portion of this cosmetic ingredients.

We found out that there is soon, meaning within a couple weeks, an NSA report which will be coming out. And then we also wanted to know what were the OSHA limits for exposure to formaldehyde that is in the air.

So, with all that said, our team felt
that we should table this at this point, awaiting
the NSA report and the OSHA and finding out that
OSHA limits to try and determine a basis for which
we could come to the conclusion about the
vaporized form as being insufficient or unsafe.
I will ask Tom and the two Rons to
elucidate better than what I said, if I left
anything out.

DR. BERGFELD: Ron Shank?

DR. SHANK: Dr. Mark summarized it very
well.

DR. BERGFELD: Ron Hill? Okay. Don?

DR. BELSITO: Yes. We took a slightly
tack, particularly because in our discussions
there was a good amount of concern about the fact
that this Brazilian hair care product is currently
out on the market and currently creating problems.
And to table this, we didn't think would be in the
best interest of the consumer. We prefer to move
this along.

There's also a third point that you
didn't address, and that is that apparently -- not
apparently. This is use in nail hardeners. And
the FDA has approved its use in nail hardeners up
to 5 percent.

DR. KATZ: Actually, when you're through
with your comment, that needs to be corrected.

DR. BELSITO: Okay.

DR. KATZ: Because it is actually not
approved. And when I've gone back -- and I can
either make the mention now or later.

DR. BERGFELD: Probably now.

DR. KATZ: Okay. That it is actually
not approved. There was a policy statement that
was made back in 1974 via a warning letter that
allowed its presence up to 5 percent. So, it
actually is not approved at that level, but it is
a policy statement. So I just wanted to clarify
that the FDA has not approved it.

DR. BELSITO: Okay. So --

DR. BERGFELD: Thank you.

DR. BELSITO: -- you know, we viewed the
issues as okay. Formaldehyde methylene glycol,
the nasopharyngeal carcinogenicity issue, and then
maybe setting a different limit for nail products
as we have for other products that would contact
only the nail.

Thanks to Paul we did note that in 1993,
actually, we looked at a higher concentration of
nail products. And reading from the analysis of
the submitted comments from the CIR compendium, it
said, the expert panel publicly reviewed submitted
comments relating to the use of formaldehyde at a
concentration of 4.5 percent in nail hardeners.
In its deliberation, the panel concurred that
submitted evidence was inadequate to assure
formaldehyde could be safely used above 0.2
percent in cosmetic products. And further
information could be obtained from the -- from the
published minutes of that panel meeting. So, it
looked like we actually did look at some data at
the higher concentration and could not arrive at
safety.

Having said all that, again in the
interest of moving this forward, because of the
issues with the Brazilian hair straightening
product, we wanted to go out with a conclusion as follows. In that the -- we found that formaldehyde/methylene glycol is safe for use in cosmetics if formaldehyde equivalents are minimized but no case greater than 0.2 percent.

The panel also said that it can't be concluded that formaldehyde/methylene glycol is safe in cosmetic products intended to be aerosolized or vaporized under conditions of use.

The panel found that there was insufficient data to support the use of formaldehyde/methylene glycol in nail products. And the specific data that we had talked about getting was whatever data that FDA might have. So it would be of interest -- if it's just a letter -- but we're also informed that there is data from California nail salons regarding air levels of formaldehyde in these salons that might be helpful in assessing the safety of their use in a nail product. Because obviously if a product is labeled not for application to skin, sensitization goes away. But the issue would be the -- any
volatility to the formaldehyde in air levels. So we wanted to move this ahead, again, in the interest of hopefully protecting the consumer from the Brazilian product that we feel would be considered unsafe because not only is its concentration greater than 0.2 percent methylene glycol, but also because there is vaporization with the heating process. So, our recommendation was safe methylene glycol, formaldehyde less than equal to 0.2 for products. Insufficient data for aerosolized or vaporized and insufficient at this point for nail.

DR. BERGFELD: Comment? Or questions?

DR. MARKS: Two, a couple comments. One is, we weren't really sure that the 0.2 percent was really valid. We wanted to go back to the free formaldehyde, which now that there is several different analytical methods that we can be content that will actually measure the amount of free formaldehyde because that was one of the issues in the past. So, we would set a different limit of free formaldehyde.
And then we were really concerned about reacting specifically to a product versus coming to a conclusion that would cover. I know you did that, Don, when you talked about aerosolized or vaporized. But we didn't feel as compelled right now to come to a conclusion based on a product as to trying to get what would be the right limit for aerosolized or vaporized formaldehyde. And we thought that data -- we could get that data potentially from the NSA report and OSHA limits.

DR. BERGFELD: Could I interfere and ask John Bailey a question? As the formaldehyde document exists today, the limit is 0.2 percent. And it is questionable in the vaporized or aerosolized -- so in fact, I don't hear any change in that with the various teams at this point. And -- except that there might be a reduction in the limit.

DR. BELSITO: Well, I mean the -- I think the -- when you're looking at formaldehyde you need to look at, you know, irritation under occlusion versus, you know, as used and open
application and -- I mean, I think -- you know, we
certainly can go back and re-look at that limit
and change it.

I guess I'll ask Rachel to comment on
what she perceives as the public's need to have
some immediate information on this Brazilian
product.

MS. WEINTRAUB: Sure, thank you, Dr. Belsito. I think this is an instance where we
know that consumers are having acute reactions to
a product. There's numerous complaints about
harms associated with receiving this treatment.
So I think it's important that consumers
understand that there are problems with the safety
of this product.

And in being in Dr. Belsito's team, it
seemed very much like -- and I think what you're
saying is consistent that it seems that this
product is not consistent with safe use.

So I think it's important to get the word
out to consumers as soon as possible so that
consumers understand the risks that they're taking
by using this product.

DR. MARKS: Rachel, we concur.

Certainly our team are certainly concerned about adverse effects on the consumer. I guess one could take the tack of, is it the panel's purview to get this out with some pending data which may be more accurate. And is it our role to really regulate this product? Or is it FDA's? And I guess I'd ask Linda about that.

There's certainly enough in the literature now based on the Canadian action, based on an analysis that this material -- this Brazilian blowout has way over the concentration of formaldehyde as it's formulated now. And of course we know that heating it will drive more formaldehyde out. So we really wanted to come to a conclusion that maybe would be more accurate for the long run.

And although we certainly know about the adverse events that are occurring now, the question is are we the right body to move forward to address this? I think there's enough
information already to address it.

MS. WEINTRAUB: Well, if I may -- I mean, I think that both the FDA and the Personal Care Products Association have looked to CIR in both of their statements, they've said we want CIR to look at this.

So, it's sort of been this circular -- well, almost circular sort of situation. So, you know -- and with -- there's been statements that have been put out to the public that sort of raise concerns but there's not certainty -- it's not necessarily clear. And I think from, you know, an average consumer looking at that information it's not clear what the conclusion is. So there's been a lot of looking to this body to make a determination.

DR. BERGFIELD: Linda, do you want to respond, or?

DR. KATZ: Well, I'm not necessarily -- for a determination is the right word. I probably would say that we're looking to this body to get additional information so that we will have the
information at hand that we need to be able to

take an action.

Right now we are not there. We are in
the process of doing the research that we need to
on the product specifically for which we've
received complaints. But that there are missing
pieces, and part of the missing piece is really
the safety issue as to what one could expect or
what one should look for in a vaporized product.
And that was part of the reason why we asked for
your help.

DR. BERGFELD: Ron Hill, then John.

DR. HILL: And that really was part of
the -- excuse me -- we had yesterday because I
think based on the science that's there I'm not
sure we can reach a conclusion that it's unsafe if
it's used properly. So I think, you know, the
science suggests that in truth, we don't know.
And I don't think we have enough information to
conclude conclusively that it's not safe --

DR. BELSITO: Not safe in what regard,

Ron?
DR. HILL: In using the product Brazilian blowout were it to be used in the proper circumstances. We know people are having reactions, we probably have some idea why. But I don't think we can conclusively say right now based on the science that it isn't safe and it shouldn't be used under any circumstances.

DR. BELSITO: You know, the issue is we haven't looked at methylene glycol. So, methylene glycol and formaldehyde have different functions listed in the Cosmetic Ingredient Dictionary.

So, I think from a legalistic standpoint this panel has issued no regulations for methylene glycol, which allows this Brazilian blowout to use it what looks like at very close to 5 percent. Based on the information we now know, that methylene glycol is essentially formaldehyde, it just depends upon the state of the product it's in. And that when heated, formaldehyde is released and is going to be a certain amount of formaldehyde. At 5 percent, this product probably exceeds the limits that currently exist, number
one.

Number two, I think that we all can agree that the data for nasopharyngeal carcinoma, it's not clear, you know, whether it's a linear model or it's a, you know, genotoxic threshold model. We don't have that information. So if it's linear, as EPA is suggesting -- and we know from the chemistry that we've learned that we are vaporizing formaldehyde when we heat it -- then this product is probably unsafe or insufficient for vaporization and unsafe for concentration. But right now, that data is not even out there because we haven't looked at methylene glycol.

I would also like to point out the next panel meeting is almost four months away, it's at the end of June. And then the panel meeting after that is the end of September. So if we table this we're not even going to get around to any announcements until June, and any possibility of final -- I don't even know if we can finalize it at September. It's 60 days now, right? Not 90. So we could finalize it September as opposed to if
we do something today we can get the information, hopefully, since there's four months and go out with a final report, give the FDA -- this is a serious issue. And also more serious is, I call your attention to the reports from Health Canada with what their finding in terms of concentrations in formaldehyde on shells that totally exceed. I mean, cases are reported up to 30 percent, which many of us have trouble believing.

Linda?

DR. KATZ: I went back to contact to see if that's actually correct, and I think the table may be wrong.

DR. BELSITO: Okay.

DR. KATZ: And it may be not quite that high. And the information that we've gotten was up to 7 percent. So that it may be that there -- one needs to check to make sure that it's really formaldehyde and not formalin or something else that's being measured in something.

But -- so I'm not sure the table is correct as it's actually listed.
DR. BELSITO: Okay. But still, the report --

DR. KATZ: It's higher than what -- that's right.

DR. BELSITO: -- if it could be, are much higher than we've allowed. So I really -- I think, you know, I felt strongly before. Rachel has convinced me even more. So yesterday -- that we need to move forward with this document.

DR. KATZ: John Bailey?

DR. BAILEY: Yes, clearly this is a very complicated issue on several different levels. And not the least of which is nomenclature. And from our perspective formaldehyde gas is a rare material. It's actually pretty tough to make it and hold it. So, if it's around moisture at all it becomes methylene glycol.

So, the way I kind of like to think of this is, formaldehyde equivalents. You know, you can take formalin, you can take methylene glycol, you can take paraformaldehyde, you can always calculate formaldehyde equivalents. And that's
probably the best reference to use.

Regarding looking to CIR, while we certainly respect FDA's position of having to look at it in the context of the Food, Drug, and Cosmetic Act, our expectation is that the CIR will review data, reach conclusions, publish those conclusions, and industry will follow those. And certainly within the perspective of the council, our members -- most of them have signed on to a commitment -- the Consumer Commitment Code -- to follow the CIR guidelines. So I think, you know, I think perhaps we have a little more freedom and say in that than FDA might.

Regarding the proper circumstances, I think it's possible to envision circumstances for properly ventilated facilities and properly trained individuals to use these hair smoothing products in a safe way. But the margin here is pretty narrow compared to an ordinary cosmetic. So I think you're dealing with an unusual situation.

But it also harkens back to the alpha
hydroxy acids, glycolic acid opinion where it was stated that anything used up to 10 percent or 30 -- I can't remember what it was, Alan. But nevertheless, it would be by trained professionals. So I think it's within the purview of the expert panel to make that kind of distinction.

Regarding the need to do something sooner rather than later, I think there is a lot of confusion out there and I think Don, what you're talking about is to issue a conclusion and then let that force the submission of new data and information to clarify so that this would be dealt with in the June meeting. And I think that's certainly a viable way to do that.

I think, though, the NSA and OSHA data will be very informative as to what is tolerable and maybe more information about how much is actually in the air. And perhaps a conclusion of unsafe if the formaldehyde levels in the air pass a certain threshold. And that would be set through that.
Regarding the -- I've been writing a list here. Regarding the 5 percent, it's certainly FDA policy. It's been that policy for a long time. It derives from some adverse events that go back to the 1970s. But also, in Europe they've done a similar assessment and have concluded that 5 percent in use in nail hardener products where there's protection shields and so forth -- because this is a polymerization reaction. So the formaldehyde is gone pretty fast. So, but steps do need to be taken.

The.2 percent, whether we talk about.074 or 2 percent, again in Europe they've set it at.2 percent as calculated as formaldehyde. So they've had some basis for assessment. That and I, off the top of my head, I don't know how current or how available that is, but we can certainly find out more about that to see. So, anyway.

DR. BERGFELD: Don?

DR. BELSITO: Well, I mean, again I think, you know, if we proceed with this certainly, you know, that the two big issues are
going to be sensitization, irritation, and inhalation. So, you know, it would be nice if very detailed summaries of what went before both with the initial review and the re-review that we did before that information be very nicely captured in the current document so we could look at it.

I don't think that -- I didn't pick up on the fact that it was formalin, which is typically 37 percent formaldehyde. But I think what we'll find is that the studies are all over the board and it was probably irritation under occlusion. Because we all know that patch testing even with 1 percent aqueous formaldehyde induces a significant amount of irritation that you have to read through. But I've never really seen induction of allergy with patch testing with 1 percent aqueous formaldehyde. So I really doubt that that's going to be a significant sensitizer in humans. It would be more of an irritant under occlusion phenomenon.

But again, I really feel very strongly
that we need to move ahead with this document or
we will not finish it until next year.

    DR. MARKS: So read your conclusions
again, Don. Because basically what you are
recommending is we issue a tentative.

    DR. BELSITO: A tentative with lots of
insufficients.

    DR. MARKS: Right.

    DR. BELSITO: And so the conclusion was
that formaldehyde/methylene glycol is safe for use
in cosmetic products if formaldehyde equivalents
are minimized but no case greater than 0.2
percent. The panel felt that it could not
conclude that formaldehyde/methylene glycol is
safe for use in cosmetic products intended to be
aerosolized or vaporized under conditions of use.

    The safety of formaldehyde/methylene
glycol in nail products where it would be used up
to 5 percent is insufficient and the information
we need to know for that -- because we can set
the, you know, consumer guidelines about
protection, et cetera. Where we were asking for
FDA's information, which I gather may just be a letter. And also, we were told that studies were done in California nail salons as part of Prop 65 doing air analysis on formaldehyde in these salons. We would like to see what that is.

And then obviously, the data you talked about before should come in and help us clarify that nail use.

DR. MARKS: I -- go ahead. I was going to say, I don't see a problem with moving forward hearing the discussion at this point, because we have plenty of opportunity to modify this conclusion. It's a tentative conclusion we're sending out. So I'd ask my other team members --

DR. SLAGA: I agree with that. I think -- in acids, we agree with Belsito's team. We just were hoping we could have the National Academy of Science data as well as the OSHA data to help formulate this a little better.

DR. MARKS: I would say, the difference is we didn't have Rachel at our meeting yesterday pressing the --
DR. BERGFELD: Conclusion.

DR. MARKS: -- the consumer's point of view, which we were very sensitive to.

DR. BERGFELD: Any other discussion?

I'd like to have -- I know you've stated your -- is this going to be a motion, then?

DR. BELSITO: It's a motion.

DR. BERGFELD: Is there going to be a second?

DR. MARKS: Second.

DR. BERGFELD: Rachel?

MS. WEINTRAUB: I just have one statement. Or, one question. And that is, is there also an issue about terminology and measuring the formaldehyde? Which I think needs to be clarified. Because I think the issue of free formaldehyde or methylene glycol versus having a percentage limit, I don't think those are equal.

So I think we need to figure out how to capture that and make those consistent.

DR. BERGFELD: Thank you. Dan?
DR. BAILEY: So I think that in the
draft report that Bart and I have -- the language
that Bart and I have prepared was very helpful in
defining -- describing the chemistry, defining the
terms.

One point that came up yesterday was in
our discussion was that I think the term free
formaldehyde is actually kind of ambiguous.
Because to some people it might mean the
formaldehyde side of the formaldehyde- methylene
glycol equilibrium. To other people it might mean
formaldehyde that is no covalently bound to
proteins or other things, that some of those
adducts could revert, and so forth.

So, I think it would probably be good
for us to avoid using the term 'free' formaldehyde
in our language. And as John suggested, we
discussed yesterday referring to formaldehyde
equivalents, or very similar strategy where we
said formaldehyde/methylene glycol to recognize
the fact that these species are in rapid
equilibrium.
And one last thing, I mentioned that we probably need to pay attention to is, I believe that 5 percent number for the nail products is 5 percent formalin. Is that correct? Yes. So it's 5 percent formalin, so that translates actually to a different lower number for the formaldehyde/methylene glycol in those products.

DR. MARKS: We actually calculated, and it was below actually the -- whatever free formaldehyde is, it was below the .074 percent.

DR. HILL: Twenty-three parts per million, but the methylene glycol is about 3 percent, so.

DR. BERGFELD: Don? I'm sorry -- Ron, did you have something else? Don, did you have something else?

DR. BELSITO: No further comments.

DR. BERGFELD: John, please?

DR. BAILEY: Yes. I agree about the confusion between formaldehyde, you know, methylene glycol. And I think the form to present this in the report is actually -- is definitions
where you've got a heading and a definition that follows it. Because that is something that we could use in communicating to everyone about, you know, how these are defined and how they relate to one another.

DR. MARKS: I agree, John. I termed it a "glossary."

DR. BAILEY: Right.

DR. BELSITO: Yes. Well, I mean, and as we discussed with Alan, I think throughout the report we need to keep hitting people over the head with the idea of this formalin, which is 37 percent formaldehyde, and this formaldehyde/methylene glycol. And that's going to exist in an equilibrium that is going to be very dependent upon many factors, including the particular solutions it's in, the ph, the heat, yadda, yadda, yadda. So I think we need to keep emphasizing that throughout the document.

Because, you know, both Paul and I were struck when we went through this by the total lack of absence on methylene glycol. And Paul actually
went ahead and did a search and you really can't find anything in the literature about methylene glycol. It's all formaldehyde.

So, I think we need to make that clear up front, too. Because if you read this document you go, whoa. How did the panel decide on safety of methylene glycol when there's no data on methylene glycol here.

DR. BERGFIELD: Alan, did you have a remark?

DR. ANDERSEN: I think the discussions yesterday demonstrated that it may not be possible to say often enough that methylene glycol and formaldehyde are in an equilibrium. It's part of the explanation for why many of the formaldehyde data likely informed methylene glycol safety, and vice versa.

And it's just -- it's an understanding that in the original safety assessment, as I recall, got one sentence. It was there, if you wanted to read it. But it definitely needs to be emphasized. And message received.
DR. BERGFELD: Paul, did you have a comment?

DR. SNYDER: No, no comment.

DR. BERGFELD: Then, Ron? Ron Hill, then Ron Shank?

DR. HILL: Let him.

DR. BERGFELD: Dr. Shank?

DR. SHANK: If we're changing the conclusion, I do not think we should perpetuate this 0.2 percent formaldehyde limit. Because the report was based on 0.2 percent formalin.

DR. BELSITO: I --

DR. SHANK: So we should change that now.

DR. BELSITO: Well, I don't know that we have the data to change it in this report. We can change -- it's not going out final, it's simply going out insufficient. So I think we -- that's why I asked that all of the data on sensitization, irritation -- all of the data that we saw on inhalation in the original report and our re-review be really very seriously summarized in
the next iteration that we see, so we can actually re-look at the data on that -- on this 0.2 and get the minutes from the original meeting.

I think what we'll find is the 0.2 percent is based upon irritation under occlusion, and is not really based on sensitization. But we'll see. We can change those. This is not a final. We can change everything, including saying that it's safe for use in aerosolized next time. This is just to get out to the public that, you know, we feel there's insufficient data for products that could be vaporized under condition of use. And that methylene glycol and formaldehyde are equivalent and whatever restrictions we place on one will be on the other. So, I'm not saying that 0.2 is going to be the final concentration, Ron. I just don't think we have all the data right now to set that.

DR. MARKS: I think the clarification -- first of all, I agree, Don. I think that clarification is the 0.2 percent in these studies was formalin. And then when you look at the
table, the free formaldehyde which, in the conclusion, it says that concentration of free formaldehyde should not be greater than 0.2 percent. So it's not an issue of whether the results of the studies were irritation or sensitization as what did they mean by -- was that a misprint and it really should have been formalin and is not greater --

DR. BELSITO: I mean, I understand. But we can change that concentration later.

DR. MARKS: No question. I just want to clarify, we were not concerned about the end results of the studies. It was, what did the 0.2 represent? Was it free formaldehyde or formalin?

DR. BERGFELD: Ron Hill?

DR. HILL: I just wanted to -- based on your wording, make sure that we are also pretty careful with the usage of formaldehyde equivalents. Because if you had dissolved formaldehyde present as paraformaldehyde then, yes, under conditions of very strong heating you could generate -- I hate to use the word now free
formaldehyde, but molecular CH2C double bond
(inaudible). The carbonyl form, I guess that's unambiguous. You could generate the carbonyl form. But there are kinetics associated with that, and if you just put it based on formaldehyde equivalents, that we're going to start picking up things like quaternium, which has formaldehyde equivalents, and so forth.

So we need to be pretty careful how that's used and make sure that wherever you use formaldehyde equivalents we're saying it very clearly. Because we spent time talking about things like the equilibrium in the liquid phase between the carbonyl form and methylene glycol is not necessarily the same as the equilibrium in the gas phase, and what are the implications of that. It also came up that it doesn't have to be in the carbonyl form to react with tissues. It can react as methylene glycol, apparently. So there are a lot of these things that need to be really clear.

DR. BERGFELD: Can the scientific council help us with that? The committee?
DR. BAILEY: Yes, we can put that on our agenda of things to work on and get back for the June meeting.

DR. BERGFELD: All right. So we have a motion and I believe we have a second.

DR. MARKS: We do, it's been seconded.

DR. BERGFELD: Second. And any further discussion? Seeing none, a call for a vote. All those in favor indicate by raising your hands.

Thank you, so it will go out as an insufficient with -- as stated by Don. I guess it would be massaged and cleaned up a little bit. All right.

Excellent. Moving on to the next Green document, the DEA documents by Dr. Belsito.

DR. BELSITO: Yes. This is DEA and related DEA- containing ingredients. So, in December we decided to split the document TEA, DEA, and MEA into the individual ethanolamines.

And then, to tag onto that individual ethanolamine related ingredients from the Cosmetic Dictionary.

And so, that's where we are today. And with DEA.

And in table 1 of the document, we were
presented with a huge number of cosmetic ingredients that at some point had DEA in their name. And we looked at this table of ingredients, and we thought that most but not all could be included in the report.

The ones -- and I'll have Dan comment, if he wants later -- that we felt should not be in the current report were the alkyl and PEG phosphate esters. And they're on page 40, Panel Book page 73. And there were a total of -- 1, 2, 3, 4 -- 6 of those and the disubstituted phosphate esters. And if I'm summarizing Dan correctly, while he felt there would probably be no toxicologic issues with these, there would also be an alkyl sulfonate that was generated. And since we haven't previously reviewed alkyl sulfonate safety, that we not proceed with those eight specific ingredients.

And then finally, the three alkyl substituted diethanolamines are not secondary amines as is DEA, but they're tertiary amines and should be dropped from the report. So we were
recommending that a total of, I guess, ingredients -- is that correct? 5, 6 -- 10 ingredients that I just mentioned be dropped from the report. All of the others could be kept and found as safe as used when formulated to be non-irritating. And then the usual caveats with DEA of no nitrosation, the inhalation boilerplate, and in the discussion the fact that carcinogenicity is not relevant because the murine -- it's coleman deficiency, which is not applicable. And then the usual read-across boilerplate.

DR. BERGFELD: Are you making that a motion?

DR. BELSITO: I'm making that a motion.

DR. BERGFELD: Is there a second or discussion?

DR. MARKS: I'm sure there's going to be a second. There is discussion, though.

DR. BERGFELD: Yes, go ahead.

DR. MARKS: The question is the number of ingredients. We -- so let's go on which ingredients to include.
So on Panel Book page 73, or page 40 in the report, Don, if I heard you correctly, the alkyl and PEG phosphate esters, you would delete that whole group?

DR. BELSITO: Yes.

DR. MARKS: Our team didn't have a problem with those. And if you turn over on page 41, the disubstituted phosphate esters, we thought, were okay.

So, it was everything after those -- the disubstituted phosphate esters that we would eliminate. So, the alkyl substituted and the diethanolamines, we would eliminate everything after that. So I guess the discussion is, the alkyl and PEG phosphate esters. Whether or not they really need to be eliminated, and the disubstituted phosphate esters.

And I'll ask my team to comment on -- I think we heard Don elicit it why they wanted them dropped. And we could comment on why we didn't think they had to be dropped.

Ron or Ron?
DR. HILL: I wasn't sure why I heard you wanted the phosphate PEG ones -- needed to be out?

DR. BELSITO: Because we hadn't looked at the safety of the alkyl phosphate group.

DR. HILL: Then I agree with that. I would -- in addition to what we said yesterday, I would agree with them on that.

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

DR. SHANK: The main ingredient, diethanolamine, has been reported to cause choline deficiency relating to liver cancer.

The choline deficiency animal models produced liver cancer, but not kidney cancer. Kidney cancer has not been reported. But diethanolamine produces both in animal models.

Liver cancer and kidney cancer.

The choline deficiency is one hypothesis, as the mechanophis action, but it's not the only one. I felt it was better to use the very poor absorption of diethanolamine through human skin, and its low use concentration, rather
than trying to go to a specific mechanism of
action for carcinogenicity.

That being the case, when you get to the
amides, the absorption of the amides may be
considerably greater than the free secondary
amine. And, therefore, that argument about
there's not a cancer problem for dermal
application because of low absorption goes away.
So, we were thinking of taking the amides
completely out of the report and having only
diethanolamine and its salts.

DR. BELSITO: Dan?

DR. LIEBLER: I think I follow the
logic, I just haven't had a chance to settle in
and think about that yet. I'm not sure it's
necessary to -- I understand if you want to say
the choline deficiency mechanism is not sufficient
basis on which to make a decision. Then, you go
with a consideration regarding absorption.
If you do go with considerations
regarding absorption of the amides, then I think
the implicit -- the other implicit part of that is
that these amides would be extensively hydroized
to release diethanolamine, because you're worried
about the diethanolamine as opposed to the amid.
So -- and I'm not sure that we know whether or not
that will happen, that these amides will be
extensively hydroized. At least in the skin.

And so, I think where we are in
agreement is, it looks like on the alkyl
substituted ethanolamines. In other words, the
tertiary amines. Sounds like both teams are
uncomfortable with those for probably the same
reasons, basically. And the alkyl phosphates, I
guess we're also in agreement now, or pretty
close? I mean, the alkyl phosphates, excuse me --
it surprised me, but they haven't been dealt with
and I felt that the phosphate -- alkyl phosphate
chemistry might -- or biology might drive the
effects of those compounds. So I guess, then,
we're left with the amides.

I guess I'm not as comfortable with the
assumption that the amides are going to be
extensively absorbed and hydrolyzed to release
diethanolamine. I'm not comfortable enough with
that to simply exclude them from the report at
this point. So, we could ask for data that
addresses that point, but I don't think I'm ready
to agree to delete them at this point.

DR. BERGFELD: Ron?

DR. SHANK: Then would you have a split
conclusion that the diethanolamine and its salts
are safe, but the amides are insufficient data?

DR. BERGFELD: All right, Don wants to
speak.

DR. BELSITO: Yes. Ron, I'm sure that
you're aware that we've already ruled on the
safety of some of the amide DEA products. We've
already looked at lauramide DEA and oleamide DEA,
and we that plus some additional 13-week dermal --
14-week dermal toxicity studies are in this
report. So, I guess I'm having some issues on how
we could have already ruled on safety if several
of these -- and now you want to take that whole
group out of this report.

So, what is the logic there? Because, I
mean, we've done smaller chains. And if you look at the -- there's a whole probably more than 100 amide DEA materials here. All are going to be larger, they're going to be composed of -- the plant-derived ones as well, that we just ruled on safety. So, I guess I understand what you're saying. But if we had had no data, if we had never looked at them before, I could buy that argument. Having some data and having already ruled on safety of some of them, I have difficulty with it.

DR. BERGFELD: Ron Hill?

DR. HILL: Yes, my logic is, is it even relevant to put all of these amides in here. I mean, what I think we'd find if we had skin hydrolysis data is that we won't be generating diethanolamine. And so the only relevance is actually the DEA impurity in these amides, which I think probably is quite relevant. Halyna assures us that we will be seeing this DEA amide group very shortly, even we take them out of this compound -- or, excuse me, out of this report.
And because the rat metabolism data really suggests that at least for the longer chain ones and probably all the ones -- or maybe almost all the ones that are in here, I have to go back and look at the structure. The metabolism happens at the other end. You get omega, omega -1 through -4 metabolism, and then degenerate that -- what the rat metabolism people call the half-acid amides. And that's probably what happens uniformly.

And then so the major issue becomes the DEA impurity in the amides. And the NTP studies were done with, in some cases, perhaps questionable in terms of the actual content of DEA and the way that these compounds were studied, you're not really sure about the toxicology results. And so I know that the review was done before, but maybe we need to reexamine all of the basis for those conclusions for things beyond sensitization. And I think we're going to come up that everything is fine, as long as the impurity levels are small.
So I just feel like we are including a bunch of ingredients that, in principle, have no relevance whatsoever to DEA on the basis of the potential impurity, because that's probably the main rationale. Not the potential for metabolism in the skin. That's what I think. And so, to me knowing that they're coming again very soon, it would be cleaner -- or to me, it seems cleaner to review thoroughly and get good, solid conclusions on DEA and compounds that actually contain DEA. And then we'd be able to reference that work and feel fairly confident about what was being set when we address things like the dermal penetration of DEA amides that have DEA present as an impurity.

And meanwhile, if somebody has some further information about the definite lack of hydrolysis of these things in the skin, which if somebody doesn't have it already it seemed like they could get that result pretty quickly. Then, we'd be able to make some scientifically firm conclusion.
DR. BERGFELD: Dan, and then Don?

DR. HILL: So, logic is that it's --

they're just not relevant to be in here.

DR. LIEBLER: So, actually having heard Ron's point and thinking about a little bit as he's speaking, I agree, actually. I think that the -- I agree for sort of the same line of reasoning that we would have excluded the tertiary amines. Is that their chemistry and properties are different enough that just because they have the DEA fragment in the structures doesn't mean that they really belong with this group in terms of their properties. And there probably will be significant differences in their metabolism and disposition.

I don't really want to -- I'm not saying that I think that there's anything wrong with these compounds or problems. And I'm not -- I don't think this needs to be contradicting the fact that this panel has already evaluated some of these safe as used. So, I think actually your point, Ron, makes sense. And I agree with that.
DR. BELSITO: Well, in light of the person I rely on for my chemistry and groupings' statement, I have nothing further to say.

DR. MARKS: So, is there a new motion?

DR. BELSITO: Okay. So, yes. Let's go through the list, then. (Laughter)

DR. BERGFELD: Amended.

DR. BELSITO: The new motion is to --

DR. BERGFELD: Seconded.

DR. BELSITO: -- out of the ingredients that we're asked to review -- and I think you've agreed, now, to remove the alkaline PEG phosphate esters, and the disubstituted phosphate esters. We both agreed that the alkyl substituted diethanolamine should be deleted. And we now all agree, I presume -- Paul, Curt -- that the diethanolamide should be deleted.

All of the other ingredients, which is significantly smaller than which we originally started with, will remain in the document. We'll proceed with a conclusion to be safe as used when formulated to be non-irritating. The discussion
would include the inhalation boilerplate that
there should be no nitrosation component. The
carcinogenicity can be done either as a
mechanistic or as Ron point out, with dermal
absorption. And the read across boilerplate would
be in the discussion.

DR. BERGFELD: Is there a second?
DR. MARKS: Second.
DR. BERGFELD: Any further discussion?

Paul and then John.

DR. SNYDER: I was waiting for the
chemistry discussion to --

DR. BERGFELD: Okay.

DR. SNYDER: -- calm down. But to
address Ron's concern about the carcinogenicity,
it's clear that these group of ingredients is
carcinogenic in mice. And I'm fairly confident
that the choline mechanisms -- the most plausible
mechanism, because it occurs at a very high dose
in both males and females. It does not occur in
-- liver cancer does not occur in rats. The rats
carcinogenicity data suggests, as we've seen
previously, that it's only male rats and it's
associated with an increased incidence of the
unique phenomenon of the male rat nephropathy
incidence. So, I don't think that renal cancer is
an issue at all in this, and I think the liver
cancer is specific to mice. So I just wanted to
have that on the record.

DR. BERGFELD: Ron?

DR. SHANK: You dismissed the renal
cancer in the animal models for what reason?

DR. SNYDER: Because it's only in male
rats, and it's coincides with a higher incidence
of the male rat nephropathy of -- incidence of
nephropathy. At least from the data that I
reviewed.

DR. BERGFELD: Well, obviously this will
be taken up again when we re-look at this group.

Any other discussion? John Bailey?

DR. BAILEY: Yes, I think from our
perspective we break this into two parts. One is
that many of these ingredients are salts. Between
diethanolamine and something else. So, if we're
going to review them as discrete ingredients,
which is what we're doing, then both sides of
those salts need to be -- you know, have a safety
assessment. The DEA -- and I assume that's why
you're taking the alkyl and PEF phosphate esters
out, because they haven't had the reviews, so you
can't say the salts are completely safe.

Regarding the amides, these are
covalently bound. They're very stable in general
-- the amides are very stable substances, so I
wouldn't expect them to be a problem. And I
think, you know, the skin absorption would be not
significantly different. So -- but, you know,
that remains to be discussed.

I agree that taking the amides out is
probably the most logical way to approach this.
And that's what I'm hearing that we're going to
do. And regarding the NTP studies, the cocamide,
lauramide, and oleamide -- some of these test
materials had up to 18 percent DEA in them. And
that was not necessarily taken into account by
NTP. So if you're seeing an effect, it could --
you know, it's likely to be because of the DEA and not the amid that's there.

So, I think if you're going to be talking about anything we're probably going to be talking about DEA.

DR. HILL: Yes, actually I had a quick conversation with Monice earlier this morning and she seemed to think that most everything that was in fact observed was correlated with DEA impurity levels in the products that were studied.

One question while we're still open is, on the last page of the table with the structures, the one that we didn't talk about. There is a DEA salt. It's the one called cocoamphodiopropionate. I don't know if the left-hand side -- that the acid component has been reviewed. You have a table, so I guess we could know that. I didn't look about that. But I wondered if that one should stay in or not based on the fact that it is a DEA salt.

DR. BELSITO: Sure.

DR. BERGFELD: Is that a general
agreement to say yes?

DR. BELSITO: Yes.

DR. BERGFELD: All right. So --

MS. FIUME: Cocoamphodipropionate was --

DR. HILL: Was reviewed. Okay, that's what I thought. So, that one could stay in from where I sit.

DR. BERGFELD: All those -- can I call the question now?

DR. BELSITO: Yes.

DR. BERGFELD: All those in favor of going forward with this document as stated please raise your hands. Thank you, unanimous.

I'd like to just step back and remind everyone that these add-on ingredients were supposed to be simple. And this lengthy discussion makes it not simple. So, I'd like to remind you of all that. It's simple esters and salts for the add-ons.

Yes, Dan.

DR. LIEBLER: Well, I guess I have a related point. Is that Alan mentioned the idea of
groupings and arriving at the groupings. And this
was -- this is an example of a large group of
ingredients that the panel has decided to
eliminate big chunks of. And I don't think
there's anything wrong with that process. Maybe
we'll collectively get better at this as the -- as
the science support committee and the expert panel
sort of get the feel of doing this together. But
I don't think what happened here was -- there was
anything wrong with that.

DR. BERGFELD: No.

DR. LIEBLER: It was good outcome. I'd
rather have the panel have the opportunity to
consider more ingredients and then decide to
eliminate some from a report under consideration
for reasons such as we discussed today. So, I
just want to say I'm in favor of erring on the
side of more inclusiveness at the initial stages.

DR. KLAASSEN: And I concur with that.

But I will just beg -- excuse me. I concur with
that, but I will just beg that you do rely on the
chemists and I think I sense that Ivan has a
pretty good chemical acumen. So, we rely fairly
heavily on those people in grouping these, because
--

DR. HILL: And Bart --

DR. KLAASSEN: Well, I know that. No, said the chemists. I was including Bart in that
explicitly, or implicitly, excuse me.

DR. BERGFELD: Curt?

DR. KLAASSEN: Yes, I would just like to
say that this process of adding in them early and
excluding them is so much better than what we used
to. It's kind of add them at the last minute and
then realize that they probably shouldn't have
been added. So, adding them early and then
excluding them is fine. I would agree with the
process in contrast to what we had done in the
past.

DR. BERGFELD: Ron Shank, anything?

DR. SHANK: Nothing to add.

DR. BERGFELD: Okay. Don?

DR. BELSITO: Yes. And, you know, I
think that Ivan and Bart do a wonderful job. But
I think at the end of the day, it's the CIR panel that's being asked to make those decisions. So, while I think their input is crucial as it was for the formaldehyde/methylene glycol, I would just like to reiterate that I would like to see every DEA ingredient. And then, rely on the chemists here to decide whether they should come in and out. Rely on comments from Ivan and Bart and John and any other interested party as to why they should stay or go.

But I would like to see them all, even if there's a feeling on the part of the CIR chemists or the PCPC individuals that they should not be in there. I would still like to see them in the first pass.

DR. BERGFELD: I think it's been said several times, and I think that's what will happen. Thank you.

Going on to the next Green Book, and that's the acrylate crosspolymers, Dr. Marks presenting.

DR. MARKS: A scientific literature
review for these cosmetic ingredients were issued in December of last year. Our team reviewed the available data. This is the first time we saw it, and we moved to issue a tentative report that these ingredients are safe as used in cosmetics.

DR. BERGFELD: Second or comments?

DR. BELSITO: Comment?

DR. BERGFELD: Yes, go ahead.

DR. BELSITO: We were struck on page 3 or Panel Book page 9 by the benzine impurities in carbachol 1342. The specifications state that it can contain 0.5 percent max of residual benzine. Monice was nice enough to pull a material safety data sheet on carbachol 1342, and it indicates that to -- it can be produced at 0.1 percent maximum as benzine -- as required by Canada, the EU, and Korea with no further information there. But this is only from one manufacturer.

So, we had actually thought that we would like to go insufficient on these acrylate crosspolymers at this time to get clarification regarding the level of benzine. Dr. Bailey had
indicated that that was perhaps an old
manufacturing method that was no longer applicable
to the current way that these cross-linked
acrylate polymers are produced. But this is the
first time we're seeing it. So, we would like to
go insufficient for impurities, specifically
benzine.

DR. BERGFELD: Tom?

DR. SLAGA: I agree that would be
worthwhile doing.

DR. MARKS: I withdraw our team's
motion. And we'll second the motion of Dr.
Belsito's team.

DR. BERGFELD: To go insufficient? John
Bailey?

DR. BAILEY: Why can't we go with
Monice's find on the MSDS sheet, which was .01
percent, right?

DR. BELSITO: 0.1.

DR. BAILEY: 0.1.

MS. FIUME: For the EU. It didn't give
for the U.S. For the U.S., the main impurity
specification says.5 max with a footnote from EU, Canada, and Korea. So that.5 max is sort of hanging out there in the air, unless it's addressed in a different manner.

DR. BAILEY: But if the panel issues a tentative report that restricts benzine impurities to 0.1 percent, then it's not hanging in the air anymore.

DR. BELSITO: You know, we certainly could do that. I mean, the highest level of use is 6 percent in an eye care product. So that's the highest. So, I don't -- I'm not a benzine toxicologist, so I throw that out. So.1 percent benzine in the product, maximum use at 6 percent is -- does anyone perceive that that would be a problem?

If not, then hopefully we can get the data to support that and we can go ahead with the safe as used conclusion.

DR. BERGFELD: Ron Hill?

DR. HILL: Yes, I wanted to raise one more while we were on the subject of impurities.
On same page of the book, under impurities. The last sentence in the first section says the residual monomer content of acrylates, blah, blah, blah, blah, is typically less than 2,500 ppm acrylic acid and 500 ppm residual ester. So, it has the word "typically." And I had a note that I wrote here that said, we really need this information for all the acrylates because acrylate esters are not something we want to be having dermally absorbed in high concentrations, I think. And we didn't really have that.

So, from -- I wondered if anybody else had that same concern.

DR. MARKS: I thought we had addressed that. We were going to address it in a discussion, we didn't get to editorial comments. But the -- would be monomer impurities, and that they've been addressed in previous CIR reports.

DR. HILL: Okay, I think that's the way it was dealt with, yes. I just --

DR. MARKS: So that was going to be in the discussion. But if we still go back to how
are we going to move forward, and the -- Don, you made the motion to insufficient. Do we want to change that? Our team made a motion to safe. Do we want to do a safe with a limit of benzine?

DR. BELSITO: I think --

DR. BERGFELD: Either way, you have to withdraw the motion.

DR. BELSITO: I didn't make the motion.

DR. BERGFELD: Yes, you did.

Insufficient was the motion. And Jim was seconding it.

DR. BELSITO: Okay.

DR. BERGFELD: No one seconded his --

DR. BELSITO: No, Dr. Marks' initial motion was safe as used.

DR. BERGFELD: Nobody seconded.

DR. BELSITO: Oh, okay. Someone seconded mine?

DR. MARKS: Yes, I did.

DR. BELSITO: Oh, good. Okay.

(Laughter) Whoa, okay. So, again, I throw it -- it's not my area of expertise. I'm telling you
that they -- in Europe, they can limit to 0.1. We
don't have any information as to how they came up
with that magic number, though the maximum
concentration of use is limited here, 6 percent in
eye products.

So those of you who know about benzine
toxicity, if you're prepared to do the math today
and sign off on it, I'm comfortable with it. In
terms of skin sensitization, yadda, yadda, yadda,
I'm comfortable. I can't comment on benzine
toxicity at that level.

DR. SLAGA: Can't we --

DR. BERGFELD: Tom.

DR. SLAGA: -- look at the data,
continue with this motion but get the European
data -- the EU data and look at why they came up
with 0.1?

I mean, first thought -- you know, 6
percent of 0.1 is very, very small and more likely
would have no carcinogenic or any other effect.
But they probably already made the calculation.
And why don't we just look at it?
DR. BELSITO: So, do you want to go safe as used when benzine impurity in the material is less than .1, or do you want to go insufficient --

DR. SLAGA: Insufficient until we get comparison --

DR. BELSITO: I'm fine --

DR. SLAGA: -- and see what kind of calculations they made.

DR. BELSITO: I'm fine either way. I think there are probably no safety issues, so delaying the final on this report -- I think, don't think --

DR. SLAGA: Right --

DR. BELSITO: -- it's going to be a big deal.

DR. BERGFELD: Ron Shank?

DR. SHANK: So, your motion is --

DR. BELSITO: Insufficient for impurities, specifically benzine.

DR. SHANK: -- insufficient for -- and what do you want? Is --

DR. BELSITO: I want to know what --
DR. SHANK: How much is in there or how much --

DR. BELSITO: How much is in there, and I want some benzine toxicity brought in. I want information as to why the Europeans decided to regulate it at 1. Where they got that information that allowed them to set that limit.

DR. SHANK: Okay.

DR. BERGFELD: Ron Hill, okay? Dan?

DR. LIEBLER: Yes, I like that approach.

DR. BERGFELD: Paul? Curt?

DR. KLAASSEN: Yes.

DR. BERGFELD: How about John Bailey?

DR. BAILEY: You know, I hate to continue this on for another meeting, but I think it's a reasonable request and we'll certainly do our best to get the information.

DR. BERGFELD: Thank you. So, we have a motion. We had a second. Any other discussion?

Seeing none -- yes, Monice.

MS. FIUME: I just want to clarify. So it's an insufficient data announcement --
DR. BELSITO: Right.

DR. BERGFELD: Call for the question.

All those in favor, raise your hands. Thank you, unanimous.

Moving on to last two ingredients, the first of which would be Disperse Blue. Dr. Belsito, in the Buff Book.

DR. BELSITO: Yes. We had looked at this as a re-review and decided not to reopen our original safety assessment that it was safe as used. The re-review summary was beautiful, it gave all the various margin of safety scenarios that could be conceivably thought of for this product. They were always within good margin of safety, and we're fine. We're just signing off on it.

DR. BERGFELD: Is that a motion, then?

DR. BELSITO: It's a motion.

DR. BERGFELD: Second?

DR. MARKS: Second.

DR. BERGFELD: Any further discussion regarding the Disperse Blue? None? All those in
favor, indicate by raising your hands? Unanimous.

Then the last ingredient, that is the quaternium-15, Dr. Marks.

DR. MARKS: First thing I'd like to ask is, Alan, why did you give me two ingredients with formaldehyde? But at any rate, in 1986, we published an original assessment of quaternium-15 as safe. And then in 2008, we reopened this assessment and amended it to have a conclusion with a limit of 0.2 percent.

Since that time, conclusion -- there's been -- during the original assessment and the amended assessment, there has been a question as to the quaternium-15 really release formaldehyde. And there was a paper that Dr. Belsito and colleague authored showing the co-reactivity of quaternium-15 and formaldehyde, which would suggest, indeed, there was free formaldehyde released. And Dr. George Hazelton yesterday from Dow Chemical confirmed that, so we're presented with the issue of now we really do know that formaldehyde is released.
But in spite of all that data and -- or, I should say, this new data -- our team felt that the 2008 conclusion with a limit of 0.2 percent, which was really based on sensitivity concerns, is still relevant and we decided not to reopen it. So I will move that not reopen quaternium-15.

DR. BELSITO: Second.

DR. BERGFELD: Second. Any discussion? Don?

DR. BELSITO: Yes, in not reopening it, as we discussed, I think it's not so much that my paper showed co-reactivity, but simply that there were three articles that demonstrated release of formaldehyde that were not incorporated in our quaternium-15. And we had, in our discussion, stated we're lifting the formaldehyde limit because it didn't release quaternium-15, which clearly is an error. And we look foolish with that current document, so we need to point out that there is release. However, at a level of 0.2 percent, any restrictions we place on formaldehyde
are not going to be an issue except hairspray use.

And there is a hairspray use for quaternium-15. I think we need to finesse that in the discussion, because it's like \(0.00000008\) or something like that, so.

DR. MARKS: Two.

DR. BELSITO: Yes. So --

DR. MARKS: And we felt the same.

DR. BELSITO: So, do not reopen, but we need to finesse the hairspray use given the concentration and the fact that we can drop formaldehyde because of a restriction that we put on the actual ingredient.

DR. MARKS: We concur. The discussion we should be very robust in discussing the chemistry of formaldehyde now that we know that much better. And that we should do a calculation of how much formaldehyde is released by quaternium-15, and then I would drop the word "finesse." I would say we will just mention that the amount of formaldehyde released would be so low in that hairspray because the concentration of
quaternium-15 is so low.

DR. BERGFELD: Any other discussion or
points to be made? John Bailey, anything? No.
Seeing none I'll call for the question.
All those in favor, please indicate by raising
your hands. Thank you.

I'd like to remind you that we may
revisit quaternium-15 depending on how we act on
the formaldehyde/methylene glycol group. So, you
may be revisiting it.

DR. MARKS: Would you assign that to
Belsito next time? (Laughter)

DR. BERGFELD: We're going to go on to
the last item that we have here, and this is the
boilerplate language. And Halyna had put together
a beautiful summary of what we consider the
boilerplates and some history, and there were
many, many comments regarding how to enhance that
piece. And Alan's going to discuss it.

DR. ANDERSEN: Yes, I think the specific
language -- we would be pleased to receive any
further input from the panel or other interested
party on further improving. But the -- we wanted to make sure that the strategy was clear. We have many circumstances where the same issues come up over and over again. And it is very useful to have a consistent approach to talking about those issues.

We have, over time, learned to be brief in so doing. And we will intend to continue trying to find better ways of being succinct in making these points, because frankly we're saying them a lot of times. And certainly, the Journal gets tired of repeating long paragraphs in review after review. So, we're shortening them, making them more targeted, and we will -- the intent was simply to continue to do that with the panel's assistance.

And it's good to have captured the examples we have so far where you can see the old version and you can see the shorter version. And as I took home the message yesterday from each team's discussion of it, there really isn't anything lost by being shorter and more concise
and having tailored language for the body of a
report different from what goes into a discussion.
We're moving along to better use of language to
say what it is we want to say.

The other piece that came up that I
think is worth mentioning is that we will have
more opportunities to follow similar pattern that
we did with hair dye epidemiology. Right now,
when we review a hair dye, we make a short comment
about hair dye epidemiology data in the report.
But basically we are referring the reader to the
website where there is an extensive discussion of
those data. And that seems to be really a much
more worthwhile way to approach it. We can keep
the information current on the website. It well
serves the reader, and it doesn't bog the reader
down in a long discussion. And it doesn't put us
in Dutch with the Journal editor who says, why are
you again giving me this long discussion?

So, if we can do that more, we will try
to do that more.

DR. BERGFELD: Curt?
DR. KLAASSEN: I think in general that's -- this is very good. But there is one thing that -- let's say 20 years from now a person comes back to look at this report and it says go to the website to find out about something, and that website has continued to change over the next 20 years. And so the reference that we have there today will not be there 20 years from today. And the logic will not follow -- will not -- might not follow.

That's the one thing that's kind of bad about things changing in contrast to our old references that are in black and white and print. They're always there. You can go back and look at them. So that's the only concern.

DR. ANDERSEN: Yes, I think your point is well taken, Curt. The hair dye model in implementation and in philosophy, I think we would want to ensure it continues.

The panel sense is that the available data simply aren't sufficient to support a causal relationship between hair dye use and cancer.
That's the fundamental message. And as long as that message remains what the panel wants to say in the report, then whether it's the website in 2008, 2009, 2010, that website will be updated. As long as your conclusion about those data is still, they're insufficient to support there being a causal link. Then I don't think we have misled the public. We've actually updated to be consistent.

When we get to the point where we have to say fiddlesticks, maybe these new studies do suggest something. Then, I think, we have a departure and we would have to do something dramatic so that the reader didn't miss that something is changed.

DR. BERGFELD: I'd like to make a comment then, John. It was also suggested that perhaps the yearly compendium could include these boilerplates. And the second part of that was that we should put them out for public opinion just to see what the input of the receiver might be or the industry might be on these. And that
this could become a document that was published
and become in the published literature. Actually,
at certain times -- so, I'd like to make that
suggestion.

Don?

DR. BELSITO: Well, I think there are a
couple of ways around the issue that Curt ruled.
First, I think you could call it the boilerplate
as crafted in whatever year. And if there were
different changes to it, you could then have the
boilerplate as crafted in whatever year. And
always keep those online.

And then as Alan said, if we get to the
point where we go, oh, fiddlesticks, I think that
that would automatically generate a review of
every single ingredient where we use that
boilerplate. So then there would be a huge
substantive change.

So I'm not that concerned about it
because even if it evolves and there's more
information in 2020 than there was in 2010,
presumably the intent of that boilerplate -- what
that conclusion was has not changed. Because if
it does then, again, we're reviewing every single
document where we used it.

DR. BERGFELD: Ron Hill? Then John

Bailey.

DR. HILL: And there's kind of an
analogy, too. I mean, when somebody does a set of
calculations and they use a software package and
it will say, this software package is done with
version 2.3, then somewhere along the line there
becomes a version 3 and version 4. We have a way
of knowing that the method that was used might
have changed based on updates in the software.
And I think as long as there's some sort of
analogy to track changes or using the boilerplate
from this year, then everything will be good. But
I think we do need to -- either through publishing
in the compendia or keep in the old versions and
making sure we reference, you know, the year,
we've covered it.

DR. BERGFELD: John Bailey.

DR. BAILEY: Yes. I think keeping the
old versions and having those available as a
collection would be a very wise thing. I also
think this is a very important effort. And I
certainly -- we're going to have our science and
support committee, you know, strongly engaged in,
you know, what this says and how it says it. And
I think public comment is not a bad thing for
this.

DR. BERGFELD: Any other comments as we
close our meeting? If not, I look forward to
seeing everyone in June, June 27th and 28th. And
to remember that our celebration for the 35th year
will be held in September, not in June.

So, hopefully the spring will be
delightful for all of you. Huh?

SPEAKER: Nice try.

SPEAKER: Key West.

(Whereupon, at 10:08 a.m., the
PROCEEDINGS were adjourned.)
CERTIFICATE OF NOTARY PUBLIC

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

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