BLUE BOOK 2

Propylene Glycol

CIR EXPERT PANEL MEETING
JUNE 28-29, 2010

Cosmetic Ingredient Review
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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Monice M. Fiume *MMF*
Scientific Analyst/Writer

Date: June 28, 2010

Subject: Draft Final Amended Report on Propylene Glycol, PPGs, and Tripropylene Glycol

The Panel reopened the safety assessment of Propylene Glycol and Polypropylene Glycols, to amend the conclusion to acknowledge the safety of use concentrations higher than the 50% limit stated in the original 1994 safety assessment and to add unreviewed polypropylene glycols (PPGs) and Tripropylene Glycol.
At the April 2010 meeting, the Expert Panel issued a Tentative Amended Report on Propylene Glycol, PPGs, and Tripropylene Glycol. It was concluded that Propylene Glycol, all PPG currently in the *International Cosmetic Ingredient Dictionary and Handbook*, any PPGs added in the future, and Tripropylene Glycol are safe as used when formulated to be non-irritating.

The Personal Care Products Council provided information regarding the amount of propylene oxide in PPGs used to make finished cosmetic products. That information is now included in the 'Impurities' section, and the memo is part of this submission.

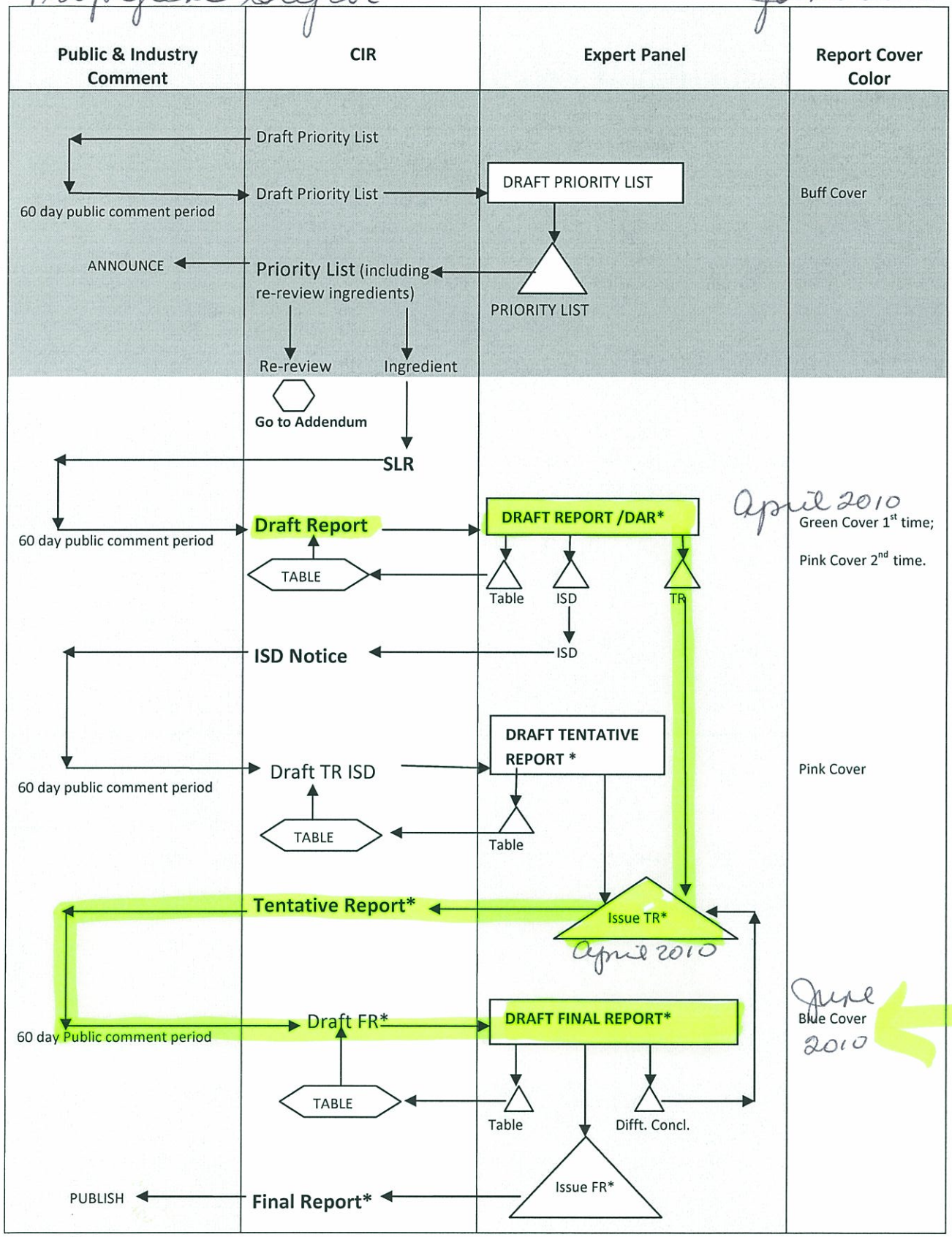
The draft Final Amended Report has been prepared for your approval.

This book contains everything you need to review this report: administrative tab (cover memo, flow chart, history, search strategy); transcript tab (transcript excerpt); report tab (draft final report); and data tab (industry data).

Reports and Data available online at http://www.cir-safety.org/jun10.shtml in .pdf of blue book 2.

SAFETY ASSESSMENT FLOW CHART

Propylene Glycol — June 2010



* For ingredient groups originating as Re-Reviews, add word "Amended" before Report; (DAR: Draft Amended Report).

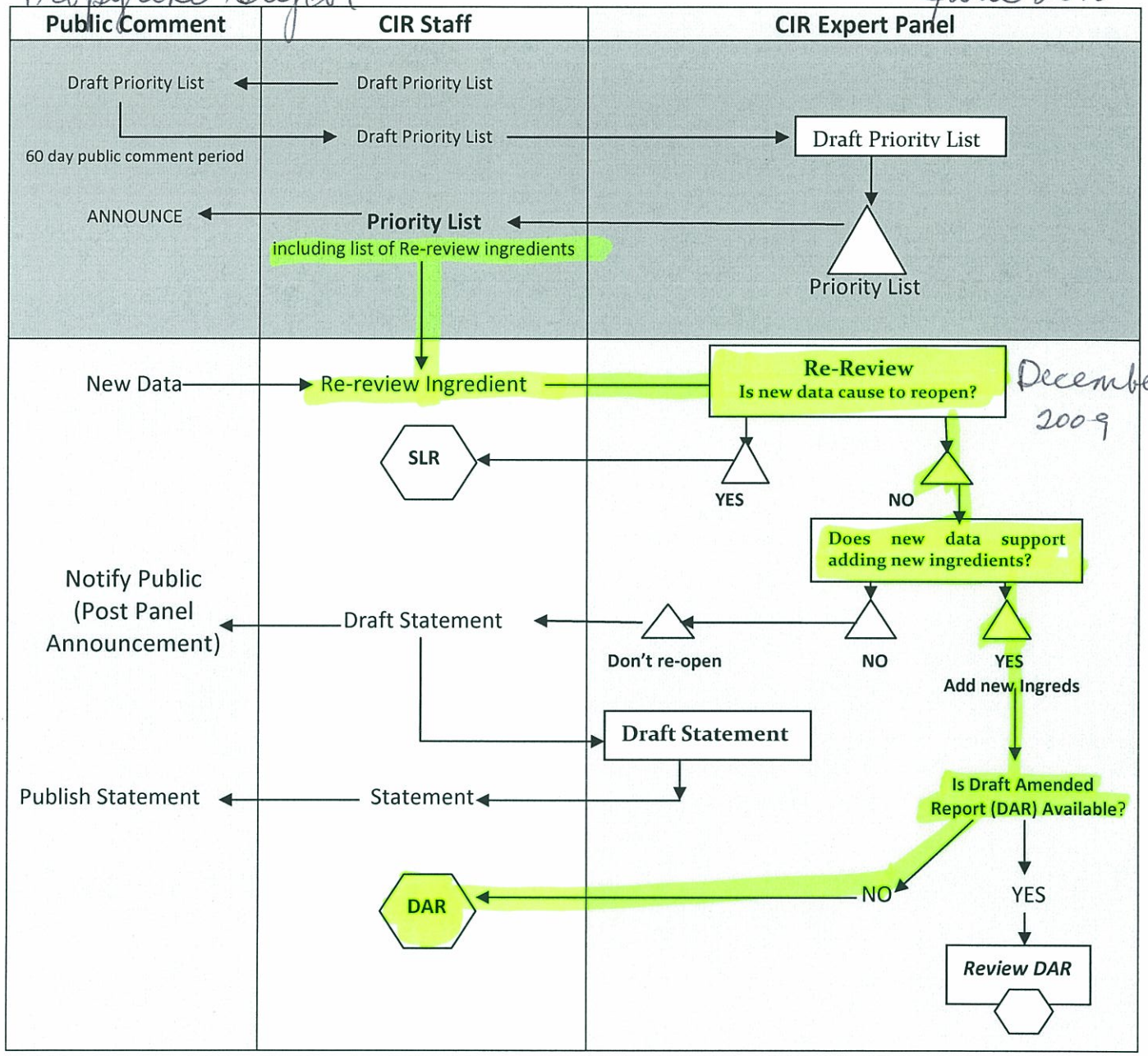
△ Expert Panel Decision

▭ Document for Panel Review

SAFETY ASSESMENT FLOW CHART: RE-REVIEW ADDENDUM

Propylene Glycol

June 2010



△ CIR Expert Panel Decision Points

▭ Document for Panel Review

⬡ Go To Safety Assessment Flow Chart

CIR Report History for Propylene Glycol

Original Assessment: 1994
Final Report on the Safety Assessment of Propylene Glycol and Polypropylene Glycols (PPGs) published in 1994 with the conclusion that these ingredients were "safe for use in cosmetic products at concentrations up to 50.0%." According to past minutes of proceedings discussing propylene glycol (46th meeting of the Expert Panel, March 18-19, 1993), the 50% concentration limit was based on skin irritation data, which at that time Dr. Elder described as "weak" data.

ReReview: December 7-8, 2009
The rereview was brought before the Expert Panel, with updated frequency and concentration of use data, which included use in a deodorant at 73%, additional unpublished data, as well as a request from the Council's CIR Science and Support Committee Expert Panel that the report by reopened. The Panel decided to reopen the assessment on propylene glycol to consider the increased concentration of use and to include all polypropylene glycols used in cosmetics as well as tripropylene glycol.

The Panel stated that additional data are needed to address the issue of irritation and sensitization at the high concentrations used in deodorant products. The data provided did not unequivocally establish an absence of dermal sensitization, and, while a separate maximization test appeared to be negative, the number of subjects was low. Additional subjects in an underarm deodorant use test (75 or more subjects) with Propylene Glycol at the highest use concentration in a deodorant product may yield data to resolve these questions.

In addition, industry should confirm current practices regarding limiting the levels of propylene oxide impurities to less than detectable amounts and CIR staff should include language in the discussion section regarding the ability of these ingredients to enhance dermal penetration of other chemicals.

Draft Amended Report: April 4-5, 2010
Additional data satisfactorily addressed any concerns regarding the concentration of use in deodorants and irritation and sensitization. Also, the Council provided information regarding the amount of propylene oxide in PPGs used to make finished products.

The Panel issued a Tentative Amended Report with the conclusion that PG, the PPGs, and subsequent PPGs that may be added to the Dictionary, and tripropylene glycol are safe as used when formulated to be non-irritating.

SEARCH STRATEGY

PROPYLENE GLYCOL, PPGs, TRIPROPYLENE GLYCOL

Toxline (8/25/09)
Propylene Glycol (year 1990+) – 2144
PPG – 89
Tripropylene Glycol – 63

Toxline (updated 2./20/10 years 2009-2010)
Propylene Glycol – 82
PPG – 2
Tripropylene Glycol – 1

Searched all preliminary databases/reference sources in August 2009

UPDATED SEARCH IN PREP FOR JUNE 2010 PANEL MEETING
Toxline searched – 5/11/10 (only for entries made in the last 3 mos)

Propylene Glycol – 6
PPGs – 1
Tripropylene Glycol – 0

No relevant data were found.

these additions.

DR. MARKS: Okay. Next, propylene glycol. So, in '94, a final report was issued. Then at the December -- that these glycols were safe in cosmetic products at concentrations up to 50 percent. And at the December meeting, the panel was informed it was being used greater than 50 percent. We are at the point now of issuing a tentative amended report. We've received an HRIPT with an antiperspirant formulation containing 86 percent propylene glycol and there was no evidence of sensitization. So, that was the concern as to address the issues -- the issue of sensitization. And now, the increased concentration in use.

So, I think we can issue a tentative amended report that's safe as used, and delete the 50 percent concentration in the previous conclusion.

Any comments? Any editorial things that need to be addressed in the report? It's really -- again, I think the format, the way you present the books with the administrated transcripts,

reports, and data is very nice. And it's nice, also, to have the report when it's edited, the lines on either side so we can focus on those.

I guess one of the comments I have in the abstract, it says propylene glycol is relatively non-toxic and is non-carcinogenic. Is -- does relatively non-toxic run as -- is that fine with you? I guess it depends on your relativity. When I read that, I'm wondering --

DR. SHANK: (inaudible)

DR. MARKS: Yeah, yeah.

DR. HILL: And there was the issue I flagged last time, which was that the original conclusion was based on 5 ppm or less of propylene oxide in the finished product. And I had made the comment that that was in 1994. Do we still have assurance that manufacturing is being done up to snuff so that that's still in fact the case?

DR. ANDERSEN: I think the discussion ought to capture that the panel expects that that practice has continued.

DR. HILL: And that's what I was looking

for.

DR. ANDERSEN: Yeah.

DR. HILL: And I'm not sure it made it into the discussion. So, if you --

MS. FIUME: I just wanted to point out. We went back to try and find that information and besides being in a letter from Dow, that was not -- we were not able to find that. According to Dow's website -- and I do have a typo on page 2, it should be 0.008 -- according to USP the USP grade propylene glycol that is manufactured by Dow contains diethylene glycol and ethylene glycol at concentrations that are non-detectable, which is the quantification limit of.008 percent weight by weight.

We could not find anything regarding that other impurity.

DR. HILL: Propylene oxide?

MS. FIUME: Propylene oxide.

DR. HILL: Yeah, because I'm not the least bit concerned about those.

MS. FIUME: Right, no. We found nothing

on propylene oxide as it even being in there.

DR. ANDERSEN: Other than that original letter.

MS. FIUME: Other than that original letter.

DR. HILL: Well, and I believe the letter from Dow.

MS. FIUME: But according to the USP and looking back at any USP information that I can find, it doesn't even mention propylene oxide in its specifications.

DR. HILL: Yeah. But --

DR. ANDERSEN: Well, but I think -- if I can take Ron's comment all the way around -- since the industry has asserted that it manufactures to a limit, we can throw that back at them and say, we expect that performance to continue.

DR. HILL: That was my hope.

DR. MARKS: So, you capture that in the -- do you want me to mention that tomorrow? I think that's an important point you have.

So you would have it -- how, Ron, I can

get with you later in terms of that -- you expect that propylene glycol to be at the same maximum concentration as with diethylene glycol and ethylene glycol? Would that -- no?

DR. ANDERSEN: Propylene oxide. Got to get the amine out.

DR. MARKS: Yeah, I'm sorry --

DR. ANDERSEN: Was reported to be present at a limit of 0.4, was it, percent? Whatever was in that letter, but -- and the Panel expects industry to continue --

DR. HILL: To manufacture consistent with that standard, yeah. And that number was --

DR. ANSELL: It's -- the letter states 800 ppm, but it's been corrected to 80 ppm.

DR. HILL: Okay.

DR. ANSELL: And industry performance is currently better than that.

DR. HILL: 80 ppm? 8-0 ppm?

DR. ANSELL: For PO, yes, so.

DR. HILL: Because you -- because this transcript -- maybe it's inaccurate -- on page 90

says, how it shook out is that Dow USA recognizes that the USP now allows up to 5 ppm propylene oxide. You said that that could not be verified, couldn't find any documentation to that effect? Okay.

Of the opinion that typical levels contained in products today are less than detectable amounts. And of course what was detectable in 1994 is different than it is today, that's a fact. But 80 is a lot higher number, so that sort of surprises me.

DR. MARKS: Does that raise a concern? Ron -- no.

DR. HILL: That information you had was also from Dow?

DR. ANSELL: I don't know --

DR. MARKS: Jay --

DR. ANSELL: The information I have in terms of the error was in the Dow letter. The information reported to us was just a member has recently reported in the PPGs -- 2 members have reported less than 10 ppm.

DR. HILL: Less than 10 ppm? But I heard you say 80, you said --

DR. ANSELL: Right. The original number to the Dow letter was 80. Today, they're down to less than 80.

DR. HILL: Less than --

DR. ANSELL: Yeah, 2 members report in the 10 ppm range.

DR. HILL: 10 ppm.

DR. MARKS: 10 ppm is still probably okay. I don't know about 80. It's starting to work it's way up there for propylene oxide.

MS. FIUME: Dr. Ansell, do we have -- was that submitted to CIR at all? Because I don't have anything on a propylene oxide impurity.

DR. ANSELL: I'm sure that can be arranged.

DR. MARKS: So, we'll make the editorial comment that we expect the manufacturer of propylene glycol to have a propylene oxide impurity of less than 10 parts per million, since that's what we have a letter that would support

that?

DR. HILL: And that will go out for comment, right? I mean, basically that's going to --

DR. MARKS: No, this goes --

DR. ANSELL: Yeah, but not as a specification.

DR. MARKS: No, no, this is not in the conclusion. This would be in the discussion that we note this impurity and that we have evidence to support the fact that there will be -- that toxicity or impurity will be less than 10 parts per million.

Okay. Any other comments?

DR. BERGFELD: Just a question. Yeah, I want to ask a question. On page 15, the paragraph just before draft amended conclusion dealing with the aerosols? And earlier today we decided that something of a bead -- I think it was ppm?

DR. ANDERSEN: PMMA --

DR. BERGFELD: PMMA was a bead but was in a formulation. And because it was in the

formulation, the particle size would be larger, it would not be aerosolized. So I'm wondering, if that captures that specific chemical species, the concentration, and the duration of exposure? The fact that when you put it in some mixtures, you change the particle size.

Doesn't seem to me it does.

DR. ANDERSEN: I get your point. We'll take a look at that and make sure that the boilerplate accommodates the question of the starting material size.

DR. MARKS: Okay, any other comments? Any other ingredients? I think we can adjourn for today.

DR. SHANK: Can we just leave our (inaudible)?

DR. ANDERSEN: That's my understanding, that you may leave your books here.

(Whereupon, at 2:42 p.m., the PROCEEDINGS were adjourned.)

* * * * *

DR. BRESLAWEC: There is one, if you will, that we will not incorporate. This also applies to a couple of others. The structures. We've been asked to provide a reference for the structures. And we've made kind of a categorical decision after some discussion not to provide structures for -- not to provide citations for structures unless there's a reason to. And a reason could be where there's a variation or difference between the structure presented in one dictionary as opposed to the CAS file or something like that. But other than that we will not be routinely providing citations for structures.

DR. BELSITO: Okay. Okay. Propylene glycols and polypropylene glycols. This is Pink 2.

Okay. So at the last meeting we decided to reopen it in part because we previously had concentrations only up to 50 percent and now found that there were concentrations greater than 50 percent. And also to include all the rest of the long chain polypropylene glycols that were found

in the dictionary in the handbook. And the major hang up in doing that and the increase was the reported use of one of these products up to 73 percent in a deodorant. And we did receive an HRIPT on 99 subjects looking at sensitization potential in an antiperspirant with 86 percent propylene glycol, which I think pretty much answered the major hang up in the question we had about this. So I think safe as used. I have some editorial comments here, but I think all of the major issue that we had asked for has been clarified.

DR. SNYDER: Agree.

DR. BELSITO: Paul?

DR. SNYDER: Yes.

DR. BELSITO: Okay.

DR. SNYDER: So was there (inaudible) did not include butylene glycol in the discussion?

MS. FIUME: Butylene glycol?

DR. SNYDER: Yeah.

DR. EISENMANN: It's already been reviewed in a different report.

MS. FIUME: Butylene glycol is in a different report. This is just propylene glycol, polypropylene glycols, and tripropylene glycol.

DR. BELSITO: Monice, on page 4, one, two, three, four, five, six lines up from the dermal penetration enhancement, it says 15-minute measurements were performed every 25 minutes.

MS. FIUME: This -- because I wasn't very familiar, so what's in here is as it was in the paper.

DR. BELSITO: Well, (inaudible) we said 15-minute measurements were made every 25 minutes.

MS. FIUME: I will double-check that.

DR. BELSITO: Just double-check that that wasn't --

DR. LIEBLER: I think the measurement took 15 minutes to accomplish. So every 25 minutes they started a measurement. That's the way I interpret it. And it took 15 minutes to complete the measurement. So they could rest for 10 minutes and then start another one.

DR. BELSITO: That's fine if that's what

it was. It just -- when I read it, it was like, okay.

On page 8, under Embryo Toxicity Propylene Glycol, the last line of that first paragraph, what is MI? MI or diploid oocytes were not found.

DR. SNYDER: That's a metaphase. Metaphase 1.

SPEAKER: Metaphase 1.

DR. SNYDER: That's a staging of the oocyte.

DR. BELSITO: Okay.

DR. SNYDER: She has up there define metaphase 2, mouse metaphase 2, M2 oocytes.

DR. BELSITO: Okay.

DR. SNYDER: On the next page, on page 9, again this is kind of the same thing I was talking with Bart that the italicized under Carcinogenicity, it talked about an study where rats were given 50,000 parts per million in the diet. We need to split those into a two-year study or, you know, with a typical bioassay study

or carcinogenicity study or what. So just a little bit more detail so we can -- don't have to go look at the old report.

And then on page 11, I could not -- where did the 73 percent sensitization number come from? Because I looked at the data that we received and I only found it at 35, 65.2, and 65.8. I did not see a 73 percent study.

DR. EISENMANN: That was -- we got that the last time.

MS. FIUME: That was at the last meeting. So that would have been in --

DR. EISENMANN: It was a new study. It was a (inaudible) study that he wanted more people (inaudible).

MS. FIUME: So the new information was incorporated, but that was in a Clinical Research Laboratory study that was provided at the last meeting.

DR. SNYDER: Okay. Because -- then why didn't --

MS. FIUME: So that paragraph took that

information and built on it with the new studies that were received.

DR. SNYDER: Okay.

MS. FIUME: And being that they were similar they were all put into one paragraph for brevity because they all follow pretty much the same protocol.

DR. SNYDER: But then we did have another study at 65.8. Should we include that one then, list that one in there? 65.8? Because currently, you know, currently it's on this --

MS. FIUME: It's further down. It was a different study protocol, so that's the --

DR. BELSITO: It's there from the last --

MS. FIUME: -- last sentence of that paragraph.

DR. BELSITO: Deodorant still contains 65.8.

DR. SNYDER: Oh, okay.

MS. FIUME: Its procedure was slightly different so that's why it's separated.

DR. BELSITO: I gotcha.

MS. FIUME: Now, one of the panel -- one of the council comments (inaudible) is about adding -- with the 35 percent -- the 20 percent butylene glycol also existed in the formulation. Do you agree that you would want that in text?

DR. SNYDER: Say it again. I'm sorry.

MS. FIUME: In the use study 35 percent propylene glycol was in the formulation, additionally there was 20 percent butylene glycol in that formulation.

DR. SNYDER: Right.

MS. FIUME: Do you want that indicated?

DR. SNYDER: That's what I was -- that's what I was raising. I mean, I thought --

MS. FIUME: It's a separate ingredient and that's why I don't have it included in here.

DR. SNYDER: Do you think that's important to include that? Okay, all right.

SPEAKER: I think it would be --

DR. BELSITO: (inaudible) concern is not butylene glycol.

DR. EISENMANN: I just thought because they're structurally related.

DR. SNYDER: Well, I think we should at least capture in the discussion saying that butylene glycol has been previously reviewed. Right?

DR. BELSITO: So what is -- the council's point is if it's 30 percent propylene glycol plus 20 percent butylene glycol, then that sort of gives increased support to above 50 percent?

DR. EISENMANN: Yeah, and that was also before we got the HRIPT, too.

DR. BELSITO: Right. Okay.

MS. FIUME: So you would like that included?

DR. BELSITO: No, I mean, I think because we have the higher percentage of pure propylene glycol it could potentially confuse a reader who suddenly sees butylene glycol into thinking that somehow we're including butylene glycol in this report and we're not. So I would

just keep it out. I mean, at this point it doesn't add anything more to the report. We have 68.5. We have 73 percent. I think we have what we want.

Any other comments?

DR. EISENMANN: You did see the statement in the introduction that says that the report is intending to address the safety of all chain lengths that may be added to the dictionary?

DR. BELSITO: Yeah. I mean, you're not going to go much lower than three, are you?

DR. EISENMANN: I just --

DR. BELSITO: We're at one already. Propylene glycol. I don't have a problem with the higher ones.

DR. EISENMANN: I want to make sure you're okay with that so then later on when propylene glycol is added I can automatically just put safe.

DR. BELSITO: Yes.

DR. EISENMANN: Okay. I don't know if you want to move that statement also in the

discussion and the conclusion?

DR. BELSITO: I think the conclusion -- oh, tough.

DR. SNYDER: Yeah, I don't think we can go there.

DR. BELSITO: I don't think we can go there with the conclusion. But I think in the discussion we can say if, you know, additional chain lengths are introduced, assuming that they are used, you know, similarly and the same concentration range, we would assume they're safe as used based upon the fact, I mean, it's not like we're going down. It's not like we've reviewed, you know, PPG 100 and we're saying all, you know, we've reviewed the parent molecule, propylene glycol. Pretty much found it safe for use up to 73 percent. I mean, what are we going to be concerned about with longer chains?

MS. FIUME: And that is -- actually there is a statement in the draft discussion. In the first paragraph, the last sentence does say it's intended to address the safety of similar

PPGs that may be added in the future.

DR. BELSITO: Yeah. That's fine.

DR. BAILEY: And the conclusion does have the footnote.

DR. BELSITO: Yeah. Yeah. And that's fine. Good. Any other comments? Okay. Wow.

DR. BRESLAWEC: So your recommendation on this is?

DR. BELSITO: Safe as used. It's final. Moving on to tentative final safe as used. Blue book next time.

Okay. Another re-review in Buff 2. Stearyl heptanoate. Next to the last tab. Okay. So this safety assessment was published in '95. It was safe as used. There are no new safety data. And search for TOXNET did not find data on any new data. And then search of the dictionary revealed some possible add-ons. Basically stearyl heptanoate is an ester of stearyl alcohol and heptanoic acid. So what other stearyl esters were out there that we haven't reviewed yet? And the answer is there's caprylate, palmitate, stearate,

DR. BERGFELD: So you're seconding the motion?

DR. BELSITO: I'll second it.

DR. BERGFELD: Is there any other discussion? Then I'm going to call for the vote. All those in favor of an insufficient data announcement? Unanimous. Thank you very much. I think that's a good precedent that you just set.

Moving on to Dr. Belsito on propylene glycols.

DR. BELSITO: Yes, propylene glycol. At the last meeting we decided to reopen this because previously there was a concentration of uses less than 50 percent and now there were significant increases and concentration greater than 50 percent particularly in underarm deodorants that concerned us. While we were reopening it we decided to add in all of the other long-chain polypropylene glycols, sort of a no-brainer since we were looking at propylene glycol itself, and also made a decision that based upon the data we might see that we could say that should there be

additional polypropylene glycols introduced into the dictionary in the future, those would be safe based upon the data we looked at.

So we got all of that data. We got an HRIPT on 99 subjects that looked at sensitization potential for a perspirant containing 86 percent propylene glycol and that was negative, so we felt that we could go with a final with this safe as used.

DR. BERGFELD: That's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: Is there any other discussion? We need a second.

DR. MARKS: We also felt it's safe. As a procedural issue, are we issuing a final or are we issuing a tentative amended report?

DR. BERGFELD: Dr. Andersen? What are we issuing?

DR. ANDERSEN: I think it's a tentative amended report.

DR. BELSITO: We're issuing a TAR, a tentative amended report.

DR. MARKS: That's seconded.

MS. FIUME: May I ask for a point of clarification? In the conclusion originally we had discussed formulated to be nonirritating. Does that need to be part of the conclusion?

DR. BELSITO: Yes.

DR. BERGFELD: We've had a motion that has been seconded and we've had discussion. Is there any other discussion before we call the vote? None. All those in favor of approving this in ingredient please indicate by raising your hand. Thank you. It's unanimous.

Moving on to PMMA. Dr. Marks?

DR. MARKS: At our December 2009 meeting, the CIR Expert Panel issued a insufficient data request for more information in the monomer of these acrylic polymers. We did receive information about the monomer content. It's less than 100 parts per million. A sensitization threshold of methyl methacrylate was greater than this concentration. Therefore, our team moves that a tentative report be issued

~~they felt that they would never get to that level of free formaldehyde anyway.~~

~~Other comments? Okay. So, none of the re-reviews are we going to be reopening.~~

~~DR. ANDERSON: We've got one more.~~

DR. BELSITO: Ah, one more. Okay. So, polypropylene glycols. I guess I didn't realize this was a -- I thought we already agreed to re-review this. So, okay.

MS. FIUME: Here's some updated concentration of use tables and a table prepared in response to a comment from the council.

MR. ANSELL: And we would like to invite Linda in. Since the -- are we at that stage yet?

SPEAKER: No, we're not going to wait for (inaudible).

SPEAKER: Never mind. Checkmark (inaudible).

DR. BELSITO: Well, I would just like to say, this was incredible to, you know, to just get this all put together almost like it was a green report. So, I guess that's why I didn't think it

was a re-review. I was just assuming we agreed to reopen this.

But the safety assessment on propylene glycol and polypropylene glycols is published in '94: Safe for use at concentrations up to 50 percent. There were newly published data, but, more importantly, data indicating that in industry, these are being used above 50 percent, which is part of the reason why we would consider reopening it.

And so what we've gotten is not just the newly published data. We've essentially gotten a whole new document where Monice has gone through and the italicized portion of it comes from the original report and the normal font is the newly added data. And then now we're getting additional data on concentration of use of these materials.

And the biggest, I guess, issue from my standpoint, the biggest increase was in an underarm deodorant to 73 percent. There were several other products that were higher than 50 percent, but if you recall Ann Marie Api's

presentation at the last meeting, underarm deodorants, at least when they're doing the quantitative risk assessment, get a much higher rating because of the absorption through the skin there. So, I think that that's something we need to keep in mind as we look at this data that we're going to be presented on propylene glycol and polypropylene glycols.

So with that in mind -- and I think my issue will be with sensitization. Did I interrupt you?

What I'd like to do is just call your attention to the study where they -- the conclusion was that -- this is the deodorant use study where they looked at the deodorant with 73 percent.

SPEAKER: Which page, Don?

DR. BELSITO: Well, that's what I'm trying to find, which one this was. This was -- it's -- they're not page numbered, they're actual studies. This was --

SPEAKER: It follows the updated use --

DR. BELSITO: Right. It was the deo stick 73 percent propylene glycol, and it was the repeated application study. And their comment was, there were two. There was one that was done for irritation and one that was done for sensitization.

The comment -- the summary was, under the conditions of the study test material, deo stick did not indicate a clinically significant potential for dermal irritation or allergic contact dermatitis. And that was their conclusion.

But if you look at the individual results that follow, you'll see that the virgin challenge sites, there were people getting 2+ reactions at 24 hours, a 1+ reaction at 72, and you have a couple of people who didn't complete the study because of dermal reactions. So, something was going on there. I mean, there was, in my mind, some degree of sensitization occurring. And what is more disconcerting is that this is being done on the back. It's not being

done to the axillary area where this material is going to be applied.

So, I have a problem accepting the conclusion -- the statement of, you know, that the individual made that conclusion. I would not agree with that. There -- again, there was something going on. And it -- may have all been just, you know, some irritant phenomenon except that it's coming up at the challenge sites where you didn't see much going on before then in terms of irritation from repeat application. So, I'm a little bit concerned with going to 73 percent with these ingredients for a deodorant stick.

Now, having said that, there's another study on 24 men who actually use tested this at 73 percent and the use test was negative, but that was only 24 individuals. So, that's sort of where I'm at.

DR. BERGFELD: I have a question on the testing as they marked it up on the individual results. Tell me, if you're going to assess irritation or sensitization and you have X-number

of persons within the study group, where is your threshold for irritation or sensitivity in number?

DR. BELSITO: I mean, I think your threshold --

DR. BERGFELD: (inaudible) if you have 100 and you have 5 reactors, that's high? One reactor, that's high? Where is your threshold?

DR. BELSITO: I mean, my threshold is anything above zero.

DR. LIEBLER: Well, this is -- I think this is the same question I had when I looked at this. Are there any accepted standards for statistical evaluation of data from studies like these? In other words, if you've got a -- you know, 50 subjects and 4 of them -- you know, 3 of them have a 2 and 3 of them have a 1, is that a statistically significant result or not?

And I don't know if there are any papers in the literature that discuss the statistical evaluation of data like this. But this seems like a -- something that's missing, at least for me, when I try and evaluate data like this or reports

like this.

DR. BELSITO: I mean, typically, when we have looked at skin sensitization and irritation, the cutoff threshold is anything that sensitizes. You know, irritation, we've come to the conclusion that particularly since a lot of it is pH-dependent, you know, we've used a boilerplate when formulated not to be irritating. But sensitization, our cutoff is if it sensitizes at 2 percent, then we want it at a concentration where it's shown not to sensitize, in clinical studies, so.

DR. LIEBLER: Well, the whole point of evaluating data statistically is to try and estimate the probability that the observed result would occur by chance and being unrelated to the treatment. In other words, it's possible that the people in this study had their reactions for reasons other than the treatment. There's a possibility that that is the case. And the point of a statistical analysis is to try and get an idea of what is the probability that that could

occur by random chance.

And I think without information like that, it's hard for me to interpret that, because I'm used to looking at data that has been evaluated with statistics to give us an idea of whether or not a difference observed by any kind of experiment or measurement is due to random chance.

So, I just wanted to ask whether in this field there is any history of evaluating data like that. Because it looks like people simply eyeball a bunch of tables like this and then come up with a summary like this. You could make either -- you could draw either conclusion.

DR. BELSITO: Typically what you would have is, you'd have a control group where you had the deodorant stick without propylene glycol. But there's no control here, so there's no way you can do a statistical analysis of these data.

DR. BERGFELD: Well, with the exception that you've mentioned, that some had not completed the study and inferred that they had had adverse

reactions, where, indeed, those -- I think all but one had zeros and didn't complete the study. And then there was one there that was patching positive. And it might have been like two different testing systems, but one out of the one, two, three that didn't complete.

DR. BELSITO: I think you're on the irritation study.

DR. BERGFELD: No, that's one, and then the next one --

DR. BELSITO: The next one, if you look -- like, there are several that patient number -- subject number 7 had a 2 at 24 hours and didn't complete the study. And patient number 43 had a 2 at 24 hours. Now, that's probably irritation. Didn't complete the study.

But it -- I was just concentrating on looking at the virgin challenge sites. And I think what concerns me is, when you get patients like patient number 46, who had 0 reactions and then ends up with a positive, you know, patch. Patient number --

DR. BERGFELD: And patient number 72 was negative --

DR. BELSITO: Right. But, you know, I mean -- and again, I don't know what this data means, but I wouldn't look at it and say there's nothing there. There's something going on. And again, what concerned me was that this is being placed on back skin, not axillary skin where these products are going to be used.

DR. BERGFELD: So what you're really saying is the study is inadequate to answer the question, but it does induce a suspicion.

DR. BELSITO: Yeah, it gives me pause. You know, what I would like to see is -- you know, I mean, if -- I need to go back and look at this and the list again. But the highest use, that 73 percent that's pushing the highest use, was -- is in an underarm deodorant.

DR. BERGFELD: Yeah.

DR. BELSITO: And it still is.

DR. BERGFELD: Yeah.

DR. BELSITO: And again, we know from

the data that RIFM presented that that's a special site. And when they're doing their quantitative risk assessment for sensitization to fragrances, the axillary area gets a much higher number.

So, I mean, if they, you know, get another 75 guys and put them in the deodo stick and all 75 are negative again, you know, with use, then I'd feel comfortable saying, yeah, this -- we're good to go.

And, you know, I mean, it's propylene glycol the -- you know, that it has the highest use, it seems, as the higher the molecular weight in this group, the lower it's used in cosmetic products.

DR. BERGFELD: So, you're still okay with a 50 percent. But it's --

DR. BELSITO: I'm fine with 50, I'm even fine with --

DR. BERGFELD: But the jump to 73, with only 25 males being really tested in one that you can look at, and you --

DR. BELSITO: There's other data on 63.5

or something?

DR. ANDERSON: 63+ --

DR. BELSITO: And that looked clean.

DR. BERGFELD: Okay. So say it's 64 percent.

DR. ANDERSON: But those data were maximization data.

DR. BELSITO: Right.

SPEAKER: Yeah.

DR. ANDERSON: Don't those get a bit more weight?

DR. BELSITO: Sixty-four percent maximization data?

DR. ANDERSON: Yeah, but these are in --

DR. SNYDER: Sixty-nine percent --

DR. ANDERSON: -- concentration. But the study was a maximization study. And with the exception of one individual who dropped out, Kaidbey reported no positive findings.

DR. BELSITO: And, you know --

DR. ANDERSON: I don't know how to explain that vis-à-vis the other study, but that

looked pretty clean.

DR. BELSITO: And it did. Again, my concern is that when I look at the 73 percent deodo stick study, and that's where they're looking to use 73 percent, in my mind it's not a clean study.

DR. BERGFELD: I'm just trying to establish -- but you are able to go up to 64 percent? I mean, your sense of safety at 69 --

DR. BELSITO: 69.15 percent, yeah.

DR. BERGFELD: Or 70 percent.

DR. BELSITO: Seventy percent with this, with the Kaidbey study. But I just -- you know, and so that 73 percent, I would just -- I would have a hard time saying 73 percent is okay in a deodorant stick and then look at that data that I'm looking at and I don't have good explanations. So, you know, I would be a lot more comfortable if they would just empanel another 75 guys --

DR. BERGFELD: That's what I was saying --

DR. BELSITO: -- or gals --

DR. BERGFELD: -- what are you going to ask for?

DR. BELSITO: Another, you know --

DR. BERGFELD: Up to 150?

DR. BELSITO: -- use test. They got 24 males; 100 I think is fine.

DR. BERGFELD: A hundred is fine?

DR. BELSITO: You know, with the Kaidbey data, you know, another 75 males use testing this deodorant stick and then I can say, you know, I don't know what was going on with that other study. There's something quirky going on with it. And leave it at that.

DR. BERGFELD: So a use study, not a (inaudible).

DR. BELSITO: No, a use study. Because you can't do a repeat insult patch in the underarm. You know, I'd like to see, you know, under conditions of use, again, based upon what we heard from RIFM, where the axillary areas is a special area. If you can show me 100 people use testing this in the axillary and nothing's

happening, I'll be very happy.

DR. SNYDER: So, essentially what we've done is we -- in this, we've agreed to reopen and we've already assessed what the data needs are going to be.

DR. BELSITO: That's -- yeah. I -- that's all I've done. I haven't heard from you people. I've been doing all the talking here. So, go ahead, Paul.

DR. SNYDER: No, I mean, I agree. I mean, I think it should be reopened and I think the discussion has been appropriate.

I was -- what was the original basis for the 50 percent limit on the original report? I couldn't --

DR. LIEBLER: I had the same question.

DR. SNYDER: I couldn't ferret that out of the original report. And so my -- I wasn't certain where that came from.

DR. BELSITO: I think it came from our, you know -- the panel goes in waves as to what we want. And at one point we would set concentration

limits on the highest sensitization issue. So, it would probably -- the 50 percent came because industry was happy with it. We're being told it was only used up to 50 percent and the highest sensitization irritation study we got was 50 percent. And so, we said, okay, that's nice, we'll go at 50 percent.

DR. SNYDER: So in today's terminology, we would have said -- formulated to be non-irritating, most likely. Or was it sensitization in the original report?

SPEAKER: Irritation.

DR. BELSITO: Irritation.

DR. ANDERSON: Yeah, and it was an anomaly in terms of characterizing conclusions, because the motion was safe as used, which normally is the end of it. And then up to 50 percent was tacked on in recognition that that was the highest concentration current then in use. At this point in time, you would usually just say safe as used.

DR. LIEBLER: Yeah, if you look at the

minutes from the panel meeting -- the previous panel meeting, Dr. Elder wanted to know how the panel's 50 percent concentration limit would be affected if the 70 percent propylene glycol were found to be a sensitizer in the ongoing study. He reminded the panel that the 50 percent concentration limit is based on data that are rather weak. He wanted to make sure that the relative to whatever the results of RIPT are and the panel would still be comfortable with this 50 percent concentration limit.

So, I couldn't tell where the 50 percent actually came from and the discussion indicates that it was -- looks pretty fuzzy in hindsight.

So, I share Paul's concern as to where this magic number 50 percent really comes from.

DR. BERGFELD: Well, back then we were into restricting concentrations a little bit more than now. And if we only had data to a certain percentage and were comfortable with that, we put it in. So, I can only give you that bit of history.

DR. SNYDER: And then I guess the other thing is because we are going to reopen, we probably should discuss the add-ons, then.

DR. ANDERSON: Yeah, I think the going back to the original report gives you the focus for what the explanation is. And, you know, you can take it for what it's worth. The comparator was a 50 percent concentration and 100 percent concentration in 16 subjects, which would explain Bob Elder's use of the word "weak."

Fifty percent was clean, no reactions; 100 percent had three 1+ reactions. All of the other data are at concentrations lower. So, there was 16 subjects at 50 percent who were clean.

DR. BELSITO: So, let me summarize what I think our team feeling is that we're going to proceed to reopen it. We're going to add on all of the polypropylene glycols, because we're doing propylene glycol and that will be the major one anyway. If propylene glycol is clean, the others will be because they're larger molecular weight.

And my recommendation would be that if

industry wants the 73 percent in underarm deodorant, it would be nice to see another 75 or so humans use test that deodorant. And if that were clean, then I would be fine explaining away or not even having to explain away the data that we saw on the deodorant stick repeat insult patch testing.

DR. SNYDER: And tripropylene

DR. BELSITO: Yeah. Adding -- doing all the add-ons, yeah.

Okay. And then just one comment on the document on page 8 that didn't make sense to me. On the third paragraph, it says, "In the second part of this experiment, the metabolism of PG was further investigated," and here rats were given oral doses of PG and were treated with pyrazole. And it says, "The peak concentration of PG in the blood of these animals was significantly reduced compared with the rats dosed with PG that were not pre-treated."

Now, pyrazole, I thought, blocked the enzyme that would metabolize propylene glycol, so

shouldn't the blood levels be significantly increased?

MS. FIUME: I can go back. This would be in the original report, so -- I will try and pull the document because this would have been one of the original documents. So, I don't have those published studies right now.

DR. SNYDER: I think that "these" refers to the previous sentence in which it was 30 rats that were dosed at the highest does irrespective of their pre-treatment.

DR. LIEBLER: So it should be -- it simply isn't clear, though. I mean, you can try to interpret it, but it isn't clear and we should probably take a close look at the report.

DR. BELSITO: Yeah, because I would think that the rats treated with pyrazole should have higher blood levels because there would be no metabolism of the propylene glycol.

And then the only other thing is this has hairspray uses, so the usual boilerplate in the cosmetics section.

DR. BERGFELD: I didn't see in that cosmetics section that you would mention the deodorant, that 73 percent. Did I miss that? I'm on page 6.

MS. FIUME: I don't have that pulled out separately, I just have what the maximum came out to be. I will add it there. It is in the table that it's 73.

DR. BERGFELD: Yeah, I saw that.

MS. FIUME: But I'll bring it in there.

DR. BELSITO: Other comments? Dan.

DR. LIEBLER: Yeah, on the second paragraph, page 9. There's a paragraph, talks about analysis of the dermal absorption of PG using thermal emission decay FTIR. And the last sentence says, at 12-32-107 157, meetings, "PG was only found as deep as 6 to 7 microns, indicating that it never reached the dermis approximately 10 microns below the stratum corneum."

Maybe I don't know my terminology here, but it sounded like that -- this is probably incorrect as most of the other data for PG

supports substantial dermal absorption, and I'm looking at, like, the paragraph above it. So, am I misreading this or is this statement probably incorrect?

MS. FIUME: It's probably what came from the published study. I will double-check it to make sure that it is captured correctly.

DR. LIEBLER: They told me less than three hours, so -- less than three hours, okay, I see. Yeah, Paul mentions that. The other thing is sometimes when somebody throws a new technology at a problem, they don't really know how well it performs. And it might be that this analytical platform doesn't measure things very well at all depths in the skin.

DR. BRONAUGH: The timeframe could be important, too.

DR. LIEBLER: So, the timeframe could be important, as Bob Bronaugh just said.

DR. ANDERSON: So, at a minimum, it would be appropriate to put a huge red flag here that would suggest uncertainty about the relevance

of these data if, indeed, you didn't just throw them out entirely.

DR. BELSITO: Again, I think timeframe. So, I mean, it's data that we put into the whole gamish and figure out what's the -- where we are at with it.

Other comments? Monice?

MS. FIUME: I just want to let you know the one table that you received, Carol may bring it up tomorrow, so I want you to be familiar with it.

Throughout the original report, and probably in some of the things that I have, there's a difference in how the polypropylene glycols can be named, whether it's based on chain length or molecular weight. And the difference generally is whether or not it has a dash in the name. So, I tried to put together a table to approximate if it's based on the chain length, what the molecular weight name is indicated based on the dictionary, where it had that type of name under the trade names, and what the calculated

molecular weight is.

There are some in the original report that have a number that look like they're based on molecular weight, but I wasn't completely sure as to what the INCI name would be that would match it.

So, that table may -- Carol, may address that table tomorrow. So I just wanted you to be familiar with what that is.

DR. BELSITO: Great. Yeah.

SPEAKER: (inaudible)

MS. FIUME: Some of them are very close, but some of them, like PPG 30 --

SPEAKER: That's way off.

MS. FIUME: Yeah. That's way off.

DR. SNYDER: You would never link some of those, but I think it helps us to understand what was actually looked at.

MS. FIUME: Okay.

DR. BELSITO: Other comments? Okay.

DR. KLAASSEN: This table actually fit the -- incorporate it in the report.

MS. FIUME: I will. I just received that comment last week. So I just put this together for your use now and then I will add it to ~~the report.~~

~~DR. BELSITO: All right, good job Monice. Okay. Minutes to refill our coffee cups before we move on to the next group? So, five minutes max. 11:10 we'll be back.~~

~~(Recess)~~

~~DR. BELSITO: So the next one is Blue Book. We're looking at dimethyl stearamine, and this is a final in September.~~

~~SPEAKER: Mic.~~

~~DR. BELSITO: Next one is in the Blue Books, dimethyl stearamine. Back in September we issued a tentative amended safety assessment. We've got some technical comments from the council that have been incorporated into the draft.~~

~~There was an issue about the Bass, et al., citation with 50 percent inhibition of cytotoxicity, I believe, as to how that should~~ be ~~worded and whether it was correct. And we're~~

MS. EISENMANN: (inaudible) look at the ~~original. I think so.~~

~~MS. FIUME: Yeah. I'm trying to think if this is the one. At the time --~~

~~DR. MARKS: Eyeshadows, powders. Yeah, it's all --~~

~~MS. FIUME: It's the same type of --~~

DR. MARKS: Yep, nothing new. Next is polypropylene glycols, the PPGs. And that is -- which one is that in?

MS. FIUME: It's the same book. It's the middle tab. I have a couple of handouts.

This is a table addressing INCI names, which are by chain-length versus molecular weight and updated frequency of use.

DR. MARKS: Thanks. So in 1994, the panel published a final report with assessment of propylene glycol and polypropylene glycols, which concluded that these ingredients were safe for use in cosmetic products with a concentration up to 50 percent. And since that time and that publication there have been a significant increase in the

number of uses. And also the concentrations of propylene glycol have increased above 50 percent.

MS. FIUME: It's now used in a deodorant at 73 percent.

DR. MARKS: Yes. So, my feeling was we should reopen to increase the concentration and also increase the number of PPGs.

DR. SHANK: I agree.

DR. HILL: Me, too.

DR. SLAGA: I agree, too.

DR. MARKS: Okay. And then now the next question is if we reopen it, can we issue a tentative amended report with the data we have now indicating that it's safe? As long as it's formulated to be non-irritating. And that's basically -- where is this? The letter from John Bailey dated September 30th, which gives -- precedes some testing laboratory with RIPTs of deodorants containing up to 73 percent of propylene glycol, and which were safe. Non-irritating, non-sensitizing. It's interesting.

Then the suggestion from John's letter

or memo was the conclusion of safe when formulated to be non-irritating. And I think, John, at least my spin on that, is when you look at the original report there was conflicting results and interpretations as to whether patch testing with this alone is irritating. And so I think that covers the issue -- that would cover the issue. Formulated to be non-irritating would deal with those conflicting reports before because it's certainly non-irritating in a deodorant product up to in the 70 percents.

DR. BAILEY: I would agree.

DR. MARKS: Any -- with all this new data, any safety alerts that you're concerned about, Ron? The Rons or the Tom? RRT?

DR. SHANK: I have no safety concerns.

DR. MARKS: Okay. How do you want to proceed? Do you like the idea of just moving straight on to issuing a tentative amended?

DR. SLAGA: I have no problem with that.

DR. MARKS: Safety assessment and just basically that way we get the -- we can get to the

final.

DR. SHANK: Can we do that?

DR. BRESLAWEC: Yes.

DR. SHANK: We can.

DR. BRESLAWEC: For re-review.

DR. SHANK: Because we haven't opened it yet.

DR. BRESLAWEC: Well, I think you just decided to open it.

DR. SHANK: Okay.

DR. SLAGA: That means you have to vote on it.

DR. BRESLAWEC: You have to vote. Yes.

DR. SHANK: But can you decide to reopen and conclude all at the same time?

DR. MARKS: It's not the final conclusion. It's just the tentative, so there will be a comment period.

DR. HILL: Comment period.

MS. FIUME: Tripropylene glycol has also been asked as an add-on. Is that okay?

DR. MARKS: Yes. Let's see in the

reports I did. So we'll reopen, issue a tentative amended safety report that these propylene glycol and propylene glycols are safe with a conclusion they're safe as long as formulated to be non-irritating. That would be the conclusion.

Okay. That will take care of the increased concentration. And it also takes care of the add-ons.

Sound good?

DR. SLAGA: Yep.

DR. MARKS: Halyna, should we be more wordy with these or --

DR. BRESLAWEC: I think we're okay on this one. I thought I should ask Monice. Are we okay with this?

~~DR. MARKS: Okay. Are we to the re-review summaries now? Is this the last ingredient?~~

~~SPEAKER: It was.~~

~~DR. HILL: We can eat lunch according (inaudible).~~

~~DR. MARKS: Okay. Any comments about~~

~~Moving on to the next re-review, Dr. Belsito, the polyoxymethylene urea.~~

~~DR. BELSITO: Polyoxymethylene urea was published in 1995, with the conclusion that the ingredient is safe if the concentration of formaldehyde in formulation does not exceed 0.2 percent. There is some new data, some uses have increased, concentration of use data has not significantly changed. We're asked if we wanted to add on some other ingredients. We did not feel that they were appropriate to be added on and we would make a motion not to reopen this document and to affirm the prior conclusion.~~

~~DR. MARKS: Second.~~

~~DR. BERGFELD: Second. Any further discussion regarding this ingredient? Seeing none, call the question, all those in favor -- unanimous. Thank you.~~

Moving on to the third ingredient in this category, the polypropylene gycols, PPGs. Dr. Marks?

DR. MARKS: In 1994, the CIR Expert

Panel published a safety assessment of propylene glycol and the propylene glycols with the conclusion they're safe for use in cosmetic products with concentrations up to 50 percent.

Since that publication, there have been -- we now find there are products that contain greater than 50 percent of these cosmetic ingredients. There has also been a marked increase in use to now over 9,000 products containing these ingredients.

We felt with the new data, particularly the RIPT data and the memo that came from Dr. Bailey in September 30th of this year from the PCPC, that we should reopen these ingredients and that we issue a tentative amended safety assessment that these ingredients are safe as long as they're formulated to be non-irritating.

DR. BERGFELD: That's a motion?

DR. MARKS: That's a motion.

DR. BERGFELD: Is there a second?

DR. MARKS: Reopen.

DR. BERGFELD: Reopen.

DR. MARKS: And then there could be a second motion in terms of issuing this tentative amendment. It's a sort of different issue.

DR. BERGFELD: So the motion is to reopen. Is there a second?

DR. BELSITO: Just for that?

DR. BERGFELD: Yes, just for that.

DR. BELSITO: Second.

DR. BERGFELD: Second. Any further discussion? Call the question, all those in favor raise your hands? It's unanimous. Second motion.

DR. MARKS: Was to go ahead with the new data. We felt that we could move forward directly to issuing a tentative amended safety assessment. This may also be a first. I'm not sure, but in the vein of moving things forward we felt we could do that with the safety -- the new safety data we have.

DR. BERGFELD: That's a motion?

DR. MARKS: That's correct, to issue a tentative amended safety assessment with the conclusion that these ingredients are safe and

that they be formulated to be non- irritating. And that takes into consideration the issues of the first report where there were conflicting results concerning the irritation of patch -- the patch test results that could be irritating these ingredients and also some of the other data.

DR. BERGFELD: Belsito team. Second or comment?

DR. BELSITO: No, no second. Well, if you look at the data there was some sensitization with propylene glycol at 73 percent in a deodorant stick when it was done by patch testing and it was not -- I mean, it wasn't straightforward. The authors -- the summary that the authors have was that there was no significant sensitization, but there are clearly some people who are reacting possibly as an irritant during the induction phase or possibly irritant or allergic during the challenge phase if you look at the details of those studies and that raised concern. Because if you remember from Dr. Api's report on the quantitative risk assessment that we received, the

underarm is a more highly absorptive area and is an area where typically in the fragrance industry they will have reduced concentrations of fragrances for use in that area because of sensitization issues.

So, here we have a deodorant stick containing 73 percent propylene glycol giving some quirky responses on the back. Now, we do have use testing of a 73 percent deodorant stick in 24 males that were negative and I think that's heartening. But before going ahead with this safe as used conclusion, I would like to see some additional use testing of that deodorant stick with 73 percent propylene glycol in say another 75 individuals to see what kind of response we have before calling this safe as used. I'm just concerned going out with 73 percent in an underarm deodorant with very quirky results in the HRIPT.

DR. BERGFELD: Jim? Dr. Marks?

DR. MARKS: Fine. Of course, err on the safe side.

DR. BERGFELD: So, is there another

motion since the first one has not been seconded? This is on dealing with moving forward.

DR. BELSITO: The motion would be that we don't have all the data we need -- however you want to call that, insufficient or whatever -- and that we would like use testing of 73 percent deodorant stick in approximately 75 more individuals.

DR. BERGFELD: Alan, can I just have a clarification of what title we would give this request?

DR. ANDERSON: I think we actually have rather more flexibility here than in other circumstances. You have determined to reopen the safety assessment. I might have wanted you to go all the way to issuing a tentative report at this meeting, but you didn't have to do that. Reopening it and flagging the need, desire, however we want to phrase it, for additional use testing is, I think, a sufficient action.

We will come back in April with fingers crossed that there are some additional use testing

data to incorporate into the document, and you can determine at that point to issue a tentative amended safety assessment. So, we actually do -- procedurally, we're okay just to mention the additional data needs.

DR. BERGFELD: So, there's no need for a motion here?

DR. ANDERSON: That's correct.

DR. BERGFELD: Thank you. Ron Hill?

DR. HILL: And an additional small issue I had flagged, but didn't really discuss yesterday, and I'm now looking again at how it's been dealt with in the final report is the propylene oxide impurity. And there's nothing in the conclusion dealing with that. And how it shook out is that Dow USA recognizes that the USP now allows up to 5 ppm propylene oxide and is of the opinion that typical levels contained in products today are less than detectable amounts. That was the situation in 1994. I guess I would like to know that that's still the situation based on sources of ingredients.

DR. BERGFELD: Thank you.
DR. HILL: And possibly incorporate something about that in the language of the conclusion.
DR. BERGFELD: Thank you. Any other comments to look at within this document? Other safety issues? Don?
DR. BELSITO: Yeah, there are hairspray uses, so, again, the aerosol boilerplate.
DR. BERGFELD: Okay. Anything else?
DR. SHANK: If we conclude that these are safe as used when formulated to be non-irritating, doesn't that satisfy you?
DR. BELSITO: Well, propylene glycol can also cause sensitization. In fact, it's a rather -- not common, but not infrequent cause of sensitization to topical medicaments, so I'm just concerned that there's not just an irritating property here, that there could be a sensitization issue particularly. I mean, I could not interpret the HRIPT results that were done. Again, they're very quirky. There clearly was some irritation

going on there, but there clearly were a couple individuals who had no irritation through the repeat insult patch testing and then when challenged developed 2+ reactions on challenge suggesting that there was some sensitization. Again, my concern is that's back skin versus 73 percent is in a deodorant stick, may not be appropriate based upon the QRA that we've heard.
So, it's not just saying not to be formulated to -- or to be formulated not to be irritating. I think that should be part of our conclusion as well because these are -- propylene glycol is known to be an irritating chemical, but I think we need to know a little bit more about the sensitization in underarm deodorant.
DR. BERGFELD: Anything else? Well, thank you very much. We've dealt with the 11 ingredients. We're moving on now to the re-review summaries. Dr. Anderson is going to lead this discussion.
DR. ANDERSON: Okay, I think that the summaries were provided for the panel review. And

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that TEA Stearate is safe for use in cosmetics. There was one abstention.

Propylene Glycol and Polypropylene Glycols

Dr. Andersen noted that the following conclusion is included in the discussion section of the Propylene Glycol report: Patients with diseased skin may be at risk with respect to developing irritation/sensitization reactions to PG, even at low concentrations, and should minimize skin exposure. Furthermore, in previous CIR reports that were reviewed by the Expert Panel, this sentence has been included in the conclusion as a specific admonition to patients with diseased skin. Dr. Andersen proposed adding the statement to the conclusion of the Propylene Glycol report, such that the conclusion is consistent with similar determinations that have been made in the past.

Dr. McEwen stated that prior to making any substantive change in a report conclusion, another 90-day comment period would have to be allowed. Any changes that are made in a report conclusion are not viewed as merely editorial changes.

Dr. Schroeter said that early in the review of this document, the statement was moved from the conclusion to the discussion. The Panel realized that Propylene Glycol could be a sensitizer, and that the irritation and sensitization potential of this ingredient could be augmented by injured skin. He proposed that the conclusion should remain as originally documented.

Dr. Bergfeld concurred with Dr. Schroeter.

All of the Final Reports were approved by the Panel, and the 48th CIR Expert Panel Meeting was adjourned.

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by the Panel.

The Panel did not sign final report ballots on Propylene Glycol. Dr. Bergfeld noted that each Panel member had received a copy of the letter from the Dial Corporation requesting that the Panel increase the 50% concentration limit that it established for Propylene Glycol.

Dr. Belsito favored not making any changes in the Propylene Glycol report. He agreed that the conclusion could be reconsidered after additional data are received from The Dial Corporation in the future. Any decision to increase the concentration limit would have to be based on dermal absorption data at the proposed higher concentration of Propylene Glycol and irritation and sensitization data (standard protocols) at that concentration.

Dr. Elder said that The Dial Corporation has a 200-person repeated insult patch test (sensitization study) underway, and that Propylene Glycol is being tested at a concentration of approximately 70%. He also wanted to know if the Panel would reevaluate the Propylene Glycol report sensitization data, along with irritation and dermal absorption data that are available.

None of the Panel members disagreed with reevaluating the safety of Propylene Glycol after additional data have been received.

Dr. McEwen questioned the relevancy of dermal absorption data at this point, and did not understand why these data should be requested. He recalled that the 50% concentration limit had been established because of skin irritation. He agreed

that sufficient data are present in the report in order to address any further concerns about toxicity.

Dr. Schroeter said that skin irritation data could be obtained from the RIPT that is underway. He also noted that dermal toxicity data are included in the Tentative Final Report and also questioned the need for dermal absorption data.

Dr. McEwen requested that the Tentative Final Report on Propylene Glycol be tabled until the May 24-25, 1993 Panel meeting. He said that the RIPT underway should be completed in no more than six weeks.

Dr. Elder wanted to know how the Panel's 50% concentration limit would be affected if 70% Propylene Glycol were found to be a sensitizer in the ongoing study. He reminded the Panel that the 50% concentration limit is based on data that are rather weak. He wanted to make sure that relative to whatever the results of the RIPT are, that the Panel would still be comfortable with its 50% concentration limit.

After further discussion, the Panel voted in favor of tabling the report on Propylene Glycol until the next Panel meeting.

Dr. Elder said that he agreed with Dr. Belsito. He noted that there had been a 90-day comment period for the Tentative Final Report on Propylene Glycol and that a company had just decided to test, after the end of the 90-day comment period. The Panel should only table a report that is at the Draft Tentative stage.

Dr. Bergfeld said that a letter should be sent to The Dial Corporation, stating what was discussed at this meeting. The letter should indicate that the test results or

some tentative report as to how the study is progressing should be available at the next meeting.

At the conclusion of the discussion on Propylene Glycol, Dr. Bergfeld stated that she would miss Dr. Elder and Dr. Hoffmann. This is their last Panel meeting. Dr. Bergfeld also stated that is her hope that Dr. Elder and Dr. Hoffmann would serve as consultants to the Panel in the future. She indicated that Mr. Kavanaugh, CTFA President, agrees with this suggestion.

Prior to the close of the meeting, Dr. Elder asked the Panel to applaud the CIR Scientific Analysts and support staff.

The 46th Meeting of the CIR Expert Panel was adjourned.

45th Mtg
Nov. 30- Dec 1, 1992

motion.

Drs. Elder and Hoffmann agreed that the time frame for completion of the mouse dermal carcinogenicity study and dermal absorption study would be three years.

Dr. Bergfeld noted that the 90-day comment period to the Insufficient Data Announcement would end just prior to the March 18-19, 1993 Panel meeting. So, a decision on HC Blue No. 1 will be postponed until industry indicates whether the studies requested by the Panel will be performed. If a commitment to perform the tests is not received, the review of HC Blue No. 1 will appear on the agenda for the March Panel meeting, at which time the Panel will either conclude that there are insufficient data to support safety or that the ingredient is unsafe.

DIMETHYL LAURAMINE

The Panel voted in favor of issuing a Formal Insufficient Data Announcement on Dimethyl Lauramine. The following data were requested:

(1) chemistry (pH, impurities, and UV spectral analysis)
(2) 28-day dermal toxicity
(3) ocular irritation
(4) human dermal irritation and sensitization
(5) human photosensitization (only if Dimethyl Lauramine absorbs UVA or UVB)
(6) genotoxicity (at least 2 different assays)
(7) carcinogenicity, only if genotoxicity tests are positive.

PROPYLENE GLYCOL

Dr. Hoffmann began discussion of this ingredient by stating that the UV absorption information requested by the Panel had been received. Propylene glycol did not absorb in the UVA or UVB range, so phototoxicity is not of concern. Dr. Hoffmann's team agreed that the ingredient was "safe as used" up to 50%. The

concentration was limited to test concentrations in available studies.

Dr. Schroeter said that his Team concurred with the conclusion. A motion for the conclusion, and a second, was made. All were in favor of the conclusion: Propylene Glycol is "safe as used" in cosmetics up to concentrations of 50%.

Some deletions in the document were made. On page 47, the second paragraph was deleted. On page 51, the second paragraph was deleted. On page 62, the first paragraph was deleted.

Dr. Bergfeld then closed the 45th Meeting of the CIR Expert Panel.

Draft Final Report of the Cosmetic Ingredient Review Expert Panel

on the Safety Assessment of Propylene Glycol, PPGs, and Tripropylene Glycol as Used in Cosmetics

June 28-29, 2010

The 2010 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Monice M. Fiume, Scientific Analyst/Writer.

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ABSTRACT

Propylene Glycol is an aliphatic alcohol widely used in cosmetics that functions as a skin conditioning agent, viscosity decreasing agent, solvent, and fragrance ingredient. Polypropylene glycols, including PPG-3, PPG-7, PPG-9, PPG-12, PPG-13, PPG-15, PPG-16, PPG-17, PPG-20, PPG-26, PPG-30, PPG-33, PPG-34, PPG-51, PPG-52, and PPG-69, have far fewer uses than propylene glycol and function primarily as skin conditioning agents, with some solvent use. Tripropylene glycol functions as a humectant, antioxidant, and emulsion stabilizer. The majority of the safety and toxicity information is limited to propylene glycol. The Expert Panel determined that the available information would be used to support the safety of all the polypropylene glycols as well as tripropylene glycol. Propylene glycol is generally non-toxic and is non-carcinogenic. A wide range of genotoxicity studies were negative. Clinical studies demonstrated an absence of dermal sensitization at use concentrations, although concerns about irritation remained. The Expert Panel concluded that propylene glycol, the polypropylene glycols, and tripropylene glycol are safe as used in cosmetic formulations when formulated to be non-irritating.

INTRODUCTION

Propylene glycol and polypropylene glycols (PPGs) have previously been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel.[1] In 1994, the safety assessment was published with the conclusion that these ingredients were "safe for use in cosmetic products at concentrations up to 50.0%." At the time of that original report, the specific PPG chain lengths were not identified. However, concentration of use data were reported for PPG-9, PPG-26, and PPG 425. Currently, the *International Cosmetic Ingredient Dictionary and Handbook* names PPG-3, PPG-7, PPG-9, PPG-12, PPG-13, PPG-15, PPG-16, PPG-17, PPG-20, PPG-26, PPG-30, PPG-33, PPG-34, PPG-51, PPG-52, and PPG-69. This report is intended to address the safety of these specific PPGs currently listed in the *International Cosmetic Ingredient Dictionary* as well as all chain lengths that may be added in the future.

This report is an update of the 1994 safety assessment, and as such, it contains information that was published after the 1994 assessment was issued. When available, *a brief summary of information from the original safety assessment as well as from this update is included in italics* prior to major sections throughout this document.

Tripropylene glycol, which has not been reviewed, is also included in this report. Tripropylene glycol is different from PPG-3. The PPG-x designations all acknowledge that these ingredients are produced in a polymerization reaction that can lead to some different chain length compounds, since the process in not end blocked. Tripropylene glycol is an ingredient that contains only the "3" chain length.

CHEMISTRY

Definition and Structure

Propylene glycol (PG; CAS No. 57-55-6) is an aliphatic alcohol that conforms generally to the formula in Figure 1.[2] Tripropylene glycol (CAS No. 24800-44-0) is an organic compound that conforms to the formula in Figure 2.[2] Synonyms for PG and tripropylene glycol are listed in Table 1.

The polypropylene glycols (PPGs; generic CAS No. 25322-69-4) are polymers of propylene oxide that conform generally to the formula in Figure 3.[2] According to the *International Cosmetic Ingredient Dictionary and Handbook*, international nomenclature cosmetic ingredient (INCI) names for the PPGs refer to the average "n" value corresponding to the propylene oxide chain length of the polymer; i.e., PPG-3 would have an average chain length of 3. (Synonyms for PPGs are also listed in Table 1.)

As stated above, the INCI names for cosmetic PPGs refer to the chain length. However, different naming conventions are used in identifying PPGs and the potential for confusion exists. When the official INCI name for each ingredient is used,

the name is given as PPG, dash, and then the average number of units, e.g., PPG-3. However, the PPGs can also be identified using the average molecular weight as part of the name; this is indicated as PPG, space, average mol. wt., e.g., PPG 200. Table 2 gives the INCI name, molecular weight name where available, and calculated molecular weight of the PPGs.

Physical and Chemical Properties

The physical and chemical properties of PG, tripropylene glycol, and the PPGs are summarized in Table 3.

Method of Manufacture

Tripropylene glycol (as well as dipropylene glycol) is formed by sequential addition of propylene oxide to PG.[3] The products are formed simultaneously and separated by distillation.

Impurities

In the original safety assessment on PG, Dow Chemical Co recommended that United States Pharmacopoeia (USP)-grade PG be used in cosmetics.[1] According to recent information, the USP has set safety limits of diethylene glycol and ethylene glycol content at a maximum of 0.1%.[4] USP grade PG manufactured by Dow contains diethylene glycol and ethylene glycol at concentrations that are non-detectable (quantification limit of 0.008 percent wt/wt). Dow also has stated that they meet or exceed all requirements currently found in the European Pharmacopoeia, Japanese Pharmacopoeia, and Food Chemicals Codex. Two companies submitted information regarding the concentration of propylene oxide in PPGs used to make finished products.[5] Both companies report a maximum of 10 ppm propylene oxide.

USE

Cosmetic

PG is used in cosmetic formulations as a skin conditioning agent (humectant or miscellaneous), viscosity decreasing agent, solvent, or fragrance ingredient.[2] The PPGs function primarily as skin conditioning agents, with some functioning as solvents. Tripropylene glycol functions as a humectant, antioxidant, or emulsion stabilizer

At the time of the original safety assessment, according to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), PG was used in 5676 cosmetic formulations at concentrations ranging from 0 to >50%.[1] PPG-9 and PPG-26 were used in 6 and 10 cosmetic formulations, respectively, at concentrations of 0.1-5%, and PPG 425 (thought to be synonymous with PPG-9) was used in 1 cosmetic formulation at a concentration range of 1-5%.

The frequency and concentration of use of PG has increased. Recent VCRP data indicate that PG is used in 9094 cosmetic formulations (out of 34,391total formulations reported).[6] Polypropylene glycol (chain length not specified) is reported to have 45 uses. PPG-9 is reported to be used in 84 cosmetic formulations, and PPG-12 is used in 3, PPG-15 in 1, PPG-17 in 3, PPG-26 in 2, and PPG-30 in 5 cosmetic formulations. Tripropylene glycol is used in 8 formulations. A survey of current use concentrations conducted by the Personal Care Products Council (the Council) reported that PG is used at concentrations of 0.0008-99%.[7] PG, which is used in 313 of the 580 deodorant products reported to the VCRP,[6] is used at concentrations of 3-73%; this is the greatest leave-on concentration used.[7] The highest concentration of use of PG is in a product that will be diluted; that is 99% in bath oils, tablets, or salts. Additionally, the Council survey results reported that PPG-9 is used at 0.05-22%, PPG-12 at 1%, PPG-17 at 1-2%, PPG-26 at 0.2%, and PPG-34 at 20%. Tripropylene glycol is used at concentrations up to 22%; the 22% is in an underarm deodorant. Table 4 presents details of the historical and current product formulation data for PG and the PPGs, as well as current data for tripropylene glycol.

PG is used in hair sprays, and effects on the lungs that may be induced by aerosolized products containing this ingredient are of concern.

The aerosol properties that determine deposition in the respiratory system are particle size and density. The parameter most closely associated with deposition is the aerodynamic diameter, d_a, defined as the diameter of a sphere of unit density possessing the same terminal settling velocity as the particle in question. In humans, particles with an aerodynamic diameter of ≤ 10 µm are respirable. Particles with a d_a from 0.1 – 10 µm settle in the upper respiratory tract and particles with a d_a < 0.1 µm settle in the lower respiratory tract.[8,9]

Particle diameters of 60-80 µm and ≥80 µm have been reported for anhydrous hair sprays and pump hairsprays, respectively.[10] In practice, aerosols should have at least 99% of their particle diameters in the 10 – 110 µm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 µm.[11] Therefore, most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

PG, PPGs, and tripropylene glycol are not included in the list of ingredients that are prohibited for use in the European Union[12] or on the list of ingredients restricted or prohibited for use in Japan.[13]

Non-Cosmetic

PG is generally recognized as safe (GRAS) as a direct food additive when used in accordance with good manufacturing practices, and it is approved as a direct and indirect food additive.[14] According to the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the acceptable daily intake (ADI) of PG is 25 mg/kg/bw/day.[15] In Japan, the Ministry of Health, Labour, and Welfare (MHLW) specified that according to the food sanitation law, PG has no potential to cause harm to human health.[16]

PG is used as an inactive ingredient in a number of FDA-approved drug products. It has been approved at concentrations up to 98.09% in topical drugs and 92% in oral solutions.[17] PG is approved as an over-the counter (OTC) ophthalmic demulcent at concentrations of 0.2-1%.[14] There is inadequate evidence to establish PG as GRAS and effective in OTC pediculicide drug products.

PG has many uses in pharmaceuticals, food, and manufacturing.[18] It is used in organic synthesis, especially for PPG and polyester resins.[19]

PPG is approved as a secondary direct food and additive and as an indirect food additive.[14] PPG has many industrial uses.[19]

Tripropylene glycol also has many uses in pharmaceuticals, food, and manufacturing. It is used as an intermediate in resins, plasticizers, pharmaceuticals, insecticides, and the production of ethers and esters.[20]

GENERAL BIOLOGY

Metabolism and Excretion

The 1994 assessment reported that in mammals, the pathway of PG metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases.[1] When PG was administered i.v. to human subjects (patients), elimination from the body occurred in a dose-dependent manner. Animal studies using PPGs with avg mol wts of 425-2025 indicated that PPGs are readily absorbed from the gastrointestinal (GI) tract and excreted in the urine and feces.

Absorption

Propylene Glycol

Dermal penetration of PG from a ternary cosolvent solution through hairless mouse skin was 57% over a 24 h period. Using thermal emission decay (TED)-Fourier transform infrared (FTIR) spectroscopy, it appeared that PG did not reach the dermis.

The dermal penetration of [^{14}C]PG through excised female hairless mouse skin from the ternary cosolvent containing 10 mol% oleic acid and 6 mol% dimethyl isosorbide in 84% PG was determined.[21] Over a 24-h period, the cumulative penetration of PG was 57.1% of the applied amount.

The dermal absorption of PG was determined in the outermost layers of skin using TED-FTIR spectroscopy. [22] PG was applied to the fingertip of one human subject for 30 min using PG-soaked cotton wool. The site was wiped and allowed to dry for 1 min. The thickness of the surface layer of stratum corneum probed was 0.71 µm. Measurements were performed every 25 min over a 3 h period, with one measurement taking 15 min. The concentration of PG remaining at the surface of the stratum corneum decreased over time. At 12 and 32 min, the maximum concentration of PG was found at a depth of <1 µm, while at 107 and 157 min, the maximum concentration of PG was found at a depth of 3-4 µm. At a depth of 6 µm, the greatest concentration of PG, 0.2%, was seen at 32 min. The authors suggested that PG molecules diffuse into stratum corneum only to a depth of 6-7 µm, approximately. The researchers also suggested that PG molecules do not reach the dermis.

Dermal Penetration Enhancement

PG can act as a penetration enhancer for some chemicals and under some conditions. Often, it works synergistically with other enhancers. The mechanism by which PG enhances penetration has not been definitively identified.

Propylene Glycol

PG has been described as a penetration enhancer, and penetration enhancers act by various mechanisms to perturb diffusional pathways through the skin. Proposed mechanisms of penetration enhancement by PG include alteration of barrier function by its effects on a keratin structure or a PG-induced increase in the solution capacity within the stratum corneum.[21]

Examples of the effect of PG on penetration are summarized in Table 5.

Cytotoxicity

Propylene Glycol

Propylene glycol is moderately cytotoxic to human fibroblasts and keratinocytes.

The cytotoxicity of PG was determined in assays that measured inhibition of human foreskin fibroblasts and keratinocytes, inhibition of collagen contraction by fibroblasts, and changes in cell morphology of fibroblasts and keratinocytes. [23] Fibroblast and keratinocyte proliferation was inhibited within 3 days after administration of PG; no significant changes in cell proliferation occurred with a 6-day administration. PG was a moderately potent inhibitor, with an IC_{50} (concentration causing 50% proliferation inhibition) of 280 mM for fibroblasts and 85 mM for keratinocytes. The effect of PG on collagen contraction by fibroblasts was concentration dependent throughout the entire study. The concentration causing 50% contraction inhibition was 180 mM.

The effect of PG on changes in cell morphology also was examined.[23] A gradual detachment of cells from the culture accompanied by changes in cell shape occurred in confluent keratinocyte cultures when the concentration of PG was increased above 5%. After 24 h, replacing medium containing 5% PG with PG-free medium resulted in almost complete recovery within 48 h. However, this recovery did not occur with 7% PG. Similar results were observed with fibroblasts, and the concentration inducing irreversible cell damage in both fibroblast and keratinocytes cultures was 660 mM PG.

Other Biological Effects

Oral administration of PG to rats affected some intestinal uptake parameters. It did not produce any renal effect.

Propylene Glycol

Groups of 6 inbred male Wistar rats were dosed orally by gavage, daily, with 294.23 mg PG/100 g body wt (as 1 ml 28.4%/100 g) for 10 (Group 1), 20 (Group 2), or 30 days (Group 3), and the effects on a number of intestinal parameters were determined.[24] Control groups received an equal volume of saline for 10, 20, or 30 days. After termination of dosing,

animals were fasted overnight and then killed. All animals survived until study termination. Body weight gains were statistically significantly decreased for animals in Group 1 and increased for animals in Groups 2 and 3. A number of enzyme activities were enhanced; statistically significant increases were seen in sucrase activity in Groups 1 and 2 and lactase and γ-glutamyl transpeptidase activity in Group 3. Absorptive function was assessed by measuring nutrient uptake. Statistically significant increases of D-glucose and calcium uptake were seen in all groups and of glycine, L-asparate, and L-lysine uptake was seen in Groups 1 and 2. Scanning electron microscopy revealed that PG did not affect the intestinal mucosal surface.

Nineteen male Han:Wistar rats were given drinking water containing 40 g/l PG for 2 weeks; a control group of 16 rats was given tap water.[25] The animals were placed in metabolism cages during the last 24 h of dosing and urine was collected. PG administration did not have any effect on urinary excretion of oxalic or alkoxyacetic acid, nor did it affect pH or urinary metabolites. PG did not cause any renal effects.

ANIMAL TOXICOLOGY

In both the 1994 safety assessment[1] and currently, few toxic effects were seen in dosing with PG and PPGs. The oral LD_{50} of PG was >21 g/ kg for rats. The LD_{50} of PPG, mol wts 300-3900, ranged from 0.5-40 g/kg for rats, while the oral LD_{50} of PPG, mol wts not given, ranged from 1.5-17 g/kg for guinea pigs . The dermal LD_{50} of PG was >11.2 g/kg for mice and was 13 g/kg for rats. The dermal LD_{50} of PPG, mol wts 425-2025, was >20 ml/kg for rabbits. All mice survived in a short-term study in which mice were given 10% PG in drinking water for 14 days, and all rats and mongrel dogs survived oral dosing with up to 3.0 ml 100% PG 3 times per day for 3 days. In a subchronic study, a dose of ≤50,000 ppm PG given in the feed for 15 wks did not produce any lesions. PPG 750 did not cause any adverse when given at 0.1% for 10 days, but a concentration of 1% produced slight increases in liver and kidney weight. The highest no effect level of PPG 1200 fed to rats and dogs for 90 days was 0.3%. No adverse effects were seen in a 90-day study in which rats or dogs fed 501 or 810 mg/kg/day, respectively, PPG 2000. In a subchronic dermal study, 1 ml/kg PPG 2000 did not cause adverse effects in rabbits, but 5 and 10 ml/kg caused a slight depression in growth. Subchronic inhalation data reported some effects due to PG exposure of 2.2 mg/l air for 6 h/day, 5 days/wk, for 13 wks, but these effects were inconsistent and without dose-response trends. In the 1994 safety assessment, no toxic effects were reported in chronic studies when rats or dogs were given feed containing 50,000 ppm or 5 g/kg, respectively, PG.

Acute Oral Toxicity

Polypropylene Glycols

The acute toxicity of PPG 425 was evaluated using 2 groups of 3 rats (strain and gender not specified).[26] The rats were given a single oral dose of 250 or 1000 mg/kg PPG 425 by gavage and observed for 14 days. Animals of the low dose groups had convulsions and loss of coordination whereas animals of the high dose group had convulsions. One high dose animal died on day 1. All low dose animals and the remaining 2 high dose animals survived until study termination.

Acute Parenteral Toxicity

Propylene Glycol

An acute study was performed in which female ICR mice were dosed i.p. with 2600, 5200, or 10400 mg/kg PG.[27] All except the high dose mice survived 6 days after dosing. (The number of high dose mice that died was not given.) Signs of toxicity, such as lethargy and ruffled hair coats, were not observed in the 2600 and 5200 groups.

Short-Term Oral Toxicity

Propylene Glycol

Groups of 8 male and 8 female CD-1 mice were given 0.5, 1.0, 2.5, 5.0, and 10.0% PG in the drinking water for 14 days. [28] Negative controls were given untreated drinking water. Body weight gains of test animals were similar to or greater than controls. No animals died during the study.

Subchronic Inhalation Toxicity

Propylene Glycol

Male and female Sprague-Dawley rats (number per group not given) were exposed to 0.16, 1.0, or 2.2 mg PG/l air for 6 h/day, 5 days/wk, for 13 wks in a nose-only inhalation study. [29] There was no difference in body weights for any of the male dose groups, while mid and high dose females had significantly decreased body weights starting on days 64 and 50 of the study, respectively. Feed consumption was decreased for the females starting on days 50 and 43, respectively. Relevant differences occurred in some hematological parameters, serum enzyme activities, and lung, spleen, liver, and kidney weights; however these differences were inconsistent and without dose-response trends. The mid and high dose animals had increased goblet cells and increased mucin within these cells.

Ocular Irritation

In studies reported in the 1994 assessment[1] and currently, undiluted PG and PPG, mol wt 425-2025, were, at most, slight ocular irritants.

Propylene Glycol

The ocular irritation potential of PG was determined using groups of 6 male and female New Zealand white albino rabbits.[30] First, a single application of 1 drop of PG was instilled into the conjunctival sac of the left eye of each rabbit, and the eye was not rinsed. In the second part of the study, 1 drop of PG was instilled into the conjunctival sac of the left eye every 24 h for 3 consecutive days. At both times, the contralateral eye was untreated and served as the control. The eyes were examined on days 1, 2, 3, and 7. With the single application, slight to moderate conjunctival hyperemia was observed on day 1 and resolved by day 2. The highest total score was 19/550, well below the category of marginal irritant (score of 65). Multiple instillations resulted in similar observations, with slight hyperemia lasting up to day 3 in 2 rabbits. The highest total score following multiple installations was 38/550, again below the category of marginal irritant.

Dermal Irritation/Sensitization

Dermal irritation studies were reported in the 1994 assessment[1] and currently. In one study using nude mice, 50% PG may have caused skin irritation, while in another study, 100% PG was minimally irritating to hairless mice. Undiluted PG was at most a mild dermal irritant in a Draize test using rabbits with intact and abraded skin. No reactions to undiluted PG were observed with guinea pigs, rabbits, or Gottingen swine. Using nude mice, hypertrophy, dermal inflammation, and proliferation were observed with 50% PG. These effects were not seen in hairless mice with undiluted PG. PG (concentrations not given) was negative in a number of sensitization/allergenicity assays using guinea pigs. In one study using guinea pigs, 0.5 ml PG was a weak sensitizer. PPG (concentration not stated), avg mol wts 425-2025, was not an irritant to rabbits.

Propylene Glycol

The dermal irritation potential of 100% PG was evaluated with male hairless SKH1 hr/hr mice.[31] PG was instilled in polyvinyl chloride cups (vol 0.3 cm^3) on the dorsal side of 3 mice. The test substance remained in contact with the skin for 24 h. At the end of the 24 h, the animals were killed and a sample of the exposed skin was examined microscopically. PG was minimally irritating, with a total score of 7 (maximum score =77).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In studies reported in the 1994 assessment[1] and currently, PG did not have any adverse reproductive or developmental effects when evaluated in mice at doses of ≤5.0% PG, rats at doses of ≤1600 mg/kg PG, rabbits at doses of ≤1230 mg/kg PG, or hamsters at doses of ≤1550 mg/kg PG.

Propylene Glycol

The reproductive and developmental effects of PG were evaluated using mice, rats, rabbits, and hamsters.[32] Groups of 25 or 28 female albino CD-1 outbred mice were mated and 22, 22, 22, 20, and 23 gravid mice were dosed by oral intubation with 0.0, 16.0, 74.3, 345.0, and 1600.0 mg/kg aq. PG on days 6-15 of gestation. Groups of 25-28 female albino Wistar rats were mated and 22, 23, 22, 20, and 24 were dosed as above, respectively. Positive control groups of 23 mice and 21 rats were given 150.0 or 250.0 mg/kg aspirin, respectively. Body weights were recorded at various intervals and general observations were made daily. Caesarian sections were performed on days 17 and 20 for all mice and rats, respectively. All fetuses were examined macroscopically for visceral or skeletal defects. Administration of PG did not affect maternal or fetal survival in mice or rats, and there were no statistically significant differences in fetal anomalies between test and negative control groups in mice or rats.

Groups of 11, 11, 12, 14, and 13 gravid female Dutch-belted rabbits were dosed by oral intubation with 0, 12.3, 57.1, 267.0, or 1230.0 mg/kg aq. PG on days 6-18 of gestation. A positive control group of 10 gravid rabbits was given 2.5 mg/kg 6-aminonicotinamide. Body weights were recorded at various intervals and general observations were made daily. Caesarian sections were performed on day 29. All fetuses were examined macroscopically and kept for 24 h to evaluate survival. The pups were then examined viscerally and for skeletal defects. Administration of PG did not affect maternal or fetal survival, and there were no statistically significant differences in fetal anomalies between test and negative control group.

Groups of 24-27 female golden hamsters were mated and 21, 24, 25, 22, and 22 gravid hamsters were dosed by oral intubation with 0.0, 15.5, 72.0, 334.5, and 1550.0 mg/kg aq. PG on days 6-10 of gestation. Positive controls were given 250.0 mg/kg aspirin. Body weights were recorded at various intervals and general observations were made daily. Caesarian sections were performed on day 14. All fetuses were examined macroscopically and for visceral or skeletal defects. Administration of PG did not affect maternal or fetal survival, and there were no statistically significant differences in fetal anomalies between test and negative control groups.

PG was used as a vehicle in a reproductive and behavioral development study.[33] It was administered to 15 gravid Sprague-Dawley rats orally by gavage on days 7-18 of gestation at a volume of 2 ml/kg. PG did not have any effects on reproductive or behavioral development parameters.

Embryotoxicity

In the 1994 safety assessment, embryonic development was reduced or inhibited completely in cultures of mouse zygotes exposed to 3.0 or 6.0 M PG, respectively.[1] A current study examining induction of cytogenetic aberrations found an increase in the frequency of premature centrosphere separation (PCS) with 1300-5200 mg/kg PG. In zygotes from PG-dosed mice, hyperploidy was increased.

Propylene Glycol

Female ICR mice were used to determine whether PG induced cytogenetic aberrations in mouse metaphase II (MII) oocytes that predispose zygotes to aneuploidy.[27] Groups of mice were first given an i.p. injection of 7.5 IU eCG to augment follicular maturation followed 48 h later with 5 IU hCG to induce ovulation. After 3 h, mice were dosed i.p. with 1300, 2600, or 5200 mg/kg PG in distilled water. A control group was given distilled water only. For the MII portion of the study,

ovulated oocytes were collected from 20 test animals/group and 30 control animals and processed for cytogenetic analysis 16 h after administration of PG. The number of oocytes collected from test animals was non-statistically significantly increased compared to controls. A statistically significant change in hyperploidy, hypoploidy, or single chromatids was not observed. An increase in the frequency of PCS at each dose was statistically significant, and the incidence of premature anaphase was statistically significantly greater in the 5200 mg/kg dose group as compared to controls. Neither metaphase I nor diploid oocytes were found.

For the zygote portion of the study, the female mice were paired with males after being given hCG; the males were removed 16 h after dosing with PG. Mated females were given colchine 22 h after dosing with PG; zygotes were collected 18 h later. There were 30, 40, 49, and 66 mice in the control, 1300, 2600, and 5200 mg/kg groups, respectively. The increase in hyperploidy was statistically significant in all test groups compared to controls. A statistically significant change was not seen for polyploidy or hypoploidy, and zygotes containing PCS, premature anaphase, or single chromatids were not found. The authors noted that there was not a statistically significant difference in the proportion of zygotes collected for each group compared to oocytes. However, the number of zygotes analyzed compared to the number placed on slides was significantly decreased in the test groups; a relatively large portion of these zygotes had clumped chromosomes.

GENOTOXICITY

In the 1994 assessment, ≤10,000 µg/plate PG was not mutagenic in Ames tests with or without metabolic activation.[1] *PG, tested at concentraitons of 3.8-22.8 mg/ml, was a weak, but potential, inducer of sister chromatid exchanges (SCEs), causing a dose-dependent increase in SCEs in a Chinese hamster cell line. However in another SCE assay using human cultured fibroblasts and Chinese hamster cells with and without metabolic activation, PG was not mutagenic. PG, 32 mg/ml, induced chromosomal aberrations in a Chinese hamster fibroblast line, but not in human embryonic cells. PG was not mutagenic in mitotic recombination or basepair substitution assays, or in a micronucleus test or a hamster embryo cell transformation assay. (Concentration used not specified.) Current data report that ≤10,000 µg/plate tripropylene glycol was not mutagenic in an Ames assay.*

Tripropylene Glycol

In a preincubation study with tripropylene glycol using *Salmonella typhimurium* strains TA1535, TA100, TA97, and TA98, the results were negative using concentrations of 0-10,000 µg/plate with and without metabolic activation.[34]

CARCINOGENICITY

In the 1994 safety assessment, PG was not carcinogenic in a 2 yr chronic study in which rats were given ≤50,000 ppm PG in the diet.[1] *Dermal application of undiluted PG (volume not stated)to Swiss mice in a lifetime study produced no significant carcinogenic effects. PG was not carcinogenic in other oral, dermal, and subcutaneous studies.*

CLINICAL ASSESSMENT OF SAFETY

Synergistic Penetration

PG acts synergistically with fatty acids, such as oleic acid, to enhance dermal penetration in clinical studies.

Propylene Glycol

PG penetration is enhanced by the addition of fatty acids, such as oleic acid.[35] The synergistic penetration enhancement of PG and oleic acid was demonstrated by Tanojo et al. (1997) by evaluating transepidermal water loss (TEWL) and determining attenuated total reflectance (ATR)-FTIR.[36] TEWL was determined using 10 subjects (number of males and females not specified) with application of occlusive chambers containing nothing, 300 µl PG, or 300 µl 0.16 M oleic acid in PG, for 3 or 24 h. The fourth site was not treated and not occluded. TEWL measurements were started 3 h after chamber removal to reduce volatile solvents on the skin surface in order to avoid interference with the Evaporimeter™. The site

treated with oleic acid/PG increased water loss for a longer period in comparison to the PG only or empty sites. The 3 and 24-h applications of PG resulted in an enhanced water loss ratio of 1.1. With oleic acid/PG, these values were 2.0 and 2.1, respectively.

For the ATR-FTIR portion, an occlusion system containing PG or oleic acid/PG was applied to the forearm of each subject; a third site was untreated. The chambers were removed after 3 h, and ATR-FTIR spectra were recorded. Upon removal at the site where oleic acid/PG was applied, the absorbance at the wavelength measuring free acid indicated the presence of extra free acid, while the absorbance at the wavelength characteristic of esterified ester lipids was similar to untreated and PG-treated sites. The absorbance ratio for these 2 wavelengths leveled off to that of the untreated site 3 h after removal of the chambers, indicating migration of oleic acid into lower cell layers or lateral spreading within the stratum corneum. The researchers also examined ATR-FTIR when the oleic acid/PG site was tape-stripped 5 times, removing 50% of the thickness of the stratum corneum, 2 h after removal of the application chambers. The results indicated oleic acid accumulates in a deeper layer after the tape stripping.

Dermal Irritation/Sensitization

In studies reported in the 1994 assessment[1] and currently, PG induced skin irritation reactions in normal subjects and in patients. Reactions were observed at concentrations as low as 10% in predictive tests and 2% in provocative tests. Use studies of deodorants containing 35-73% PG did not report any potential for eliciting irritation or sensitization. PG generally did not induce sensitization reactions when tested at 12-86%. In a modified Draize sensitization study with 203 subjects, PG (0.2 ml; concentration not stated) induced 19 cutaneous reactions at challenge.

Propylene Glycol

It has been reported that intradermal injection of 0.02 ml undiluted PG produces a wheal-and-flare reaction within minutes, while the same volume applied epidermally does not produce any reaction. It has also been stated that subjective or sensory irritation sometimes occurs in volunteers after application of various concentrations of PG.[37] Some researchers have proposed classifying skin reactions to PG into 4 groups: (1) irritant contact dermatitis; (2) allergic contact dermatitis; (3) non-immunologic contact urticaria; and (4) subjective or sensory irritation.

Predictive Testing - Irritation

The results of the clinical dermal predictive irritation and sensitization studies on PG described in this section are summarized in Table 6.

Propylene Glycol

A 24-h single insult occlusive patch test (SIOPT) was performed on an undiluted deodorant formulation containing 69.15% PG using 20 subjects (gender not specified).[38] A clear stick deodorant was used as a reference control. The test sites were scored on a scale of 0-4. With the test formulation, 4 subjects had a score of ± (minimal faint uniform or spotty erythema) and 3 subjects had a score of 1 (pink-red erythema visibly uniform in the entire contact area.) The primary irritation index (PII) for the deodorant containing 69.15% PG was 0.25. This product was significantly less irritating than the reference control, which had a PII of 0.93 and 17/20 subjects with scores between ± and 3.

In another SIOPT, a deodorant formulation containing 68.06% PG was tested undiluted using 20 subjects (gender not specified) [39] A deodorant currently in use was used as a reference control. Three subjects had a score of ± and 1 had a score of 1 to the test formulation. The PII for the test formulation was 0.13, which was not significantly different than the PII of 0.15 for the reference control.

The irritation index for PG and 0.16 M oleic acid/PG was determined using 12 subjects (number per gender not specified) by applying occlusive chambers containing these 2 test substance to the volar forearm for 3 or 24 h. [40] An empty

chamber was applied to a third site, and the fourth site was an untreated control. Laser Doppler velocimetry (LDV) was used to measure blood flow upon removal. After 3 and 24 h, the irritation index for PG was 1.1 (6 subjects) and 1.2 (10 subjects), respectively, indicating a 1-fold increase in blood flow to the test site. The irritation index for oleic acid/PG was 2.1 (6 subjects) and 3.9 (10 subjects) after 3 and 24 h, respectively. Visually, the 24-h application of PG produced only slight erythema, while the 24-h application of oleic acid/PG produced clearly visible irritation.

Thirty-day use studies were completed with 26 male, 40 female, and 24 male subjects to evaluate the potential for deodorant sticks containing 35,[41] 65.2,[42] and 73% PG,[43] respectively, to induce dermal irritation and/or sensitization. The subjects were instructed to apply the product to the underarm once daily for 30 days. None of the subjects had any irritation or sensitization reactions, and the researchers concluded that the deodorant sticks containing 35, 65.2, or 73% PG did not demonstrate a potential for eliciting dermal irritation or sensitization. In a 4-wk use study completed with 26 male subjects following the same procedure, a deodorant stick containing 65.8% PG also did not demonstrate a potential for eliciting dermal irritation or sensitization.[44]

Predictive Testing – Sensitization

Propylene Glycol

A maximization test was completed with 25 subjects, 18 male and 7 female, to determine the sensitization potential of a deodorant containing 69.15% PG.[45] During the induction phase, an occlusive patch containing 0.1 ml of 0.25% aq. sodium lauryl sulfate (SLS) was applied for 24 h to the outer arm, volar forearm, or the back of each subject. That patch was removed and an occlusive patch containing 0.1 ml of the test substance was applied to the same site for 48-72 h, after which time the patch was removed and the site examined. If there was no irritation, the sequence was repeated with the SLS and test article patches for a total of 5 induction exposures. If irritation occurred at any time, the SLS patch was excluded. After a 10-day non-treatment period, a challenge was performed in which a previously unexposed site opposite the test site was first pretreated with an occlusive patch containing 0.1 ml of 5% aq. SLS for 1 h. Then an occlusive patch containing the test substance was applied for 48 h, and the site was scored 1 and 24 h after removal. All the scores were 0 for all subjects following challenge. No sensitization reactions were seen to a deodorant containing 69.15% PG.

An RIPT was completed with 101 subjects, 30 male and 71 female, to determine the sensitization potential of a stick deodorant formulation containing 73% PG.[46] During the induction phase, semi-occlusive patches containing 0.2 g of the test material were applied to the upper back of each subject for 24 h, 3 times per wk, for a total of 9 applications. The first patch was scored (scale of 0-4) immediately after removal, while all others were scored prior to application of the next patch 24-48 h later. During the induction phase, a score of 2 (moderate reaction) resulted in moving the patch to an adjacent site while a second score of 2 or scores of 3-4 (marked-severe) resulted in discontinuation of dosing. The challenge was performed approximately 2 wks after the final induction patch using the same procedure but at an adjacent previously untested site. Challenge sites were scored 24 and 72 h after application. Scores of + (barely perceptible or spotty erythema) to 2, with some dryness, were observed throughout the study. Four subjects discontinued dosing during the induction phase because of a second moderate reaction. While the authors stated that a stick deodorant formulation containing 73% PG "did not indicate a clinically significant potential for dermal irritation or allergic contact sensitization," the Expert Panel questioned that conclusion since repeated reactions were observed.

Another RIPT was completed with 99 subjects to determine the sensitization potential of a stick antiperspirant formulation containing 86% PG.[47] (Initially, 113 subjects were enrolled in the study; withdrawal was not due to adverse effects.) Occlusive patches containing 0.2 g of the test formulation were applied to the infrascapular region of the back 9

times during induction and once during challenge. One "+" reaction was observed during the entire study. There was no evidence of sensitization with an antiperspirant containing 86% PG.

Provocative Testing-Sensitization

Propylene Glycol

Thirty-six patients with chronic venous insufficiency (CVI) were patch tested with 5% PG in petrolatum by application to the back for 2 days. [48] Twelve patients were male; 2, 5, and 5, had 1st, 2nd, and 3rd degree CVI, respectively. Twenty-four patients were female; 5 and 19 had 2nd and 3rd degree CVI, respectively. (Procedural details not provided.) The results were read after 2 and 3 days; doubtful reactions were read after 4 days. The sensitization rate as a percentage of all patients was 8.3%. The sensitization rate of patients with 2nd and 3rd degree CVI tested with PG was 10 and 8.3%, respectively. Significant differences were found between males and females; 12.5% of females were sensitized while 0% of males were sensitized.

During the period 2000-2004, 308 patients, 111 males and 197 females, with contact dermatitis were patch-tested using the European standard series and some additional chemicals, including PG.[49] Patches were applied to the upper back using Finn chambers that were held in place with Scanpor tape. The patches were removed after 2 days, and the sites were evaluated after 30 min and 4 days. PG, 5% in petrolatum, did not cause any positive reactions.

Photoallergenicity

PG did not produce a photoallergic response in a provocative photopatch test.

Propylene Glycol

Over a 2-yr period, 30 males and 52 females with photoallergic contact dermatitis were photopatch tested with a standard series of sunscreens as well as some additional chemicals, including PG.[50] (Dose not given.) The allergens were applied in duplicate on the back and covered with opaque tape. After 24 h, the tape was removed, the test sites evaluated, and one set of test sites was irradiated with a UVA dose of 5 J/cm^2 (using a Daavlin UVA cabinet), giving an irradiance of 10.4 mW/cm^2; this provided a 320-400 nm spectrum. The test sites, which were not covered after irradiation, were evaluated 24 and 72 h later. While some positive reactions were observed to other test agents, PG did not produce a photoallergenic or contact allergy response.

Enhancement Of Irritation Effects

Addition of PG to an isopropanol vehicle enhanced the irritant reactions of benzoic acid; maximal enhancement was seen with 5% PG.

Propylene Glycol

The effect of the addition of PG to an isopropanol vehicle on the irritant reaction of benzoic acid was determined in a non-occlusive test using 15 subjects, 7 males and 8 females.[51] Benzoic acid in isopropanol was tested at concentrations of 31, 62, 125, and 250 mM without PG as well as with the addition of 1, 2, 5, 10, and 25% PG. The vehicles were also tested. Visual appearance, laser Doppler flowmetry, and skin color (using a Minolta chromameter) were measured at 20, 40, and 60 min after application. PG enhanced the strength of the reactions to 125 and 250 mM benzoic acid, but not to 31 or 62 mM benzoic acid. (This was observed using all 3 measurement methods.) Enhancement was observed with the addition of 1% PG, and maximal enhancement was attained with 5%. No reaction to application of the vehicles was observed.

Retrospective Analyses

Retrospective analysis of pools of patient patch test data indicated that ≤6.0% of patients tested had positive reactions to 30% aq. PG.

The NACDG performed a number of retrospective analyses on various dermatological conditions. These studies are summarized in Table 7.

Case Reports

A few case reports have been described concerning PG and hand dermatitis or atopic dermatitis. Patch test results generally had a positive reaction to PG in these case studies. Improvement was seen with the avoidance of PG-containing products.[52,53]

SUMMARY

Propylene glycol (PG) and polypropylene glycols (PPGs) have previously been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel, and it was concluded that these ingredients were safe for use in cosmetic products at concentrations up to 50.0%. This rereview was opened because concentration of use of PG is now greater than 50% and, also, to include all the PPGs identified in the *International Cosmetic Ingredient Dictionary and Handbook*, i.e., PPG-3, PPG-7, PPG-9, PPG-12, PPG-13, PPG-15, PPG-16, PPG-17, PPG-20, PPG-26, PPG-30, PPG-33, PPG-34, PPG-51, PPG-52, and PPG-69, as well as tripropylene glycol.

PG is an aliphatic alcohol that is manufactured as a reaction product of propylene oxide and water. Tripropylene glycol is manufactured by sequential addition of propylene oxide to PG and contains only a 3 chain length. PPGs are manufactured by the addition of propylene oxide to dipropylene glycol and have average chain lengths of their "n" value; for example, PPG-3 would have an average chain length of 3. USP grade PG (used in cosmetics) manufactured by Dow contains diethylene glycol and ethylene glycol at concentrations that are non-detectable (quantification limit of 0.008 percent wt/wt). Two companies reported that the concentration of propylene oxide in PPGs used to make finished products is ≤10 ppm propylene oxide.

In 1984, PG was reported to the FDA as being used in 5676 cosmetic formulations at concentrations of 0 to >50%. As of 2009, use of PG has increased significantly, and PG was reported to FDA as being used in 9747 cosmetic formulations. Concentration of use has also increased, with bath oil/tablet/salt preparations containing up to 99% PG and leave-on formulations, including deodorants, containing up to 73% PG. The PPGs are not as widely used as PG, and the maximum reported concentration is 22%. Tripropylene glycol is used in 8 formulations, 7 of which are deodorants, at up to 22%.

In mammals, the major pathway of PG metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases. When PG was administered i.v. to human subjects (patients), elimination from the body occurred in a dose-dependent manner. Animal studies using PPGs with avg mol wts of 425-2025 indicated that PPGs are readily absorbed from the GI tract and excreted in the urine and feces.

Dermal penetration of PG from a ternary cosolvent solution through hairless mouse skin was 57% over a 24 h period. Using thermal emission decay (TED)-Fourier transform infrared (FTIR) spectroscopy, it appeared that PG did not reach the dermis.

PG can act as a penetration enhancer for some chemicals and under some conditions. Often, it works synergistically with other enhancers. The mechanism by which PG enhances penetration has not been definitively identified.

In both the 1994 safety assessment and currently, few toxic effects were seen in dosing with PG or PPGs. The oral LD_{50} of PG was >21 g/ kg for rats. The LD_{50} of PPG, mol wts 300-3900, ranged from 0.5-40 g/kg for rats, while the oral LD_{50} of PPGs, mol wts not given, ranged from 1.5-17 g/kg for guinea pigs . The dermal LD_{50} of PG was >11.2 g/kg for mice and was 13 g/kg for rats. The dermal LD_{50} of PPG, mol wts 425-2025, was >20 ml/kg for rabbits. All mice survived in a short-term study in which mice were given 10% PG in drinking water for 14 days, and all rats and mongrel dogs survived oral dosing with up to 3.0 ml 100% PG, 3 times per day, for 3 days. In a subchronic study, a dose of ≤50,000 ppm PG given

in the feed for 15 wks did not produce any lesions. PPG 750 did not cause any adverse when given at 0.1% for 10 days, but a concentration of 1% produced slight increases in liver and kidney weight. The highest no effect level of PPG 1200 fed to rats and dogs for 90 days was 0.3%. No adverse effects were seen in a 90-day study in which rats or dogs fed 501 or 810 mg/kg/day, respectively, PPG 2000. In a subchronic dermal study, 1 ml/kg PPG 2000 did not cause adverse effects in rabbits, but 5 and 10 ml/kg caused a slight depression in growth. Subchronic inhalation data reported some effects due to PG exposure of 2.2 mg/l air for 6 h/day, 5 days/wk, for 13 wks, but these effects were inconsistent and without dose-response trends. In the 1994 safety assessment, no toxic effects were reported in chronic studies when rats or dogs were given feed containing 50,000 ppm or 5 g/kg, respectively, PG.

Undiluted PG and PPG, mol wt 425-2025, were at most slight ocular irritants. Dermal irritation studies were reported in the 1994 assessment and currently. In one study using nude mice, 50% PG may have caused skin irritation, while in another study, 100% PG was minimally irritating to hairless mice. Undiluted PG was at most a mild dermal irritant in a Draize test using rabbits with intact and abraded skin. No reactions to undiluted PG were observed with guinea pigs, rabbits, or Gottingen swine. Using nude mice, hypertrophy, dermal inflammation, and proliferation were observed with 50% PG. These effects were not seen in hairless mice with undiluted PG. PG (concentrations not given) was negative in a number of sensitization/allergenicity assays using guinea pigs. In a study using guinea pigs, 0.5 ml PG was a weak sensitizer. PPG (concentration not stated), mol wt 425-2025, was not an irritant to rabbits.

PG did not have any adverse reproductive or developmental effects when evaluated in mice at doses of ≤5%, rats at doses of ≤1600 mg/kg, rabbits at doses of ≤1230 mg/kg, or hamsters at doses of ≤1550 mg/kg. Embryonic development was reduced or inhibited completely in cultures of mouse zygotes exposed to 3.0 or 6.0 M PG, respectively. A current study examining induction of cytogenetic aberrations found an increase in the frequency of premature centrosphere separation with 1300-5200 mg/kg PG. In zygotes from PG-dosed mice, hyperploidy was increased.

PG, ≤10,000 µg/plate, was not mutagenic in Ames tests with or without metabolic activation. PG, tested at concentrations of 3.8-22.8 mg/ml, was a weak but potential inducer of sister chromatid exchanges (SCEs), causing a dose-dependent increase in SCEs in a Chinese hamster cell line. However in another SCE assay using human cultured fibroblasts and Chinese hamster cells with and without metabolic activation, PG was not mutagenic. PG, 32 mg/ml, induced chromosomal aberrations in a Chinese hamster fibroblast line, but not in human embryonic cells. PG was not mutagenic in mitotic recombination or basepair substitution assays, or in a micronucleus test or a hamster embryo cell transformation assay. (Concentration used not specified) Tripropylene glycol, ≤10,000 µg/plate, was not mutagenic in an Ames assay.

PG was not carcinogenic in a 2 yr chronic study in which rats were given ≤50 000 ppm PG in the diet. Dermal application of undiluted PG to Swiss mice in a lifetime study produced no significant carcinogenic effects. PG was not carcinogenic in other oral, dermal, and subcutaneous studies.

PG acts synergistically with fatty acids, such as oleic acid, to enhance dermal penetration in clinical studies. Addition of PG to an isopropanol vehicle enhanced the irritant reactions of benzoic acid; maximal enhancement was seen with 5% PG.

PG induced skin irritation reactions in normal subjects and in patients. Reactions were observed at concentrations as low as 10% in predictive tests and 2% in provocative tests. Use studies of deodorants containing 35-73% PG did not report any potential for eliciting irritation or sensitization. PG generally did not induce sensitization reactions when tested at 12-86%, although results were questionable in a RIPT of a deodorant containing 73% PG. Additionally, in a modified Draize sensitization study with 203 subjects, PG (0.2 ml, concentration not stated) induced 19 cutaneous reactions at challenge. PG

did not produce a photoallergic response in a provocative photopatch test. Retrospective analysis of pools of patient patch test data indicated that ≤6.0% of patients tested had positive reactions to 30% aq. PG.

DISCUSSION

The CIR Expert Panel reopened the safety assessment of propylene glycol and polypropylene glycols to address the safety of current high-use-concentrations of PG, as well as to add all the PPGs currently listed in the *International Cosmetic Ingredient Dictionary and Handbook*. This report is intended to also address the safety of similar PPGs that may be used as cosmetic ingredients ~~in~~ the future.

Since tripropylene glycol is similar to PG and the PPGs, its safety can be supported by the existing data and therefore the Panel decided to include tripropylene glycol in this safety assessment.

Propylene oxide is used in the manufacture of PPGs, but should not appear in cosmetic formulations because of safety concerns. The Panel expects that PPGs contain ≤10 ppm propylene oxide, ensuring the safety of formulations in which PPGs are used.

PG and PPGs were not considered to be acute or chronic toxicants in oral or dermal studies, were not genotoxic or carcinogenic, and were not reproductive or developmental toxicants, suggesting that use in cosmetics would be safe in regard to these endpoints.

At the time of the original safety assessment, a concentration limit of 50% PG and PPGs was established based on the results of existing irritation and sensitization studies. The potential for skin irritation was especially of concern under occlusive conditions, and this potential could be concentration-dependent. An RIPT performed using a stick antiperspirant containing 86% PG produced no evidence of sensitization. Additionally, use studies of deodorant sticks containing 35-73% PG did not demonstrate a potential for eliciting dermal irritation or sensitization. Therefore the Panel determined that PG would not present a sensitization risk at the concentrations currently in use.

The Expert Panel did note that propylene glycol may act as a penetration enhancer. Some cosmetic ingredients have been regarded as safe based on the fact that they do not penetrate the skin. If propylene glycol enhances penetration of such ingredients, then they should not exist together in formulation.

Additionally, PG is used in aerosols. The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration and the duration of the exposure and their site of deposition within the respiratory system. In practice, aerosols should have at least 99% of their particle diameters in the 10 – 110 µm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 µm. Particles with an aerodynamic diameter of ≤ 10µm are respirable. In the absence of significant inhalation toxicity data, the Panel determined that PG can be used safely in hair sprays because the product particle size is not respirable.

The CIR Expert Panel, as noted earlier, considers that the available data for PPG-3 through PPG-69 would extend to any PPGx to be used in cosmetics in the future. Because propylene glycol is considered safe, there are no concerns regarding residual monomers in PPGs. Were the "x" to be 32, for example, ample evidence suggests that its toxicity would be no different from PPG-30 or PPG-33. Were the "x" to be 120, the ingredient would be sufficiently large so that no dermal penetration would be possible.

AMENDED CONCLUSION

. The CIR Expert Panel concluded that propylene glycol, PPG-3, PPG-7, PPG-9, PPG-12, PPG-13, PPG-15, PPG-16, PPG-17, PPG-20, PPG-26, PPG-30, PPG-33, PPG-34, PPG-51, PPG-52, PPG-69, any additional PPG-x (where x is any whole number ≥3) that may become a cosmetic ingredient in the future, and tripropylene glycol are safe as cosmetic ingredients in the present practices of use and concentration as described in this safety assessment when formulated to be non-irritating.[1]

[1] Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

FIGURES

Figure 1. Propylene Glycol

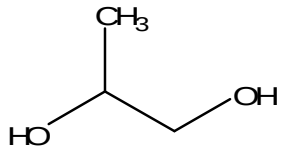


Figure 2. Tripropylene Glycol

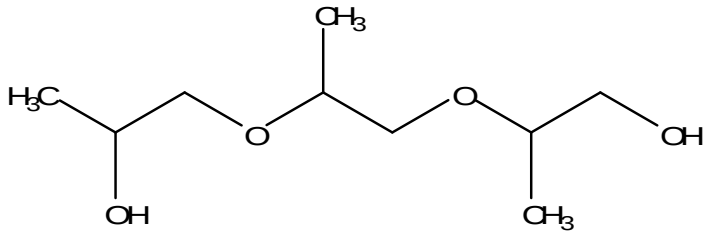
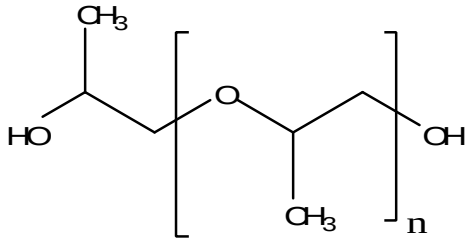


Figure 3. Polypropylene Glycol



n = average propylene oxide chain length and is reflected in the name, e.g. PPG-12 would have n=11

TABLES

Table 1. Synonyms

Chemical Name	Synonyms/Other Technical Names
propylene glycol	1,2-dihydroxypropane[2,18,19] 2-hydroxypropanol[2,18] methyl glycol[19] methylene glycol[19] methylethyl glycol[2,18] methylethylene glycol[18] monopropyl glycol[54] monopropylene glycol[18] propane-1,2-diol[18] 1,2-propanediol[2,18,19] propane-1,2-glycol[54] α-propylene glycol[54] 1,2-propylene glycol[18] propyleneglycolum (EP)[2] trimethyl glycol[18]
tripropylene glycol	2-(2-(2-hydroxypropoxy)propoxy)propan-1-ol
PPG-n (n = average chain length)	polyoxypropylene (n) [2] polypropylene glycol (n) [2]

Table 2. PPG INCI names, molecular weight names, and calculated molecular weights

PPG INCI Name (PPG-n; n = avg. number of moles of propylene oxide)	Molecular Weight name as indicated by the trade name listed in the Dictionary	calculated molecular weight (n x 58) + 18
PPG-3	PPG 200	192
PPG-7		424
PPG-9	PPG 400 or PPG 425	540
PPG-12		714
PPG-13		772
PPG-15		888
PPG-16	PPG 950	946
PPG-17	PPG 1000	1004
PPG-20	PPG 1200	1178
PPG-26	PPG 2000	1526
PPG-30	PPG 4000	1758
PPG-33		1932
PPG-34		1990
PPG-51		2976
PPG-52	PPG3000	3034
PPG-69		4020

In original report, but not specifically listed in table:

PPG 225
PPG 300
PPG 750
PPG 1025
PPG 2025
PPG 3900

Table 3. Chemical and physical properties

Characteristic	Description
PROPYLENE GLYCOL	
color and form	colorless viscous stable hygroscopic liquid[19]
odor	practically odorless[19]
molecular weight	76.09[18]
solubility	miscible in water, acetone, and chloroform; soluble in ether[18] miscible with water, alcohol, and many organic solvents[19]
melting point	-59°C[18] -60°C[19]
boiling point	187.3°C[19] 188.2°C[18]
freezing point	-59ºC[55]
density/specific gravity	1.036 @ 25°C /4°C[18] 1.0381 @ 20°C/20°C[19]
disassociation constant (pKa)	14.8 @ 25°C[18]
octanol/water partition coefficient	log K_{ow} = -0.92[18]
index of refraction	1.4323 @ 20°C[18] 1.4293 @ 27°C[19]
TRIPROPYLENE GLYCOL	
color and form	colorless liquid[20,56]; slightly viscous[20]
odor	odorless[20,56]
molecular weight	192.26[20]
solubility	soluble in water, methanol, and ether; miscible with alcohol[20] miscible in water[56]
melting point	<-30°C[20,56]
boiling point	271°C[20,57]
density/specific gravity	1.019 @ 20°C/20°C[20]
octanol/water partition coefficient	log P_{ow} = -0.5[56,57]
index of refraction	1.4449 @ 20°C/D[20]
reactivity	combustible[19]
POLYPROPYLENE GLYCOLS	
color and form	clear, colorless or practically colorless, viscous liquid[58]
molecular weight	dependent on chain length
solubility	lower mol. wt. polymers are soluble in water[19] soluble in such organic solvents as aliphatic ketones and alcohols, but is insoluble in ether and most aliphatic hydrocarbons (mol. wts. not defined)[58]
pH	between 6-9[59]
density	1.002-1.007[55]
reactivity	non-volatile; combustible[19]

Table 4. Current and historical concentration of use data

Product Category	Freq. of Use – 1984[1]	Freq. of Use 2009[6#]	Conc. of Use (%) 1984[1]	Conc. of Use (%) 2009[7]
PROPYLENE GLYCOL				
Baby Products				
baby shampoos	7	6 (56)	0.1-10*	0.005-0.4
baby lotions/oils/powders/creams	8	18 (137)	1-10*	0.02
other baby products	3	26 (143)	0.1-5	0.001-0.003[1]
Bath Preparations				
bath oils/, tablets, and salts	29	23 (314)	0-50*	1-99
bubble baths	123	24 (169)	0-25*	1-5
bath capsules	not reported	1 (4)	not reported	not reported
other bath preparations	48	64 (234)	0-50*	not reported
Eye Makeup Preparations				
eyebrow pencil	1	3 (144)	1-5	2-14
eyeliner	55	94 (754)	0-25	0.2-16
eye shadow	175	40 (1215)	0.1-25*	0.03-18
eye lotion	4	66 (254)	0-10	0.02-47
eye makeup remover	17	21 (128)	0.1-50	0.03-2
mascara	60	130 (499)	0-25*	0.3-16
other eye makeup preparations	43	115 (365)	0-10*	7[2]
Fragrance Preparations				
colognes and toilet waters	96	304 (1377)	0-50	0.3-6
perfumes	28	117 (666)	0-50	0.03-5
powders (dusting/talcum, excl. aftershave talc)	10	3 (221)	0-5*	0.005-1
sachets	28	not reported	0-50	not reported
other fragrance preparations	43	120 (566)	0- >50	0.2-70
Hair Preparations				
hair conditioners	58	446 (1226)	0-10*	0.08-42
hair sprays (aerosol fixatives)	10	60 (312)	0-5*	0.003-4
hair straighteners	22	129 (178)	1-10	4-25
permanent waves	43	7(69)	0-50*	0.3-10
rinses (non-coloring)	13	9 (33)	0-10*	0.5-10
shampoos (non-coloring)	211	494 (1361)	0-25*	0.06-5
tonics, dressings, other hair grooming aids	31	468 (1205)	0-25*	0.3-40
wave sets	18	11 (51)	0-25	not reported
other hair preparations	16	318 (807)	0.1-50*	0.3-38
Hair Coloring Preparations				
hair dyes and colors (requiring caution stmt)	288	1361 (2393)	0.1-25*	5-15
hair tints	not reported	20 (21)	not reported	10
hair rinses (coloring)	29	NR	0.1-10	1
hair shampoos (coloring)	3	16 (40)	0-10	not reported
hair color sprays (aerosol)	not reported	7 (7)	not reported	not reported
hair lighteners with color	1	5 (21)	1-5	not reported
hair bleaches	6	13 (149)	1-10	not reported
other hair coloring preparations	5	23 (168)	1-50*	6-16
Makeup Preparations (Not Eye)				
blushers (all types)	85	17 (434)	0- >50*	0.2-67
face powders	29	15 (661)	0-5	0.009-0.2
foundations	262	134 (589)	0-25*	4-57
leg and body paints	3	4 (29)	1-5	0.03-0.4
lipstick	1181	39 (1883)	0-10*	0.1-8
makeup bases	334	42 (117)	0-25*	0.1-21
rouges	30	not reported	0-25*	not reported
makeup fixatives	4	3 (45)	0.1-1*	not reported
other makeup preparations	131	75 (485)	0-50*	2-19
Manicuring Preparations				
basecoats and undercoats	not reported	3 (79)	not reported	not reported
cuticle softeners	12	11 (27)	0-10	4
nail creams and lotions	7	6 (14)	0.1-5	0.02-12
nail polish and enamel	not reported	8 (333)	not reported	0.008-0.9
nail polish and enamel removers	2	2 (24)	0-1	0.0008-6

Table 4. Current and historical concentration of use data

Product Category	**Freq. of Use – 1984[1]**	**Freq. of Use 2009[6#]**	**Conc. of Use (%) 1984[1]**	**Conc. of Use (%) 2009[7]**
other manicuring preparations	6	15 (138)	1-50	not reported
Oral Hygiene Products				
dentrifrices	2	4 (59)	1-25	0.02-10
mouthwashes and breath fresheners	3	9 (74)	1-5	0.04-5
other oral hygiene products	1	4 (86)	0.1-1	not reported
Personal Cleanliness Products				
bath soaps and detergents	39	502 (1665)	0-10	0.01-25
deodorants (underarm)	124	313 (580)	0- >50*	3-73
douches	7	4 (14)	0-50	1
feminine deodorants	not reported	9 (19)	not reported	not reported
feminine hygiene products	2	no category	0.1-10	no category
other personal cleanliness products	53	272 (792)	0-50	2-10[3]
Shaving Preparations				
aftershave lotions	97	174	0-50*	0.02-8
beard softeners	3	not reported	10-25*	not reported
preshave lotions (all types)	8	1 (22)	0-5*	not reported
shaving cream	34	37 (122)	0-25*	4-40
shaving soap	not reported	3 (10)	not reported	not reported
other shaving preparation products	13	59 (134)	0.1-25*	not reported
Skin Care Preparations				
cleansing	276	398 (1446)	0-50*	0.5-39
depilatories	6	14 (42)	0-25	0.006-13
face/hand/body preps (excl. shaving) (1984) face and neck (excl shaving) (2009) body and hand (excl shaving) (2009)	417	 558 (1583) 648 (1744)	0-50*	 5-30 0.009-68
face and neck sprays	not reported	no category	not reported	6
body and hand sprays	not reported	no category	not reported	1-10
foot powders and sprays	1	11 (47)	1-5	0.03
hormone products	5	no category	0-25	not reported
moisturizing products	358	846 (2508)	0-50*	0.2-41
night preparations	105	121 (353)	0-50*	0.004-20
paste masks (mud packs)	83	136 (441)	0-25*	0.1-11
skin lighteners	19	no category	1-25*	not reported
skin fresheners	136	84 (259)	0-25*	0.002-7
wrinkle-smoothing products (removers)	14	no category	0-25*	not reported
other skin care preparations	149	415 (1308)	0- >50*	2-20[4]
Suntan Preparations				
suntan gels/creams/liquids	76	43 (107)	0-25*	0.01-5
indoor tanning preparations	12	86 (240)	1-10*	1-33
other suntan preparations	15	19 (62)	0-25*	10
Total for Propylene Glycol	**5676**	**9747 (34,391)**	**0- >50***	**0.0008-99**
POLYPROPYLENE GLYCOL				
Fragrance Preparations				
colognes and toilet waters	not reported	30 (1377)	not reported	not reported
perfumes	not reported	4 (666)	not reported	not reported
Hair Coloring Preparations				
hair dyes and colors (requiring caution stmt)	not reported	6 (2393)	not reported	not reported
hair bleaches	not reported	1 (149)	not reported	not reported
Makeup Preparations (not eye)				
blushers (all types)	not reported	1 (434)	not reported	not reported
Personal Cleanliness Products				
other personal cleanliness products	not reported	1 (792)	not reported	not reported
Shaving Preparations				
aftershave lotion	not reported	1 (367)	not reported	not reported
Skin Care Preparations				
cleansing	not reported	1 (1446)	not reported	not reported
face and neck preparations (excl. shaving)	not reported	1 (1583)	not reported	not reported
Suntan Preparations				
indoor tanning preparations	not reported	1 (240)	not reported	not reported

Table 4. Current and historical concentration of use data

Product Category	Freq. of Use – 1984[1]	Freq. of Use 2009[6#]	Conc. of Use (%) 1984[1]	Conc. of Use (%) 2009[7]
Total for Polypropylene Glycol	**not reported**	**47**	**not reported**	**not reported**
PPG-9				
Bath Preparations				
other bath preparations	2	3 (234)	1-5	not reported
Eye Makeup Preparations				
eye lotion	not reported	not reported	not reported	11
Hair Preparations				
shampoos (non-coloring)	4	74 (1361)	0.1-5	0.5
Personal Cleanliness Products				
bath soaps and detergents	not reported	not reported	not reported	22
other personal cleanliness products	not reported	33 (792)	not reported	not reported
Skin Care Preparations				
cleansing	not reported	not reported	not reported	0.05-0.4
depilatories	not reported	not reported	not reported	4
face and neck creams, lotions, and powders	not reported	not reported	not reported	15
skin fresheners	not reported	not reported	not reported	4
Total for PPG-9	**6**	**110**	**0.1-5**	**0.05-22**
PPG-12				
Hair Preparations				
hair conditioner	not reported	2 (1226)	not reported	not reported
tonics, dressings, other hair grooming aids	not reported	1 (1205)	not reported	not reported
Skin Care Preparations				
face and neck creams, lotions, and powders	not reported	not reported	not reported	1
Total for PPG-12	**not reported**	**3**	**not reported**	**1**
PPG-15				
Eye Makeup Preparations				
eyeliner	not reported	1 (754)	not reported	not reported
Total for PPG-15	**not reported**	**1**	**not reported**	**not reported**
PPG-17				
Skin Care Preparations				
face and neck (excl. shaving)	not reported	3 (1583)	not reported	1
moisturizing creams, lotions, and powders	not reported	not reported	not reported	1
Suntan Preparations				
suntan gels, creams, and liquids	not reported	not reported	not reported	2
Total for PPG-17	**not reported**	**3**	**not reported**	**1-2**
PPG-26				
Bath Preparations				
bath oils, tablets, and salts	1	not reported	1-5	not reported
Fragrance Preparations				
perfumes	not reported	1 (666)	not reported	not reported
Makeup Preparations (not eye)				
blushers	3	not reported	1-5	not reported
Personal Cleanliness Products				
deodorants	4	not reported	0.1-5	not reported
Skin Care Preparations				
face and neck creams, lotions, and powders	not reported	not reported	not reported	0.2
moisturizing products	1	not reported	1-5	not reported
paste masks (mud packs)	not reported	not reported	not reported	0.2
other skin care preparations	1	1 (1308)	1.5	not reported
Total for PPG-26	**10**	**2**	**0.1-5**	**0.2**
PPG-30				
Hair Preparations				
tonics, dressings, other hair grooming aids	not reported	1 (1205)	not reported	not reported
Skin Care Preparations				
cleansing	not reported	3 (1446)	not reported	not reported
face and neck (excl. shaving)	not reported	1 (1583)	not reported	not reported
Totals for PPG-30	**not reported**	**5**	**not reported**	**not reported**
PPG-34				
Skin Care Preparations				

Table 4. Current and historical concentration of use data

Product Category	**Freq. of Use – 1984[1]**	**Freq. of Use 2009[6#]**	**Conc. of Use (%) 1984[1]**	**Conc. of Use (%) 2009[7]**
paste masks (mud packs)	not reported	not reported	not reported	20
Total for PPG-34	**not reported**	**not reported**	**not reported**	**20**
PPG 425				
Hair Coloring Preparations				
hair bleaches	1	not reported	1-5	not reported
Total for PPG 425	**not reported**	**not reported**	**1-5**	**not reported**
TRIPROPYLENE GLYCOL				
Fragrance Preparations				
perfumes	not reviewed	1 (666)	not reviewed	not reported
Personal Cleanliness Products				
deodorants (underarm)	not reviewed	7 (580)	not reviewed	21-22
Skin Care Preparations				
moisturizing creams/lotions/powders	not reviewed	NR	not reviewed	0.00004
Total for Tripropylene Glycol	**not reviewed**	**8**	**not reviewed**	**0.00004-22**

[#]total number in category given in parentheses; not provided with 1984 data
*unknown concentrations were also reported
[1]0.003% in a rinse-off product
[2]7% in a brow and lash gel
[3]2% in a shower gel; 6% in a foot scrub
[4]6% in a vaginal area moisturizer/lubricant

Table 5. Penetration enhancement by PG

Test Chemical	Barrier	Methods	Results
dihydroergotamine (DHE) mesylate	excised male New Zealand white rabbit skin	- in vitro diffusion using Franz diffusion cells; several vehicles were used to examine their effect on the penetration of 16.0 mg/ml DHE; the penetration of various concentrations of DHE in PG was also examined	-the avg amount of DHE that penetrated from a water base during 24 h was 0.3 µg, with a max. rate of absorption of 0.02 µg/h during the 9-12 h period; with a PG-vehicle, the avg amount of DHE that penetrated was 7.25 µg, with a max rate of absorption of 0.3 µg/h during the 12-24 time period; for comparison, the amount absorbed with PEG-400 and liquid paraffin vehicles was 3.05 and 4.14 µg DHE over 24 h -the avg amount of DHE that penetrated with 8, 16, 30, and 50 mg/ml DHE in PG was 3.78, 7.25, 14.47, and 38.98 µg over 24 h[60]
betamethasone 17-valerate (BMV); hydrocortisone 17-butyrate HCB); hydrocortisone (HC) (topical glucocorticoids [GCs])	excised human abdominal skin	-the multilayer membrane system (MMS) was used to evaluate the penetration of the GC/PG gel formulations; time intervals for the penetration studies were 200 min and 24 h -the relationship between the physicochemical properties of the drugs in binary PG/water mixtures and the rate and extent of their penetration was studied -in vitro penetration through skin was determined	-with BMV gels, PG acted as a cosolvent as penetration was thermodynamically controlled; 10-80% PG was evaluated – BMV penetration was almost unaffected with 10-40% PG, was slightly increased with 40-60% PG, and was decreased with >60% PG; the greatest amount of BMV in whole skin was found with 40% PG - penetration of HCB with 10-80% PG was evaluated, and the greatest penetration was with 20% PG - with HC, the rate and penetration increased with increasing PG contents from 5-80% in suspension-type gel formulation; the enhancement effect of PG masked the thermodynamically-controlled behavior of HC; increased penetration of HC with increasing PG concentration was detected in the stratum corneum and the viable epidermis, but the amount permeating into the dermis was independent of PG content[61]
pyrene butyric acid (PBA)	excised female human breast skin	-dermal penetration through skin was determined using glass diffusion cells -the MMS was used for liberation studies -the effect of fatty acids was also evaluated	-high PBA release rates from PG were seen in the MMS -PBA and PG appear to penetrate simultaneously into the stratum corneum; at 1000 min, the ratio is increased indicating an accumulation or deposition of PBA due to more rapid PG-transfer into the epidermis -PG penetrated better with the addition of fatty acids; mode of enhancement is non-specific[35]
aspirin	excised porcine ear epidermis	-in vitro studies using Franz cells, FTRI, and TEWL were used to determine penetration enhancement by PG, ethanol, and combinations of the 2	in all of the studies, the percutaneous absorption of aspirin was increased greatest with 80% ethanol/20% PG; these results were very similar to ethanol alone; PG alone did not significantly increase absorption of aspirin[62]
diclofenac sodium (DFS)	excised male Wistar rat skin	-DFS gels were dissolved in water, a 20-60% PG/water mixture, or 30-40% PG/3-5% isopropyl myristate (IPM)/water (pH 7.2)	-PG acted as a cosolvent, not a penetration enhancer -PG/IPM synergistically enhanced drug flux; maximum enhancement ratios were with 40% PG[63]

Table 6. Clinical dermal irritation/sensitization studies with propylene glycol – Predictive

Dose	Subjects	Procedure	Results
IRRITATION			
69.15% in a deodorant	20	24-h SIOPT	PII – 0.25; significantly less irritating than the reference control[64]
68.06 in a deodorant	20	SIOPT	PII – 0.13[65]
PG	12	occlusive chambers for 3 or 24 h; LDV	irritation index – 1.1 (3 h); 1.2 (24 h) – slight erythema[40]
0.16 M oleic acid/ PG	12	occlusive chambers for 3 or 24 h; LDV	irritation index – 2.1 (3 h); 3.9 (24 h) – clearly visible erythema[40]
35% in a deodorant	26 M	30 day use study	no potential for eliciting irritation or sensitization[41]
65.2% in a deodorant	40 F	30 day use study	no potential for eliciting irritation or sensitization[66]
73% in a deodorant	24 M	30-day use study	no potential for eliciting irritation or sensitization[67]
65.8% in a deodorant	26 M	4-week use study	no potential for eliciting irritation or sensitization[68]
SENSITIZATION			
69.15%	18M; 7F	maximization test	no sensitization reactions[69]
73% in a deodorant	30M; 71F	RIPT	scores of + to 2 observed throughout the study; 4 subjects discontinued during induction due to a repeat moderate reaction[70]
86% in a deodorant	99	RIPT	one + score observed throughout the study; no sensitization[71]

Table 7. Retrospective analyses with propylene glycol

No. of patients	Years studied	% PG	Methods	Findings
not given	1984-1996	10 aq.	data were collected from NACDG-reported studies; the SPIN for each allergen was calculated as the proportion of the population allergic by the weighted clinician-assessed likelihood of relevance of the reaction	the SPIN rank for PG has changed over time: 23 in 1984-1985; 40 in 1992-1994; 41 in 1994-1996[72]
45138 patients (16210 males; 28928 females)	1992-2002	20 aq.	analysis of a large pool of IVDK patch-test data, examining possible relevance of patient characteristics	- 1044 patients (2.3%), 412 males and 632 females, had positive reactions; 895, 129, and 20 patients had 1+, 2+, and 3+ reactions, respectively; of the 895 1+ reactions, 114 were to PG only - 1041 doubtful, 43 follicular, and 271 irritant reactions were observed - there were little difference between patients with positive and negative reactions to PG; the greatest difference was the high portion (27.2% vs. 13.1%) of patients with leg dermatitis – this was the only sig. risk factor - the most common concomitant reactions were with fragrance mix, balsam of Peru, lanolin alcohol, amerchol L-101, and nickel sulfate[73]
23359 patients	1996-2006	30 aq.	retrospective cross-sectional analysis of NACDG patch-test data to evaluate the patient characteristics, clinical relevance (definite – positive reaction to a PG-containing item; probable – PG was present in the skin contactants; possible – skin contact with PG-containing material was likely), source of exposure, and occupational relationship	- 810 patients (3.5%) had reactions to PG; 12.8% of the reactions were definitely relevant, 88.3% were currently relative (definite, probable or possible relevance), 4.2% were occupation related - 135 patients were positive to only PG; in these patients, the face was the most commonly-affected area (25.9%), a scattered or generalized pattern was next (23.7%) - the most common concomitant reactions were with balsam of Peru, fragrance mix, formaldehyde, nickel sulfate, and bacitracin[74]
1494 patients w/ SGD (patient pop. 10061)	2001-2004	30 aq.	retrospective analysis of cross-sectional NACDG data using only patients with SGD as the sole site affected	89 patients (6.0%) had positive reactions to PG 94% of the reactions were currently relative, with 30.3, 20.2, and 42.7% being of definite, probable, and possible relevance[75]
10061 patients	2001-2004	30 aq.	retrospective analysis of cross-sectional NACDG data to determine reactions to foods	109 patients (1.1%), 37 males and 72 females, had 122 reactions to foods; of those 122 reactions, 5 were to PG[76]

IVDK – Information Network of Departments of Dermatology
NACDG – North America Contact Dermatitis Group
SGD – scattered generalized distribution
SPIN – significance-prevalence index number

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: John Bailey, Ph.D. 4/7/10
Industry Liaison to the CIR Expert Panel

DATE: April 7, 2010

SUBJECT: Concentration of Propylene Oxide in Polypropylene Glycol Ingredients

One company that uses polypropylene glycols in cosmetic products reports propylene oxide specifications in the range of 0.001 ppm to less than 10 ppm in the raw materials they use.

A second company reports a limit of 10 ppm in the raw materials they use in their cosmetic products.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: John Bailey, Ph.D. 3/29/10
Industry Liaison to the CIR Expert Panel

DATE: March 29, 2010

SUBJECT: Comments on the Draft Report on Propylene Glycol, Tripropylene Glycol and PPGs
CIR Expert Panel Meeting April 5-6, 2010

p.1 - The conclusion in the Abstract needs to be changed to reflect the Conclusion section (safe as used when formulated to be none irritating).

p.1 - In the Introduction, it would be helpful if it was made clear that this report provides brief summaries of the original report and updates the information. Including a date when the last literature search was completed might also be helpful.

p.2 - The Dow Chemical letter (reference 4) states that the quantification limit is "0.008 percent wt/wt" not 0.08% as indicated on p.2 of the report.

p.3 - It is not clear what is meant by "the form of PG metabolism". Perhaps the word "form" should be "pathway" or "route"?

p.5 - In the summary of the Other Biological Effects section, it would be helpful to include doses or exposure concentrations.

p.5 - In the Acute Exposure summary, it is not clear what is meant by "relatively harmless". It would be helpful to provide the lowest doses resulting in effects and/or the highest doses that did not result in effects.

p.6-9 - In the summaries of the Subchronic Exposure, Chronic Exposure, Ocular Irritation, Dermal Irritation/Sensitization, Reproductive and Developmental Toxicity, Embryotoxicity, Genotoxicity and Carcinogenicity sections it would be helpful to include doses and/or exposure concentrations.

p.9 - For the NTP genotoxicity study of Tripropylene Glycol (reference 33), please add that the study was done with and without metabolic activation over a dose range of 0 to 10,000 µg/plate.

p.10 - Please add exposure concentrations to the summary of the clinical Dermal Irritation/Sensitization section.

p.10 - Please change "This score was significantly less irritating..." to "This product was significantly less irritating..."

p.11, 31 Table 6 - It would be helpful to note that the deodorant stick that contained 35% Propylene Glycol also contained 20% Butylene Glycol.

p.12 - What concentration or dose of Propylene Glycol was tested in the photoallergenicity study (reference 49)?
p.12 - Please define LDF.
p.13 - In the first paragraph of the Summary, (if the CIR Expert Panel agrees) please add the statement from the introduction and draft Discussion that the review applies to all chain lengths that may be added to the Dictionary.
p.13 - In the discussion of the penetration study using TED-FTIR spectroscopy, it would be helpful to note that the study was done in humans exposed to Propylene Glycol for 30 minutes.
p.14 - In the Summary, it would be helpful to include some doses/exposure concentrations resulting in effects.
p.14-15 - In discussing the use studies in the Summary, please make it clear that they were studies of products containing Propylene Glycol.
p.15 - If the CIR Expert Panel agrees, it would be helpful to add the statement that the review applies to all chain lengths that may be added to the Dictionary to the Conclusion.
p.17 - Reference 17 needs a date.
p.22, Figures 1-3 - Please provide a reference for the Figures.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: John Bailey, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 23, 2010

SUBJECT: Comments on the Tentative Amended Report on the Safety Assessment of Propylene Glycol, PPGs and Tripropylene Glycol as Used in Cosmetics

General Comment: During the Team meetings at the April 2010 CIR Expert Panel meeting, Dr. Snyder requested that doses or concentrations be included in section summaries of all CIR reports. His team agreed with him. This has not yet been done for this report.

p.2 - The two companies reporting the level of propylene oxide in raw materials were referring to the level of propylene oxide in ingredients (PPGs) used to make finished cosmetic products, not the raw materials used to manufacture PPGs.

p.4 - In the description of reference 22, please provide the units for the concentration of Propylene Glycol at the surface of the stratum corneum ("0.42 at 12 min to 0.07 after 182 min").

p.5 - Although the authors of reference 25 may have used the term "urinalytes" it does not seem to be a real word. Searching for this word on Google only brings up the paper by these authors. Please change this to urinary metabolites.

p.5 - Please revise the summary of the Acute Oral Exposure section to include some doses at which effects were observed. It is not clear what is meant by "generally harmless". If it means that death occurred only at relatively high doses, it should be stated more specifically. If a person had a convulsion it probably would not be considered "generally harmless".

p.5 - Please revise the summary now under the heading Subchronic Inhalation Exposure section to include doses. As this summary includes more than just inhalation exposure studies, the heading also needs to be revised.

p.6 - Please revise the summary of the Chronic Exposure section to included doses or concentrations.

p.6 - Please revise the summary of the Ocular Irritation section to include the concentrations that were tested.

p.6 - Please revise the summary of the Dermal Irritation/Sensitization section to include the concentrations that were tested. In what species was Propylene Glycol negative for sensitization?

p.6 - Please revise the summary of the Reproductive and Developmental Toxicity section to include the doses or concentrations tested.

p.7 - In the summary of the Embryotoxicity section, please add the concentration tested in the cytogenetic aberration study.
p.8 - Please add the doses/concentrations tested to the summary of the Genotoxicity section.
p.8 - If available, please add the volume of Propylene Glycol used in the mouse dermal carcinogenicity study.
p.9 - In the summary of the Dermal Irritation/Sensitization section, please add the concentration of Propylene Glycol tested in the modified Draize sensitization study.
p.9 - Please revise "the stick deodorant sticks"
p.11 - What dose or concentration of Propylene Glycol was tested in the photoallergy study (it is not stated in either the section summary or the study summary)?
p.13 - What concentrations were tested in the Ames tests?
p.13 - What concentration of Propylene Glycol resulted in 19 reactions? What concentrations of Propylene Glycol were tested in patients?