Caprylyl Glycol

CIR EXPERT PANEL MEETING

DECEMBER 13-14, 2010

ADMINISTRATIVE

Cosmetic Ingredient Review
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November 18, 2010

Memorandum

To: CIR Expert Panel

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Subject: Draft Report on Caprylyl Glycol and other 1,2-Glycols

A copy of the draft report on these ingredients is included along with the following: CIR report history, Minutes from the June and August 2010 Panel meetings, Literature search strategy, Data profile, Comments on the draft report from the Personal Care Products Council, a Council recommendation to delete ingredients from draft report, and unpublished data received from the Council on September 16, 2010 (See CIR report history). These data are identified by a vertical line in the right margin of the report text.

At the August 30-31, 2010 CIR Expert Panel meeting, the Panel issued an insufficient data announcement with the data requests stated in the CIR report history. After reviewing the unpublished data received, the Panel needs to determine whether or not the available data remain insufficient for evaluating the safety of caprylyl glycol and other 1,2-glycols in cosmetic products. The Panel also needs to address the Council's recommendation to delete ingredients from the draft report. If it is determined that the available data are sufficient for evaluating the safety of 1,2-glycols in cosmetic products, then a tentative report with a "safe as used" or "safe with qualifications" conclusion could be issued at the December 13-14, 2010 Expert Panel meeting.

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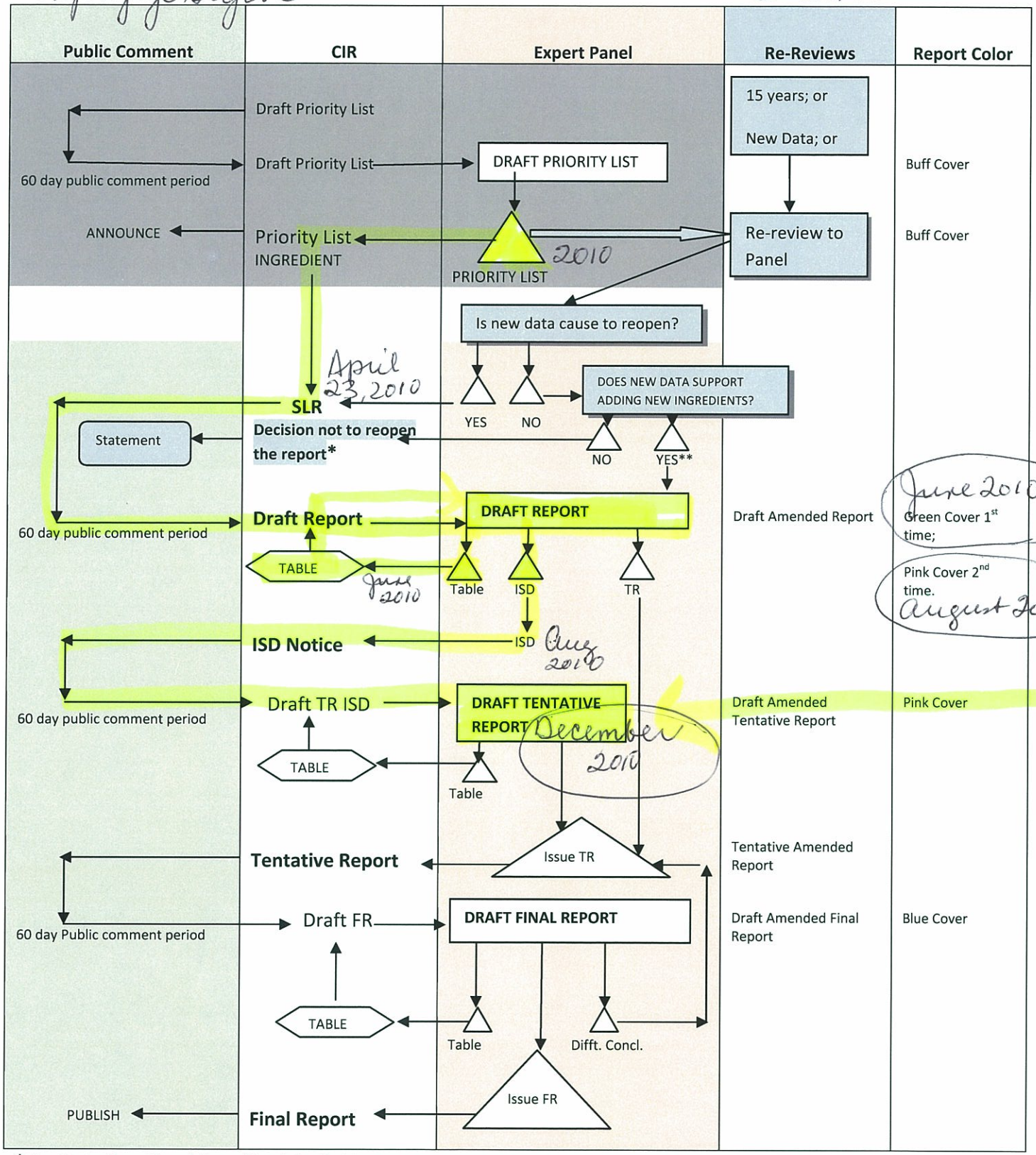
SAFETY ASSESSMENT FLOW CHART

Caprylyl Glycol — December 2010



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

Expert Panel Decision

Document for Panel Review

Option for Re-review

CIR History of:

Caprylyl Glycol and other 1,2-Glycols

The availability of a scientific literature review (SLR) on this group of ingredients was announced on April 23, 2009. Comments from the Personal Care Products industry were received during the 60-day comment period.

1st Review, Belsito and Marks Teams/Panel: June 28-29, 2010

The draft safety assessment was tabled pending ingredient use concentration data from industry and any available data on the skin irritation and sensitization potential of longer chain 1,2-glycols, e.g., C15-18 Glycol. The Panel requested the addition of data on Propylene Glycol from the CIR final safety assessment and amended final safety assessment on this ingredient for use in the safety assessment of other 1,2-glycols, i.e., in the absence of safety test data. Development of a draft discussion that includes CIR boilerplate statement on skin penetration enhancement property of certain 1,2-glycols was also requested.

2nd Review, Belsito and Marks Teams/Panel: August 30-31, 2010

Use concentration data received from industry are included in Table 3.

The Panel issued an insufficient data announcement with the following data requests: (1) dermal absorption data on caprylyl glycol or similar lipid-soluble 1,2-glycol; (2) if significant dermal absorption occurs, then a reproductive /developmental toxicity study may be needed; (3) if significant dermal absorption occurs, then a 28-day dermal toxicity study to evaluate other systemic toxicity endpoints, using caprylyl glycol or another appropriate lipid – soluble 1,2-glycol, may be needed; and (4) genotoxicity data

3rd Review, Belsito and Marks Teams/Panel: December 13-14, 2010

The following data were received from the Council on September 16, 2010: (1) RIPT on leg and foot gel containing 0.5% 1,2-hexanediol; (2) in-use safety evaluation on body wash containing 0.15% 1,2-hexanediol; (3) RIPT on lipstick containing 0.5% caprylyl glycol; (4) ocular irritation study on lash gel serum containing 3% pentylene glycol; and (5) RIPT on foundation containing 0.112% pentylene glycol. Additionally, a letter recommending that the current report include only ingredients with 4 to 12 carbons (1,2-butanediol, pentylene glycol, 1,2-hexanediol, caprylyl glycol, decylene glycol, and lauryl glycol) was received from the Council on October 28, 2010.

Ingre-dients	Toxline &PubMed	ChemIDplus	Multidatabase (See legend*)	DART	Household Products	Beilstein	Registry	Kosmet	Napralert	RTECS	CAplus
AG	0	1	0	0	0	0	1	0	0	0	0
CG	3	**1**	0	0	0	0	1	0	0	0	13
HG	0	0	0	0	0	0	0	0	0	0	0
LG	6	1	0	0	0	0	1	0	0	0	7
MG	15	1	0	0	0	0	1	0	0	0	5
OG	0	1	0	0	0	0	1	0	0	0	1
SG	0	1	0	0	0	0	1	0	0	0	5
CPG	9	1	0	0	1	0	1	0	0	0	17
DG	5	1	0	0	0	0	1	0	0	0	14
PG	28	1	0	0	0	0	1	0	0	1	24
12B	67	1	0	0	0	0	1	1	0	1	46
12H	6	1	0	0	1	0	1	0	0	0	24
C4G	1	0	0	0	0	0	29	0	0	0	0
C5G	0	2	0	0	0	0	1	0	0	0	0
C8G	1	0	0	0	0	0	1	0	0	0	0
C2G	0	0	0	0	0	0	1	0	0	0	0
NG	55	1	1 - CCRIS	0	0	0	1	0	0	1	50
BEP	0	1	0	0	0	0	1	0	0	1	8
IP	0	1	0	0	0	0	1	0	0	0	5
TP	147	1	1 - HSDB	1	1	0	1	0	0	1	10
MP	7	1	1 – HSDB	0	0	0	1	0	0	1	9
14B	253, with limitations	1	1 – CCRIS; 1 – HSDB; 1-Genetox	10	1	0	1	0	1	1	225
11D	4	1	0	0	0	0	1	0	0	1	27
HD	313	2	1 – HSDB; 1 - CCRIS	1	0	0	1	0	0	1	78
OD	14	1	0	1	0	0	1	0	1	0	27
15P	38	1	0	0	1	0	1	0	0	1	62
PD	80, with limitations	1	0	1	1	0	1	0	1	1	186

*Data in Table: Publications used (Total no. in search); Multidatabase = HSDB, CCRIS, ITER, IRIS, Gene-Tox, and LacMed;

Searches Performed on 3/8-12/2010
Search updated on 10/15/2010 using PubMed and Toxline – no pertinent hits

Ingredients

1,2-glycols

(AG) Arachidyl Glycol OR 1,2-Eicosanediol OR 39825-93-9

(CG) Cetyl Glycol OR 1,2-Dihydroxyhexadecane OR 1,2-Hexadecanediol OR 1,2-Hexadecylene Glycol OR 2-Hydroxycetyl Alcohol OR 6920-24-7

(HG) Hexacosyl Glycol OR Hexacosil glicol

(LG) Lauryl Glycol OR1,2-Dihydroxydodecane OR 1,2-Dodecanediol OR 1,2-Dodecylene Glycol OR 1119-87-5

(MG) Myristyl Glycol OR 1,2-Tetradecanediol OR 21129-09-9

(OG) Octacosanyl Glycol OR 1,2-Octacosanediol OR 97338-11-9

(SG) Stearyl Glycol OR 1,2-Dihydroxyoctadecane OR 1,2-Octadecanediol OR 20294-76-2

(CPG) Caprylyl Glycol OR Capryl Glycol OR 1,2-Dihydroxyoctane OR 1,2-Octanediol OR 1,2-Octylene Glycol OR 1117-86-8

(DG) Decylene Glycol OR 1,2-Decanediol OR 1119-86-4

(PG) Pentylene Glycol OR 1,2-Dihydroxypentane OR 1,2-Pentanediol OR 5343-92-0

(12B) 1,2-Butanediol OR 1,2-Butylene Glycol OR 1,2-Dihydroxybutane OR 584-03-2

(12H) 1,2-Hexanediol OR 1,2-Dihydroxyhexane OR 6920-22-5

(C4G) C14-18 Glycol OR Ethylene Glycol Fatty Acid Ester (2)

(C5G) C15-18 Glycol OR Alkylene (15-18) Glycol OR Cetyl Stearyl Vicinal Glycol OR Glycols, C15-18 OR 70750-40-2 OR 92128-52-4

(C8G) C18-30 Glycol OR Ethylene Glycol Fatty Acid Ester (1)

(C2G) C20-30 Glycol OR Alkylene (20-30) Glycol

Branched 1,3-glycols

(NG) Neopentyl Glycol OR 2,2-Dimethyl-1,3-Dihydroxypropane OR Dimethylolpropane OR 2,2-Dimethyltrimethylene Glycol OR Neopentanediol OR Neopentylene Glycol OR 1,3-Propanediol, 2,2-Dimethyl- OR 126-30-7

(BEP) Butyl Ethyl Propanediol OR 1,3-Propanediol, 2-Butyl-2-Ethyl OR 115-84-4

(IP) Isopentyldiol OR 1,3-Butanediol, 3-Methyl- OR 1,1-Diemthyl-1,3-propanediol OR 3-Hydroxy-3-Methylbutanol OR Isoprene Glycol OR 3-Methyl-1,3-Butanediol OR 3-Methyl-1,3-butylene Glycol OR 2568-33-4

(TP) Trimethyl-1,3-Pentanediol OR 1,3-Pentanediol, 2,2,4-Trimethyl- OR TMPD (alcohol) OR 144-19-4

(MP) Methylpropanediol OR β-Hydroxyisobutanol OR 2-Methyl-1,3-Propanediol OR 2163-42-0

Terminal glycols

(14B) 1,4-Butanediol OR Butane-1,4-diol OR Tetramethylene Glycol OR 110-63-4

(11D) 1,10-Decanediol OR Decamethylene Glycol OR 112-47-0

(HD) Hexanediol OR 1,6-Dihydroxyhexane OR Hexamethylenediol OR Hexamethylene Glycol OR 1,6-Hexanediol OR 629-11-8 OR 26762-52-7

(OD) Octanediol OR 1,8-Octanediol OR 629-41-4

(15P) 1,5-Pentanediol OR 1,5-pentylene glycol OR 111-29-5

(PD) Propanediol OR 1,3-Propanediol OR 1,3-Dihydroxypropane OR 1,3-Propylene Glycol OR Trimethylene Glycol OR 504-63-2 OR 6264-14-2

″Arachidyl Glycol″ OR 39825-93-9 OR ″Cetyl Glycol″ OR 6920-24-7 OR ″Hexacosyl Glycol″ OR ″Lauryl Glycol″ OR 119-87-5 OR ″Myristyl Glycol″ OR 21129-09-9 OR ″Octacosanyl Glycol″ OR 97338-11-9 OR ″Stearyl Glycol″ OR 20294-76-2 OR ″Caprylyl Glycol″ OR 1117-86-8 OR ″Decylene Glycol″ OR 1119-86-4 OR ″Pentylene Glycol″ OR 5343-92-0 OR ″1,2-Butanediol″ OR ″1,2-Butylene Glycol″ OR 584-03-2 OR ″1,2-Hexanediol″ OR 6920-22-5 OR ″C14-18 Glycol″ OR ″Ethylene Glycol Fatty Acid Ester″ OR ″C15-18 Glycol″ OR 70750-40-2 OR 92128-52-4 OR ″C18-30 Glycol″ OR ″C20-30 Glycol″

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Caprylyl Glycol Check List for December, 2010. Writer – Wilbur Johnson																		
				Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Caprylyl glycol		X		X						X		X	X	X				
Arachidyl glycol																		
Hexacosyl glycol																		
Lauryl glycol										X								
Myristyl glycol																		
Octacosanyl glycol																		
Stearyl glycol				X														
Decylene glycol		X			X		X			X	X	X	X	X		X		
Pentylene glycol				X			X			X		X		X				
		X																
1,2-butanediol			X	X	X	X	X	X		X	X		X		X	X		
1,2-hexanediol		X								X		X		X	X			
C14-18 glycol																		
C15-18 glycol				X														
C18-30 glycol																		
C20-30 glycol																		
Propylene glycol	X	X	X	X			X		X	X	X	X	X	X	X	X	X	X

TRANSCRIPTS/MINUTES

DR. MARKS: Okay. Next is Caprylyl glycol, Green 2.
DR. HILL: I think that's potayto, potahto, by the way.
DR. MARKS: So this is the first time 44
the Panel's seen this. A scientific literature review was issued in April. And we have things like -- issues like read-across data okay. Obviously, what data needs are there?
And I'll open it up to Rons and Tom.
DR. SHANK: I had no data needs.
DR. SLAGA: I also (inaudible) the data in evaluating the safety of, you know, 1, 2-glycols (inaudible).
DR. MARKS: Okay. So, no data in each, Ron. And then on page 21, and 22, are formulas for the 1,2-glycols. Those all -- nothing should be deleted out of that. Do you --
DR. SHANK: Actually, I recommend -- I think propylene glycol, because it's a reference. Throughout the report, we refer to propylene glycol, even though it's not a 1, 2-glycol.
Just put that in as a -- because it's a reference compound.
DR. HILL: Propylene glycol is a 1,2-glycol, is it not? I think so.
DR. MARKS: So, Ron, are you suggesting 45
-- and that's one of the questions I have -- we combine with propylene glycol? So that would be -- would that mean you open propylene glycol, which we had a "safe" with "non- irritating" conclusion?
DR. SHANK: No, I was just suggesting that the structure --
DR. MARKS: The structure --
DR. SHANK: -- be given somewhere in the report, since we refer to it frequently in the report.
DR. HILL: So, in terms of long-chain glycols here, we have only cytoxicity for cetyl glycol. We have only cytotoxicity and ocular irritation for lauryl glycol, and cetyl C16 -- right? So, we're being asked to extrapolate to -- it looks like C28 and C20, C20 to 30 mixtures, C18 to 30 mixtures. And I'm bothered by that because there's a shift in cellular processing once you get to longer chains.
And, in fact, if you look at where the data clusters, most of it's pentylene, the C4 and 46
the C6 -- very little data outside of that, based on what's in this report, at least.
DR. MARKS: We have irritation and

sensitization on the --
DR. HILL: In caprylyl, which is lead --
DR. MARKS: -- hexanediol.
DR. HILL: -- caprylyl, which is the lead ingredient.
DR. MARKS: Right -- which were okay.
DR. HILL: That's C8, right? So we really, we have data that, to me, gives a comfort level with read-across, really up to C8. Not much else I read.
And specifically, with respect to that question on page 2, which is Panel book page 4, you have some branched 1,3s that are listed in here, and they're not included, right? I mean, it's only place I see anything about that in the whole report.
MR. JOHNSON: What page are you on, please?
DR. HILL: Panel book, 4. It looks like report page 2. Or no, I'm sorry. It's Panel book page 4. It's the literature search. This is just getting literature search, right?
MR. JOHNSON: Yes. Okay. I see where you are.
DR. HILL: But there's nothing -- I'm not sure that the branched 1,3s relate to anything else in the report, do they? Nor do the terminal glycols relate to anything else that's in the report, I think.
Those are very different compounds, in terms of biology.
MR. JOHNSON: Yes -- what happened is that initially, all of those were included in one group --
DR. HILL: Mm-hmm.
MR. JOHNSON: -- but the safety assessment was only on the one key glycol.
DR. HILL: Okay. So maybe -- I guess this is not part of the report anyway.
MR. JOHNSON: No, (inaudible).
DR. HILL: So in a lot places, we can look at these categories, really data on one or two compounds -- I mean, they're all very small. So, again, we're looking at trying to extrapolate to much longer molecules. And I know that probably the rationale is, well, they don't penetrate the skin as efficiently would be maybe the best way to state that, but --
MS. EISENMANN: Well, primary uses of just (inaudible) compounds, there seems to be a little use of --
DR. HILL: Mm-hmm. I agree.
MS. EISENMANN: -- insofar, in concentration of use information is still out. It's only those three that I'm getting "uses" for.
DR. HILL: Right.

DR. MARKS: So what was the concentration of use? I had a question on that.
MS. EISENMANN: I don't have it in yet.
DR. MARKS: Okay.
MS. EISENMANN: It's not complete. So I can bring it. But I can say, generally, I think it's less -- it's 1 percent and less.

DR. MARKS: Okay.
MS. EISENMANN: But it's those three compounds that are (inaudible).
DR. MARKS: (inaudible), do you remember what you were going to say?
This brings the general question, Alan, which is -- when a grouping is established, then there will be a certain frequency of use. I guess it comes out of the BCRP, right? Related to that.
So if we're using a threshold, so many uses and then this triggers to be on the priority list, or at least looked at for the priority list. And then we subsequently reduce the size of the groupings substantially, that doesn't change anything, right? I mean, in terms of it's now on the priority list, and lets say we go from 400 to 200 in terms of frequency of use by virtue of cutting down on ingredients, does that matter? Once we've started down the road, we can go down the road?
MR. ANDERSEN: Were we to, for some reason, decide that the lead ingredient, caprylyl

glycol, didn't belong in the caprylyl glycol report, then that would give me some pause.

DR. MARKS: Sure.

MR. ANDERSEN: But --

DR. MARKS: That wouldn't be the case here.

MR. ANDERSEN: -- if we start chopping off some of the zero-use ingredients or low-use ingredients, you know, that wouldn't stop the progress on the report -- the rationale that there are over a thousand uses of caprylyl glycol would still hold sway.

MR. STEINBERG: I generally break these types of compounds by their solubility in water. Anything below the C5 diols are usually totally miscible or very soluble in water. As soon as you go to C5, the pentylene glycol's maximum solubility is about 2 percent. C6 is about 1.4. C8, the caprylyl glycol's maximum solubility in water's about.5.

That tends to be the maximum use levels of these compounds. The C10 is about a tenth of a

percent, and that's starting to be used now, also.

So I'd break them down by water solubility versus non-water solubility, which directly impacts your comments.

DR. HILL: Right, because in that case you'll be looking at emulsions and (inaudible) type (inaudible).

MR. ANDERSEN: Yes.

DR. HILL: And then that would be a very different set of behaviors, I think, in terms of even dermal, and definitely mucous membranes.

DR. MARKS: Any further comments, in terms of the safety of these compounds? I mean, we've started out by saying it looks like we have all the data needs. We can cross-read these compounds and their toxicologic findings. And we're aiming towards a "safe," is that correct?

DR. HILL: Well, again, in my assessment, my personal assessment is, if we don't extend too far up into the molecular weight range -- in other words, if we pare out -- say, we pare out anything above C8, then I'm good with that.

If we don't, I'm not good with that, because then I think we have big gaps in the data.

DR. MARKS: Tom? And, again, is it the same issue, Ron, you're concerned about the proliferative effects, whether it's plus or minus?

DR. HILL: No, I'm concerned about any effects. In this case it could be sensitization. It could be -- well, sensitization, in particular, lacking any information one way or the other.

DR. MARKS: Ron?

DR. SHANK: I didn't have any answer.

DR. SLAGA: I didn't either. It was brought up, the water solubility to get in the skin, if you get to the higher ones (inaudible), right? I don't see how that would be a (inaudible).

DR. HILL: Well, then it would be very formulation- dependent, the behavior, in terms of -- any dermal penetration capability would be dependent on exactly what they're in, what the rest of the composition of what they're in.

And I know that puts us into an area, 53

then, if we're dealing ingredient by ingredient, we don't talk about very much, but, yeah, we are at least starting to capture things like penetration enhancement -- which is good. And you could take that to a ridiculous extreme, which I don't think would benefit anybody.

But once we get that point of -- again, we'd be talking about emulsions and then what's the behavior of that, or we'd be talking about mycellular -- I'm not sure we can conclude, "Well, this doesn't get into the skin, so nothing would happen," depending on what it's in. Because by virtue of that behavior, they would be formulated differently, the preparations would be different.

If they're not even being used, I would say why put them in the report, other than we'd be giving a green light for people to do something that I'm not sure -- I mean, and of course, then we can depend on the honorable behavior of companies to make sure they don't market something that's unsafe.

But I think if concluded it safe, 54

there's an implicit green light.

MR. STEINBERG: To answer your question, the C5, 6 and 8 are used -- I'm not going to say 100 percent -- 99 percent in emulsion (inaudible).

DR. HILL: Already.

MR. STEINBERG: Yes.

DR. HILL: Yes.

MR. STEINBERG: They're not used in surfactant systems at all.

DR. HILL: And that would be my expectation. All right, so going to higher molecular weight, this changes the nature of dermal. But I'm not sure I believe that they wouldn't, depending on what they're in, wouldn't get into the skin, couldn't cause sensitization.

Now, that would be picked up -- I mean, if it was just sensitization, that would be picked up in due course with the company doing a study on these, I think.

MR. STEINBERG: Right.

DR. HILL: So, I mean at a level.

DR. MARKS: Plus, there would have been

an alert in the literature by now, if there was something significant in that way.

DR. HILL: Well, there -- if somebody decided to try to use one of these, or had in the past, and then they determined that they shouldn't take it to market because of it, I mean, we will never know that.

DR. MARKS: So you've had concerns, if you look at the log P, somewhere around -- you said C8. And I just want to capture --

DR. HILL: No, the C8 was we've got, actually, biological data.

DR. MARKS: Right. Above --

DR. HILL: In that vein. We don't have anything. We don't have anything above that to speak of.

I made myself a little table --

DR. MARKS: Okay.

DR. HILL: -- we have essentially nothing, once you get above caprylyl.

DR. MARKS: Right. So, with that caveat from Ron -- again, Ron Shank, Tom, do you feel comfortable including -- and we've certainly done it before -- these other ingredients which are not being used at this point, based on the safety data we have now, so that we could move forward with the ingredients as listed and, say, moving toward a "safe," issue a tentative report "safe?"

DR. SLAGA: Fine. That was my original (inaudible).

DR. MARKS: Right. And do you have any --

DR. SLAGA: You two have a --

DR. SHANK: Well, C15-C18 glycol is used to makeup (inaudible).

DR. HILL: It is.

DR. SHANK: Well, that's in the "Use" tables.

DR. HILL: Yeah, okay. I thought it was, because I thought that's where I read --

DR. MARKS: Yes, there are four compounds that are used. The caprylyl pentylene, the hexanediol, and the C15-18 glycols are used. So we go up, certainly, greater than C8.

DR. SHANK: But there are no safety data above C8.

DR. MARKS: Yeah.

DR. SHANK: So if you ask for dermal sensitization, say, it's unlikely you're going to get it, because these things are only used as one makeup (inaudible).

DR. MARKS: Yeah. Rachel.

MS. WEINTRAUB: So, is the idea on the table that we will not include ingredients over C8? Or say "insufficient?"

DR. MARKS: That's what I'm trying to sort out right now. Ron Hill has certainly raised that concern, although it's not just about C8. Because we are using ingredients above C8.

MS. EISENMANN: We haven't had much time on this report yet to try to get data. So it would be good to give us the opportunity to see if we could find any data.

MS. WEINTRAUB: So is that an "insufficient?"

MR. BAILEY: I don't see anything -- I mean, the whole idea of (inaudible) and read-across, regardless of frequency of use, is to be able to extrapolate and use information that's available along the, you know -- it's sort of the fundamental nature of the compound.

And I don't see -- I have a difficult time seeing anything in this group that would suggest a red flag. I mean, I just don't see it. It's a very benign group of substances.

Now, granted, we may not have all the data, you know, per se. But I think that our professional sense is that it would be highly unlikely that there's anything in this group that would raise a flag. I just don't see it. I mean, that's what my take on it, is.

DR. HILL: As a medicinal chemist, lesson number one is, you can have something that's perfectly inactive, and you add two carbons, and you can have suddenly something that's very active.

We shouldn't really ever extrapolate, unless we have comfort level that, okay, it's molecular weight 5,000, log P of 20, won't get in the skin.

MR. BAILEY: But as a medicinal chemist, do you see anything in this group that would raise a red flag? I mean, I just don't --

DR. HILL: These are so un-drug-like that -- I mean, my gut feel sense, which even a medicinal chemist, I'll admit, is always dangerous anyway to rely too much on that, doesn't help me much here.

So, I mean, yes, there are no reactive groups, in terms of binding the proteins. But no information to know one way or the other, sensitization. There's no data on anything above C12. There's very limited data on C12. There's one cytotoxicity study in ocular irritation, and there's nothing above C12.

And I disagree that the log P or the molecular weights above that level, because at C12, we're still only at molecular weight 202. We're well within things that could wander through the skin.

And, in fact, as the chains get longer, you could argue that penetration might actually go up in this particular group, because we're getting into lipophilicity ranges that should help dermal penetration, as opposed to hinder. So, you've got to admit -- for me, I have zero comfort level with extrapolating.

DR. SLAGA: Yes -- just, I had a comment. You know, for years I studied cholesterol, and very lipid soluble type compounds that are metabolized to androgens, estrogens, glucocorticoids, mineralocorticoids. Those type of compounds -- even, you know, produced in the body -- have to have very good receptor relationships or binding proteins to (inaudible). And it's the only way.

The only compound I know that has gotten through the skin is a compound that interacts with a receptor. Just by chance, it happened to be a receptor-mediated, that carries it through the skin to the (inaudible).

DR. HILL: I'm not worried about anything happening systemically here. I'm thinking of things strictly that might happen within the skin.

DR. SLAGA: Well, I'm saying that if there is a receptor-type mechanism of a natural compound, then you can get things --

DR. HILL: I think we used --

DR. SLAGA: -- through a very -- a barrier system, if you will. But other than that, I don't think --

DR. HILL: No, it will go by passive diffusion. If you've got a log P of 3 or 4, it will nicely passively diffuse through the skin. You don't need carrier proteins, you don't need anything. It's --

DR. SLAGA: Well, I'm talking about way up, the ones that are --

DR. HILL: We don't have anything like that here.

DR. SLAGA: No.

DR. SHANK: Your Figure 3. A very helpful figure.

MR. ANDERSEN: Yes, it is.

DR. HILL: Oh, okay. We do have one. But even that one, where we're looking at a log P of 12, which is C28 -- all right. Yeah, it's probably not going to get into the bloodstream. I don't think we can look at that and say it isn't going to get into the lower layers of the skin. Again, based on what we've heard from Dr. Bronaugh, and the literature that he relied on, in part, as well, when he presented.

So I just have this -- my gut is

revolting. We just toss this out, based on log P of 12, because the molecular weight's still not that high. What's the molecular weight for C28? 426. It's less than 500, well below 500.

So -- I don't know.

DR. MARKS: I think we have that problem, oftentimes, in terms of if you want to just look at sensitization and irritation. But I think at some point we have to decide -- we'll actually have to decide are we going to go back rather than forward, in trying to expand groups. 63

Because we're going to always have that issue, I have a feeling.

DR. HILL: Well, I thought the idea behind the group expansion was to quit talking about the no-brainer expansions and try to service high through-put, I guess. And I know if Wilma were sitting here, she'd be giving me a glare. But --

DR. MARKS: I don't think it's -- in this case, the no-brainer doesn't apply, because that's with re-reviews, where we were going to open up, and it was a no-brainer.

For this, where it's the first time we've seen it, that doesn't apply.

So -- again, I -- obviously there is a certain amount of uncertainty there. But, overall, I think the group, I'm not concerned about.

DR. HILL: Well, then I'll be outvoted.

(Laughter)

DR. MARKS: Well, the other team may have a -- 64

DR. HILL: I'll be probably be outvoted seven to one.

DR. MARKS: Not necessarily. As I said, the other team may have a different feeling.

I want to go back -- so, at this point I think, at least, again, the feeling, in terms of moving forward, Ron, your comfort level is to restrict the ingredients that would be in this report. My sense from Ron Shank and Tom Slaga, myself, we can leave it with these as are listed in the introduction, or in the --

DR. HILL: I mean, even if we had additional data on lauryl -- just looking at that log P table -- but there's practically nothing even on lauryl.

So then we're down to -- our big body of data is really pentylene. There's a little bit -- and we have more now on the lead ingredient, which is caprylyl. But caprylyl still has log P of 1.2, or extrapolating to log P of 6.5, 7.5 and 12.

And I'm just bothered by that idea, because we're well within molecular weights for

there to be penetration. I agree there are no structural moieties in this that cause me any strong discomfort, just looking at what's there.

Now, if you've got log P of 12, that's going to get into cell membranes and be there. And if it were to accumulate, something could happen -- or mitochondrial membranes, or other intracellular membranes -- accumulate and sit there and build up, and cause effects of we-don't-know- and-can't-predict.

DR. MARKS: Okay. So where do we want to move? Do we want to say -- do we want to move that there would be a tentative -- we're going to get more data. So one could say is more data going to change -- if we have more data, then the question would be do we just table it to look at more data? Or do we move forward with a tentative report at this point, with a "safe."

DR. SLAGA: Well, we're still waiting for more data.

DR. MARKS: Alan.

MR. ANDERSEN: I think, there are data needs the Panel should (inaudible) and issue an Insufficient Data Announcement. That would put interested parties on notice that we're looking for additional data. And there's no reason that that couldn't simply be empirical.

If there is an absence of sensitization and irritation data for the longer-chain glycols, then ask for them.

DR. SLAGA: I wouldn't mind that. (inaudible) it's the first time.

MR. ANDERSEN: That would round out the picture. Presuming there is an absence of irritation and sensitization for the longer chains, then we have an empirical basis for saying we looked at what we expect might be a relevant endpoint, and it wasn't there. It was not a finding of irritation and sensitization.

And absent those data, you are extrapolating from lower molecular weight to higher.

DR. MARKS: Mm-hmm.

MR. ANDERSEN: Traditionally, with log Ps of this magnitude -- and, Ron, I disagree with your interpretation of (inaudible). I think you can be reasonably clear, once you get outside of a window around zero, get above 4 on the high side, and below 2 on the low side for log Ps, there's nothing getting through.

DR. HILL: I disagree, because I've with pharmaceuticists who did transdermal absorptive formulations. And I think until you get up above 10, they can still diffuse through the skin if their molecular weight is sufficiently small.

MR. ANDERSEN: Small.
DR. HILL: If it's -- yes. And in this case, it is small.
MR. ANDERSEN: Hence, the empirical data --
DR. HILL: Right.
MR. ANDERSEN: -- that would take any doubt out of it. So actually sensitization and irritation would be a perfectly reasonable thing to request.
It's the first time we've looked at it. Carol made the point earlier that there may not have been a lot of time to gather data. So if we're (inaudible).
MR. BAILEY: Well, I would object to calling it "insufficient data." If the Panel feels like there's more data needed and we haven't had time to produce it, then I don't think "insufficient data" tool is necessarily the way to go. You might want to table it with a request.
But I think it really -- I mean, in my mind, the first criteria is do you really expect this to be an outcome? In other words, you know, that there would be a sensitization potential for this, number one. Number two, I mean, we bring a lot of expertise and experience to the (inaudible) that I have.
But I think if you really expect it, then I would say -- in your professional opinions -- to ask for it. If you don't expect it, then I think it's a little questionable to invoke an "insufficient data," and then ask for something that you think that you may not need anyway.
I mean, I would rather use the resources and efforts of the Science and Support Committee and this Panel to focus on those areas where you really think there's going to be an issue.
So, I mean, just for a kind of a reality check here, in the process.
I mean, we're more than happy to respond to "insufficient data." But I think it really sends a very different message than what's really (inaudible).
DR. MARKS: Well, do we expect to find any data other than for the C15-18 glycol?
MR. BAILEY: Well, you know, I don't know.
DR. MARKS: I mean, that's the only higher weight ingredient being used. So then I think we're still back to, to my mind, to the C15-18. If we have it, fine. If we don't have it, then what do you do with 28? What do you do with 20? What do you do with 14?
MR. BAILEY: Well, I think the chances, in this situation -- and there may be other

situations -- in this situation, as likely formulated in cosmetics, the changes of this interfering with the skin are approaching zero.

You know, there may be situations that -- you know, and testing (inaudible) go on to something else. But I just don't think, for purposes of what we're doing here, it's just very likely.

I mean, we could ask Bob directly. He's been doing cosmetic products and matrices for a long time.

DR. MARKS: So we have, it sounds like, two options: Table -- well, I think the first is decide is -- if we only, if we get anything more, ultimately are we going to do an "insufficient data," for the higher molecular weight ingredients?

And if we aren't, then it's sort of counter -- to me -- counter-logical that we would request it now, and then if we don't request it, not ultimately, in the end --

DR. SLAGA: Well, can we, as it was stated, to see if there is data out there? Request if there is any higher, just for --

DR. MARKS: So, that, it sounds --

DR. HILL: The company's using it. So, I mean, I agree with you. It's -- suppose there's just one company that's using it. They may just decide it is in their best interest to provide data that they have sitting behind the firewall.

DR. MARKS: So, to me -- and, Alan, again, I'll ask your input on this, because you're the one who suggested pushing it for an "insufficient data," which has a different connotation than tabling it, in my mind, to see what we can find.

Do you still like the "insufficient data?"

MR. ANDERSEN: I don't see that you have an option other than to make it "insufficient data."

This procedure is in place to keep these things moving forward. And the option to table, in my mind, has to be very specific against an expectation that you know it's there and you just need to some time to look at it.

Here, there's a real question that's been put on the table. I don't personally agree that it's a big issue, but it's on the table nonetheless. And you need something to resolve that. And I think you should ask for this.

If we think of the consequence -- if you table it, then we're in a limbo status. I don't know whether we're going to get anything or not get anything.

MS. EISENMANN: But the exception is --
MR. ANDERSEN: And, you know, (inaudible) bringing back to you.
MS. EISENMANN: The concentration of use information.
DR. HILL: Yes, because that --
MS. EISENMANN: Well, you know you're going to get it, because I'm working on it. So, I mean, that would be a reason to table.
MR. ANDERSEN: I can't argue with that. It's a perfectly reasonable piece of information that is currently on the table and is expected.

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DR. HILL: And also would probably affect the conclusions. Because if the concentrations are low, and we know skin penetration will at least be slow, and we don't have any structural alerts -- which there aren't. But it would also be nice to beat the bushes and see if a company or three that are using some of these longer-chain ingredients happen to have --
MS. EISENMANN: Right. And until I get the --
DR. HILL: -- information.
MS. EISENMANN: -- concentration of use information, I don't know who is using it, and I don't whose cage to rattle to try to get that information.
DR. HILL: Right.
MS. EISENMANN: So -- I mean, that's probably why we don't have that in, because I don't know yet who to ask for it.
MR. ANDERSEN: Well, I'm persuaded by Carol's argument that there is a justification for tabling it. I mean, that makes sense, with that strategy -- with the footnote to it that, oh, by the way, the Panel has a question about irritation and sensitization for higher molecular weights. So that if you got them, perchance, we'd love to see them.

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No reason you can't raise that flag.
DR. HILL: And I'm the kind of person that likes to encourage innovation. So I don't want to be in the position here of throwing the wet blanket where there shouldn't be, you know.
But if there's something that gives us comfort -- I mean, say, maybe a whole lot of other people will try some other new things. But it would be nice to kind of know.
DR. MARKS: Go ahead, Tom.
DR. SLAGA: Carol made the statement that there wasn't sufficient time to get the data.
Did we put this forward too soon, then? I mean, I'm just -- the procedural relationship, you know, did we rush this too forward? We should have waited a little bit more? You know, to the

next round, anyway.
MS. EISENMANN: But it takes -- I admit, it takes awhile for me to get all that data in.
DR. SLAGA: It does. And, I mean --
MS. EISENMANN: So --
DR. SLAGA: -- is there a timing that we should wait --
MS. EISENMANN: This was announced April 23rd. So the 60-day time period was June 23rd. So it did get sent to you before the 60-day time period was over.
DR. MARKS: One could argue both ways, Tom. It's probably good we didn't have the concentration of use, because it gives us a way of handling the issue of higher molecular weight and sensitization. So I'm going to suggest tomorrow, move for our team, that although I'm not the one presenting it, that we table for concentration of use data, and that we would also like to say irritation and sensitization data on the higher --
DR. SLAGA: If it were possible.
DR. MARKS: Yes -- higher weight which, in this case, is really going to be C15-18, probably, since that's the only one being used.

And then the other thing, Ron -- I want to go back -- Ron Shank, and just be sure we're clear on this.
In the introduction it says, "Propylene glycol is a very short chain 1,2-gliol [sic]." And you, if I heard you correctly, right in the beginning, you said is propylene glycol really a 1,2-gliol [sic]?
Did I hear you right?
MR. JOHNSON: Glycol.
DR. MARKS: So we need to be sure that that statement --
DR. SHANK: I was on California time. I'm sorry.
DR. MARKS: Okay. So propylene glycol is a 1,2. Thank you, Wilbur.
Okay. Any other comments? Well, that was a robust discussion.
SPEAKER: (inaudible)

DR. BELSITO: I guess what you're saying, Jay, is the issue was while you knew that caprylyl glycol was up for review and that would include other 1,2 glycols, you weren't certain which 1,2 glycols we'd keep on the list so you didn't survey? Is that it?

DR. ANSELL: We --

DR. BELSITO: Because you knew this was coming last year. I mean, this priority list that we're going to do these caprylyl glycols was determined last August of '09, correct?

DR. ANSELL: Right, and that's basically what the situation was. When we started reviewing the timeline and updating the procedures, we were really thinking about the old way where you'd identify an ingredient and then we could go out. 216

But now we're not finding what the list of -- the universe of ingredients are until much, much later in the process. And it's providing a stress on Carol and when she can get her things out.

DR. BERGFELD: Is that just this year? Is it happening just this year, or do you think this is a transitional year? Because the new update was just done.

DR. ANSELL: Well, I think the concern that came out of the April meeting is that it might not be transitional. It may be that we've changed the steps in such a way that the 60 day timeframe between -- that we envisioned -- well, that it's really going to be a structural problem that the list of ingredients is not finalized until quite late relative to when we actually announce that the family is going to come up. And --

DR. BELSITO: Well, but -- then we can correct that, Jay. Because we're going to be doing the list in August and we can decide in 217 August -- hopefully -- what the anticipated family will be.

But I mean, this is -- I guess this is -- it's just a little bit exasperating because I guess the other issue is, you know, we're looking at propylene glycol at this meeting and I think a lot of the information -- this report is quite thin. But a lot of the information from propylene glycol could be incorporated in here as a read across. And while we're on it, if we just knew what the concentrations of use of these 1,2 diglycols were, I'd be fine with going safe as used and then moving ahead. But unfortunately we

can't, and when it comes time to the next meeting when we look at it, I'm not going to remember all the propylene glycol stuff anymore. It's going to be wasting a lot of my time.

So -- I mean, I understand your position and I'm not -- I just think it's unfortunate. So, I mean, I guess at this point it's insufficient for concentration of use. Otherwise, I don't see any other data. I would like to see just summaries of the propylene glycol data brought in here.

DR. ANDERSEN: I think that you know that the concentration of use data are coming. It's not like there's a debate about that, they're just not here yet. So I think tabling it is a much more appropriate response in anticipation of the use concentration data.

DR. BELSITO: Okay. Fine. So table it, and you know, the only other point I'd make is penetration enhancer so when it comes time to writing the discussion we'd need to put that in the discussion. And assuming the concentrations of use are defendable, it's going to be safe as used.

DR. SNYDER: So the survey has been sent out?

DR. BELSITO: No.

DR. ANSELL: The survey was initiated as soon as we knew what the master list was. But that was not really until the end of April.

And you guys got it actually before the

60 day period was complete. And this is not the only report this morning which we had that issue with. There were several in which we were faced with the same problem that you had incomplete concentration of use because of just when the list of chemicals was finalized versus when we could go out.

DR. BERGFELD: How much time do you need?

DR. ANSELL: Well, we'll have to -- that we'll have to ask Carol. But she needs --

DR. BERGFELD: Did you have four months? Did you have six months? Did you need 12 months?

DR. ANSELL: Oh, no, no. I think it's --

DR. BERGFELD: This one you had two months.

DR. ANSELL: No, we didn't have -- the --

DR. BERGFELD: You had one and a half months? Six weeks?

DR. ANSELL: Yeah, I think she needs two to three months to pull this together.

DR. KLAASSEN: I guess I was thinking is that until this data is available for these documents, maybe the entire document shouldn't be sent to the committee. Are we kind of wasting our time a little bit of reading this and then forgetting most of it and having to read it again in August, for example? Maybe the committee shouldn't receive the document until that information is there. I don't -- just a suggestion.

DR. ANDERSEN: On the possibility that we would get lucky and the responses to Carol's request for data would have come pouring in, then they would have come to this meeting with this report and we declare victory. It didn't happen. I -- you know, infer circumstances where we have two meetings that are basically two months apart. I don't know that we're going to be able to fix that. It was -- yeah, we could have said, oh, let's not take a chance. But we took a chance. It didn't work out.

We'll give you all of the information next time. And with any luck, there won't be any loss of information content in reviewing it. But when we send out a literature review in April with the goal of creating just that 60 day window, and then in May have to send stuff to the panel, and it -- they aren't in yet from industry from, you know, 30 days we wouldn't have expected it to be in. So it's just -- we're pushing hard to get things through and in this case, it created a snafu. I think we will do better as we firm up

the list of the family as earlier and earlier. So, I would agree with Dr. Bergfeld that actually this -- I think this will get better. The exception to that will be if we have a great idea that comes in at the 11th hour that here's another ingredient that, guy, we just missed. It should have been included. And, you know, we're 45 days from the meeting and we call up Carol, well there's nothing she can do. I mean, she can make another request for data, but that doesn't generate responsiveness in suppliers or

formulators. So, there's always going to be the potential that something is disjointed. But we can do better by establishing the family as early as possible so that industry isn't caught -- gee, we didn't think that was in the family, et cetera. That's unfair, and I still like the idea of applying pressure on industry to get the data in.

So, thank you for doing that. But sometimes it just isn't going to work.

DR. BELSITO: Okay. So, we'll try harder and we'll try and create our super families in August with all the ingredients so that the industry has a heads-up.

DR. BERGFELD: And you'll table this?

DR. BELSITO: Yeah, it's tabled.

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Moving then on to the next ingredient in this group, Dr. Belsito, caprylyl glycol?

DR. BELSITO: This is a totally new report for caprylyl glycol for us and it's the first time we're looking at this. In looking at this, caprylyl glycol is a 1, 2 glycol so it can be used to create a family of 1, 2 glycols that are listed in the book and I won't delineate all of them here. In addition, the data is quite scant but we felt that by including summaries of the data from propylene glycol we could do some read-across and probably come up with a

safe-as-used concentration assuming that when the document comes back we have some concentrations of use which aren't in the current document. So we thought all in all we should table this and incorporate the data from propylene glycol, give the council a chance to get us concentration of use and look at it again.

DR. BERGFELD: Is there a second?

DR. MARKS: Second.

DR. BERGFELD: All those in favor of tabling? Thank you. Unanimous.

DR. MARKS: The other thing we would like to ask the council is if there is data on irritation and sensitivity for the higher weight, the C15 to 18 glycols.

DR. BERGFELD: Is there any other informal request for data? Seeing none, moving on them.

DR. BELSITO: Okay. So caprylyl glycol group. In June we tabled this so we could incorporate concentration of use data and encourage industry to provide data on skin irritation, sensitization for longer chain 1,2-glycols and the one we selected was C15-18 glycol. Industry gave us this. There was some skin sensitization and other data that we were forwarded by e-mail in the second wave. Data on the longer chain glycols, C15-18 we haven't gotten. But do we need it? I guess. And if we don't, then we really should be looking at sufficient. I mean, I read through all of this. I looked at the additional data that we had gotten in the second wave and I thought it was safe as used.
DR. LIEBLER: I agree.
DR. KLAASSEN: Safe as used.
DR. BELSITO: Paul?
DR. SNYDER: Yeah. Just so, what about the deletion of the ingredients that were in the John Bailey memo?
DR. BELSITO: That was already done. No? Are they included in this new report?
DR. SNYDER: Decylene glycol is still in here and 1,2, they're all still listed here. Hexadecanediol, there's a July 27th memo. Oh, wait a minute. That's (unintelligible). Never mind. Okay. Yeah. Yeah, we're fine. I thought they were to delete those, but that was (unintelligible).
DR. BELSITO: Yeah. I didn't really have any comments on the report itself. It looks fine. Safe as used.
DR. SNYDER: I thought on page 12, can we delete that immunological cross reactivity section? That has no basis. That's just looking for cross reactivity in an antibody.
DR. BELSITO: Page 12 of the actual report.
DR. SNYDER: CIR Panel Book page 58. Immunologic cross reactivity. Just look at the cross reactivity on antibody.
DR. BELSITO: Yeah, I mean.
DR. SNYDER: There's no toxicological significance at all.
DR. BELSITO: I don't think that has any bearing. So what we're suggesting is CIR Panel Book 58, that whole heading of immunologic cross reactivity be deleted.
DR. SNYDER: So the discussion is okay in its brevity? I guess we're not at that -- we're at pink so we're okay here.
DR. LIEBLER: I have a question for you

guys. I'm not sure how to interpret this type of data integrated here. This is on page 11 of the report at the top. And it's a paragraph that discusses an in vitro model of eye irritation. It's this embryonic chicken egg corneal and allotropic membrane assay. Maybe that's what causes salmonella. I don't know. But anyway.
MR. JOHNSON: What page is that?
DR. LIEBLER: It's page 11, near the top. It's the second full or first full paragraph. I'm not sure any of that is really relevant to mucus membrane. Or ocular irritation, excuse me. And I'd like to know from those of you who have seen more reports than I have if you feel this way as well or if there is something that we should be including?
DR. BELSITO: It's the alternative to rabbit eye test. It's been accepted as far as I know by the SCCP.
DR. LIEBLER: Really? Okay. I didn't know that there's an alternative. So that's okay to include?
DR. BELSITO: Yeah. It's like the red blood cell for phototoxicity in the absence, you know, as Europe is pushing for no use of animals in cosmetics it's what people are using as a substitute.
DR. LIEBLER: Okay. All right. Fine. I will delete my comment.
DR. BELSITO: Okay. We're done unless someone has anything more to say or add.

DR. MARKS: Our first ingredient our team is going to look at this morning is the caprylyl glycol and other 1,2-glycols. In the June meeting this ingredient was tabled for use concentration and data for skin irritation and sensitization of the longer glycols, in particular C-15 through -18. Now I think we will probably be at a point of considering issuing a tentative report. My fellow team members' comments in terms of we still have the old use table format, are there any other comments? Do we feel comfortable. I think, Ron, you brought up the C-15 to -16 glycol sensitization and irritation. I didn't see any new data on that.

DR. HILL: We didn't get any new data in the areas where I felt the most deficient which is that almost everything is depending on data we had for pentylene glycol. For me the propylene glycol data is almost hardly relevant here because it's very small compared to those larger molecules and it's biotransformed in specific ways. So it's good probably that it's there in the report since we had the previous review of propylene glycol, but beyond that in any of the larger polymers, propylene glycol seemed hardly relevant. So we're still in the position of trying to extrapolate all of these larger chains and pretty much everything than pentylene there's hardly any data.

DR. EISENMANN: Did you see the summary in the back on decylene? That's as high as we have? And I didn't get anybody reporting uses of the higher and I haven't been able to identify any suppliers of the higher or the larger compounds.

DR. MARKS: So is the use in Table 3 on page 29 maybe not correct where it has one use for the C-15 through -18 glycol?

DR. EISENMANN: That came from FDA. I wasn't able to confirm it in the concentration-of-use survey from our members.

DR. HILL: Yes, I did see the decylene summary because I've got a number of things highlighted and as I expected, there's nothing on sensitization so I wasn't expect it. We didn't have anything. Of course that's C-10.

DR. MARKS: I'll ask for the panel's input with possibly only one use and other data that suggests the other 1,2-glycols to be fine. I'm not too concerned about the C-15 through -18 glycols particularly without any alerts. We could certainly put in an insufficient data for that particular group of glycols.

DR. SHANK: Or we could delete the higher molecular weight glycols. If we don't delete them then I think we have the data are

insufficient. But having reread this report from last time, we have no reproductive developmental toxicity or mutagenicity data except for propylene glycol and 1,2-butainediol. These are both negative Log P compounds, water soluble. The others are quite lipid soluble as in caprylyl glycol is lipid soluble. So I think their behavior is going to be different and I would like to see reproductive toxicity data and mutagenicity data on probably caprylyl glycol.
DR. EISENMANN: Dr. Shank, did you see the summaries that were submitted? There was very brief OECD 414 done on 1,2-hexanediol.
DR. SHANK: 1,2-hexanediol, yes, that's small water soluble. We don't have anything on the lead ingredient, caprylyl glycol, at least not that I saw.
DR. HILL: I flagged in particular the acute IP toxicity. Granted, it's acute and I'm, quite frankly, not so concerned about the kinds of exposures we're looking at. But the trend there was the increased molecular weight and caprylyl had the greatest effect and small molecular weight values at least based on ED3 were lower in effect.
DR. SHANK: Where are you, please?
DR. HILL: It's report page 7, Panel Book page 53, and at the top of the page is the summary. This is ataxia, so I'm thinking you'd have to have awfully high systemic levels to start to see that effect. Honestly, I flagged it, but I was not very concerned. It was just another in the piece of we don't have much information on anything larger than pentylene except now decylene because of the added info.
DR. MARKS: It sounds like we should move forward. Do we want to have insufficient data needs or do we want to issue a tentative report with insufficient data?
DR. BERGFELD: Or delete.
DR. MARKS: With Ron I thought that was one way to handle the sensitization issue, but you also with caprylyl had the reproductive and mutagenicity. Since that's the lead ingredient and has lots of uses, over 1,700, so that I think the question is do we just put in an insufficient data announcement or do we move forward with a tentative report that there is insufficient data? What do you feel about that?
Tom, I assume you agree with it that you would like to see the mutagenicity.
DR. SLAGA: We're including the cutoff of the higher molecular weights, too?
DR. SHANK: My recommendation was for lauryl and higher, to delete those from the report. We have no data on those. That's C-12 and higher. For the need for reproductive

developmental toxicity and mutagenicity and genotoxicity data, at least for the lead ingredient, caprylyl glycol. We have information on the two small water-soluble ones, propylene glycol and 1,2-butainediol, but we don't have for the lipid soluble glycols and I think we should have that.

DR. HILL: Honestly, I wouldn't be expecting to see any reproductive toxicity. But, again, with those greasy ones, if they were going to stay in I would still like to know are there any growth-promoting type effects or proliferative type effects? That's what I'm interested in knowing.

DR. MARKS: Ron Shank, would say in this report you would only do four ingredients at this point, cosyl glycol and those of smaller size? Which ones would you include when you look at page 1 of the introduction?

DR. SHANK: I would include those that are C-10 and lower, decylene and lower.

DR. BAILEY: You're saying that C-10 and lower, including those within this report, you would have no concerns about the repro?

DR. SHANK: I would have the report include decylene glycol and lower chain lengths and eliminate lauryl and above. They're not used and there are no data for them. If the panel doesn't want to go that way then we have insufficient data for those, totally insufficient data. For decylene and lower expect for propylene glycol and 1,2-butainediol, I feel we need some information on reproductive developmental toxicity, mutagenicity, or genotoxicity, and I would recommend that that be focused on the caprylyl glycol as representative of the group.

DR. BAILEY: Ron, you were saying though that you would not expect those to be a concern.

DR. HILL: In the data on decylene it's not mutagenic in the Ames testing protocols at least and there's repeated dose toxicity for 28 days.

DR. SLAGA: But there isn't any mutagenicity, I agree, with the caprylyl.

DR. HILL: No, there is not.

DR. BAILEY: I agree with trimming off anything higher than C-10. I think that makes sense both in terms of data and no reported uses. I would suggest that the need for the repro developmental is not compelling as far as I can see.

DR. SHANK: Where are the data for decylene in the Ames assay?

DR. EISENMANN: It was recently after the report. There's a summary sheet with data on decylene.

DR. SHANK: Was that one of the PDF files?
DR. EISENMANN: No. It's in the book. It's after the report. There's a 28-day rat with a NOAEL of 100 and then there's an Ames test not mutagenic. That's CIR Panel Book page 89.
DR. SHANK: It's just one Ames test. That's really not sufficient.
DR. EISENMANN: But what about the combination of the repeated 28-day on decylene and then a reproductive study on 1,2-hexanediol so that you have 6 and 10 systemic toxicity studies?
DR. HILL: You would certainly expect a difference in placental penetration at the higher molecular weight and I would predict not knowing anything more that C-10 would get through the placenta better than C-6. That would be my prediction. However, I don't expect it to be a problem.
DR. SLAGA: Would mammalian mutagenicity be sufficient?
DR. SHANK: Yes.
DR. EISENMANN: Mammalian mutagenicity, is that all you're asking for or are you still asking for the developmental reproductive study?
DR. SHANK: For mutagenicity, certainly a mammalian mutagenicity study. The bacterial system alone is not sufficient. Both is better. The more you have in the battery of mutagenicity tests the clearer the interpretation. Reproductive and developmental toxicity is entirely different. That has to be an in vivo study, and we have no information whatsoever on the lipid soluble glycols. Since the caprylyl glycol is widely used, I think we should have that information.
DR. MARKS: Let's sum this up. First of all, do we issue a tentative report with insufficient data or do you think we should be an insufficient data announcement? What does the team feel about that? That's the first thing we're going to have to decide tomorrow.
DR. SHANK: I thought we eliminated the announcements.
DR. EISENMANN: There is one insufficient data announcement stage which you haven't reached yet because you tabled it last time.
DR. MARKS: Correct. When you look on the flow sheet on page 2 of the book on the safety assessment, you can see there is an ISD announcement.
DR. BERGFELD: "Notice" they call it.
DR. MARKS: Yes, notice. Do you want to do a notice or do you want to just go on to issuing a tentative report with insufficient data?

DR. SHANK: I would recommend an insufficient notice.
DR. MARKS: Under that what we're suggesting is that we're going to eliminate in this report anything above C-10. Is that correct, Ron?
DR. SHANK: That's my recommendation.
DR. MARKS: Are there any other panel members?
DR. SLAGA: Obviously they're not being used and there's no data so it makes a good cutoff. Starting with C-10 there is some data.
DR. MARKS: Then what we want with the insufficient data is reproductive and development and we can use caprylyl as the prototype on that. Is that right?
DR. SHANK: Yes.
DR. MARKS: And we need either mutagenicity or geno and really carcinogenicity also for this group.
DR. SHANK: No, not carcinogenicity. If it's mutagenic and genotoxic, then we would come back and ask for carcinogenicity.
DR. MARKS: So we just need muto and geno?
DR. SHANK: Mutagenicity or genotoxicity.
DR. SLAGA: Would it be better to have it on the decylene glycol because you already have the Ames so that then you have at least one complete?
DR. MARKS: We'll say the data need is the mutagenicity or genotoxicity data. The only thing I'd point out is that if you look at the 1,2-hexanediol in the HRIPT, 7-1/2 percent was negative, yet the use concentration is up to 10 percent. So I would want to see sensitization data that would justify the use concentration up to 10 percent or else we should put a limit at 7.5 percent, if I interpret that data correctly. Carol, do you concur with that? The HRIPT was on page 15 of this report and the use at 10 percent is on page 28. Are there any other needs?
Tomorrow I will move that we issue an insufficient data notice, that we eliminate those ingredients that are greater C-10, that we need reproductive and developmental toxicity on those ingredients we've included using caprylyl as the prototype, that we need either mutagenicity or genotox data, and that we get HRIPT on 10 percent or we'll limit the concentration on the 1,2-hexanediol.
MR. JOHNSON: One question, please, Dr. Marks. Is the request for reproduction and developmental toxicity data on caprylyl glycol

only?
DR. SHANK: No. It was my recommendation that that be the one chosen.
MR. JOHNSON: As a prototype.
DR. SHANK: As the prototype since that's the most widely used of these ingredients. But if there are data already existing on something similar, we would like to look at that.
MR. JOHNSON: One other concern regarding the data that were received from industry, we received data summaries with the panel and would be interested receiving the complete studies.
DR. MARKS: Is Eric here? What I would like to see, Wilbur, and I'll probably repeat it a couple times during the day, is whatever we get electronically it would be nice to have the beginning of that file with a summary and then, if we need to, we can look at the specifics of the study. But when we get a data, I'll use the word "dump," of over 800 pages, it's a considerable amount of time going through and looking at those whereas if we had a front cover portion that says this is what's included, this is the conclusion of the studies, and maybe some more information, if you want to create a table that would give the highlights, but one in which you could go to the first page of that particular ingredient or group of ingredients, and then scan that. And if you see issues, then you can go back and look at the specific supporting data. That would be very helpful.
MR. JOHNSON: In this situation we only received the summaries.
DR. MARKS: Right.
MR. JOHNSON: I was wondering whether or not the detailed reports would be needed by the panel.
DR. MARKS: Are there any comments to that?
DR. EISENMANN: One comment on one of the summaries. Dr. Marks, did you notice that there's an LLNA on 1,2-hexanediol up to 100 percent? Would that address your concern for sensitization that was negative? It's 10, 50, and 100 percent.
DR. MARKS: No, I overlooked that. I went right to the HRIPT. Yes, it would because then, to me, it would indicate that it was a nonsensitizer, so the chances of it being really a sensitizer would be zero. Thank you, Carol, for pointing that out. I'll eliminate that data need. Are there any other comments?
DR. HILL: This is for Wilbur. Could you see if you happen to have a copy of reference 33? If I could be supplied with that later today

that would be helpful.
DR. MARKS: Are there any other comments about this ingredient?
DR. BERGFELD: I have one on page 20. Looking at your discussion, even the discussion will change because it will identify what you've just done, are you all comfortable with the statements there as they stand especially the last part of the third sentence, then they should not exist together in formulation? They're talking about penetration enhancement of these particular chemicals.
DR. HILL: I would rather it read something like then the combined effects should be considered or something like that. I don't think there's any reason a priori to exclude using them together.
DR. MARKS: Are there any other comments about this group of ingredients? If not, then we will move on to the Pink 1.
MR. JOHNSON: Excuse me, Dr. Marks. Just for my notes, the panel does not need the detailed studies for which summaries were submitted on the caprylyl?
DR. MARKS: Correct.
DR. JOHNSON: Don't need them. Thank you.

So, moving on to the first pink document, the capryly glycol group. Dr. Marks?
DR. MARKS: So in June of this year, the panel tabled these 1,2-glycols pending some data needs. Our team reviewed what we had received and we feel we should issue -- move to issue an insufficient data notice. And some of the recommendations we made were, one, to eliminate a greater than C10 glycols. And we want reproductive and development data on the remaining ones, and also if there's absorption, mutagenicity, and genotoxicity.
DR. BERGFELD: Is that a motion?
DR. MARKS: Yes.
DR. BERGFELD: Is there a second?
DR. MARKS: So we need sufficient data notice. That's the motion.
DR. BERGFELD: Any discussion? No, it wasn't seconded.
DR. BELSITO: Yeah. We actually felt that we could go with a safe as used on this. And I'm not sure why you want the reproductive toxicity --
DR. MARKS: Yeah, I'll let Ron comment on limiting the ingredients and also on the reproductive and the development and the mutagenicity.
DR. SHANK: The only reproduction developmental toxicity mutagenicity data we have are on the two small water soluble propylene glycol and 1,2-butanediol. But many of these compounds, the larger ones, are lipid soluble -- perhaps behave very differently and we have no data on them.
So, my recommendation was to go insufficient and request data, at least on capryly glycol as the lead ingredient.
We have no data at all for lauryl glycol and higher, other than lauryl glycol was a severe eye irritant. And there are no uses for the higher glycol. So I would eliminate those from the report.
DR. BELSITO: I would ask Dan, maybe, to comment on dermal absorption and Paul, Curt, and Dan to comment on potential for repro toxicity. It's out of my league.
DR. LIEBLER: Well, I would agree that we really have little data on the longer-chain glycols here. And the group extends to the longer-chain glycols. My hunch is that we wouldn't run into problems there, but I would agree we don't have any data. So, I would be comfortable with that, actually.
DR. SNYDER: My comments would be

pursuant to the -- usually we go a stepwise process of -- first we go insufficient because we don't have dermal absorption on the longer chain. And if we don't get dermal absorption then we would defer to the reproductive. So, could we ask first for the dermal absorption before we jump to requesting reproductive studies?
DR. LIEBLER: Right. I would say that if we had low dermal absorption -- which I think we will end up with with these -- then I think we could probably consider -- reconsider safe as used.
DR. SHANK: That's fine with me. Go -- ask for dermal absorption first. If it's considerable -- well absorbed, then ask for reproductive, developmental, and mutagenicity.
DR. SNYDER: And we usually ask for a 28-day dermal at that point, also.
DR. SLAGA: We also need mutagenicity mammalian for capryly glycol.
DR. BELSITO: So we're -- all of these data we're going to ask on specifically capryly glycol?
DR. SLAGA: Yeah.
DR. BELSITO: Or can we give industry several other options for longer chain glycols in case the data exists?
DR. SLAGA: Well, the only mutagenicity with -- above the 1,2-butanediol is related to the decyclene glycol, which there's only Ames for that. It could be either one of those, it doesn't --
DR. BELSITO: Okay.
DR. BERGFELD: Dr. Bailey?
DR. BAILEY: Yeah, just to point out that we do have dermal on C10, which is on Panel Book page 89. And that we do have repro on C6, which is on page 92. So, we do have some bridging data here that I think answers, you know, some of those questions.
DR. SHANK: Could you repeat that again, please? On page 89 what?
DR. BAILEY: Yeah. On page 89, we do have the 28-day oral on the C10, the decyclene glycol. And on page 92,we do have developmental tox for the 1,2-hexanediol C6.
DR. BELSITO: And there's an Ames test on the C10 as well.
DR. BAILEY: So I mean, we do have some of this information. So I guess the question --
DR. SHANK: The developmental tox? The developmental toxicology is on 1,2-hexanediol? That's a water-soluble compound. I don't think that can carry over necessarily to the lipid-soluble molecules.
DR. BELSITO: Okay. So, just to repeat

what you're requesting for data needs.
DR. SHANK: Okay. I would request dermal absorption on capryly glycol or a similar lipid-soluble glycol. If there is dermal absorption, then reproductive developmental toxicity and mutagenicity.
DR. BELSITO: We get that from a dermal repro test?
DR. SHANK: That's right. But you can add 28 dermal toxicity and see what we get.
DR. HILL: Yeah, because I think there's always concern when you have an oral study and particularly rats of hydroxylated compounds. They're much more efficient phase 2 eliminators than humans, and many times they kick things out in bile and then you don't get the same thing that you might get from a heavy dermal exposure.
DR. BERGFELD: Dr. Snyder, any comment? No?
DR. SNYDER: No.
DR. BERGFELD: Dr. Klaassen?
MR. KLAASSEN: No comment.
DR. BERGFELD: Dr. Slaga? Anything else? Anything else? Any other comments, Dr. Belsito?
DR. BELSITO: No. I mean, I don't have a problem --
DR. BERGFELD: So are you going to second the motion?
DR. BELSITO: Second for insufficient? Sure, I'll second that.
DR. BERGFELD: Right. So the motion has been made and second to go insufficient with the data as requested in the discussion. Any further discussion?
DR. BAILEY: It's an insufficient data notice?
DR. BERGFELD: Notice.
DR. BAILEY: Right. We talked about it.
DR. BERGFELD: All right? Seeing none, call for the vote. All approving? Unanimous. Thank you.

REPORT

Draft Tentative Report

Caprylyl Glycol as used in Cosmetics

November 18, 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 Wilbur Johnson, Jr., M.S., Senior Scientific Analyst/Writer.

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INTRODUCTION

This is a safety assessment of caprylyl glycol and other 1,2-glycols, as used in cosmetic products. The 1,2-glycols are used mostly as skin and hair conditioning agents and viscosity increasing agents in these products, and caprylyl glycol and pentylene glycol are also used as preservatives. This safety assessment includes the following 1,2-glycols :

- caprylyl glycol
- arachidyl glycol
- cetyl glycol
- hexacosyl glycol
- lauryl glycol
- myristyl glycol
- octacosanyl glycol
- stearyl glycol
- decylene glycol
- pentylene glycol
- 1,2-butanediol
- 1,2-hexanediol
- C14-18 glycol
- C15-18 glycol
- C18-30 glycol
- C20-30 glycol

Of the 16 ingredients that are being reviewed in this safety assessment, the following 4 are being used in personal care products: caprylyl glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol.

A CIR final safety assessment on propylene glycol (PG) and polypropylene glycols was published in 1994. [1] PG is a very short chain 1,2-glycol, and is therefore very similar to the ingredients reviewed in this safety assessment. The CIR Expert Panel concluded that PG and polypropylene glycols are safe for use in cosmetic products at concentrations up to 50.0%. At its June 28-29, 2010 meeting, the Expert Panel issued an amended final safety assessment on propylene glycol, tripropylene glycol, and polypropylene glycols with the following conclusion: The CIR Expert Panel concluded that propylene glycol, tripropylene glycol, PPG-3, -7, -9, -12, -13, -15, -16, -17, -20, -26, -30, -33, -34, -51, -52, -69, and any PPG ≥3, 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.[2]

In the absence of safety test data on many of the 1,2-glycols reviewed in this safety assessment, data on PG from both the CIR published final safety assessment and amended final safety assessment are included to support the safety of these ingredients in personal care products.

CHEMISTRY

Definition and Structure

Other chemical names and cosmetic ingredient functions for the ingredients reviewed in this safety assessment are included in Table 1.[3] Caprylyl glycol and other 1,2-glycols are generally defined as the compound that conforms to a structure or formula. Chemical structures for the 1,2-glycols that are being reviewed are included in Figure 1.

Chemical and Physical Properties

Available data on the properties of the following ingredients are included in Table 2: caprylyl glycol, arachidyl glycol, cetyl glycol, lauryl glycol, myristyl glycol, octacosanyl glycol, stearyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol. Information on hexacosyl glycol was not found. No information on the chemical and physical properties of C14-18, C15-18, C18-30, and C20-30 glycols were found. Because these ingredients are mixtures of various length glycols, their chemical and physical properties are expected to reflect their individual components.

Methods of Production

The commercially practiced synthesis of ethylene glycol, the simplest of the 1,2-glycols, commonly occurs via a thermal oxidation of ethylene oxide with water.[4] The commercial production of other 1,2-glycols, including those currently under review herein, are commonly synthesized via either catalytic oxidation of the corresponding alkene oxide, or reduction of the corresponding 2-hydroxy acid**.**

C15-18 glycol, for example, has been prepared via oxidation of the corresponding C15-C18 1,2-alkylene oxides (and the 1,2-alkylene oxides have been synthesized via epoxidation of the corresponding 1,2-alkenes). [5]

Stearyl glycol has been prepared via the reduction of 2-hydroxyoctadecanoic acid with lithium aluminum hydride.[6] This reaction is followed by the quenching of any unchanged lithium aluminum hydride with excess ethyl acetate, filtering of salt, and subsequent drying of the resulting solution.

The production of 1,2-butanediol, much like the synthesis of ethylene glycol, is commonly carried out via a continuous reaction and distillation operation. [7]

Impurities

1,2-butanediol is $\geq$ 99% pure and also contains water, 1,4-butanediol, and 1-acetoxy-2-hydroxybutane. [7]

Analytical Methods

Cetyl glycol has been analyzed using silica gel thin-layer chromatography, and has been identified using IR and mass spectroscopy.[8,9] Decylene glycol has been analyzed via gas chromatography, and has been identified using mass, IR, and NMR spectroscopy**.** [9, 10] Gas chromatography-mass spectrometry (GC-MS) has been used in the analysis of stearyl glycol**.**[6]

Lauryl glycol, myristyl glycol, caprylyl glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol have been identified using mass, IR, or NMR spectroscopy. [9]

UV absorption data on caprylyl glycol or any of the other 1,2-glycols reviewed in this safety assessment were not found in the published literature. Based on the chemical formulas included in Figure 1, there is no reason to suspect that any meaningful UV absorption would be associated with these 1,2-glycols.

Reactivity

For 1,2-butanediol at temperatures above 90°C, explosive vapor/air mixtures may be formed.[11] Additional information on the reactivity of 1,2-butanediol, in relation to EPA's proposed national rule on the reduction of ozone formation, is included in the section on Noncosmetic Use later in the report text.

USE

Purpose In Cosmetics

Most of the ingredients reviewed in this safety assessment function as skin and hair conditioning agents and viscosity increasing agents in personal care products.[3]

Scope And Extent Of Use In Cosmetics

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2010, the following ingredients were being used in personal care products: caprylyl glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol.[12] These data are summarized in Table 3. Independent of these data, the results of a survey of ingredient use concentrations that was conducted by the Personal Care Products Council in 2010, also in Table 3, indicate that three 1,2-glycols were being used at the following concentrations: caprylyl glycol (0.00003 to 5%), pentylene glycol (0.001 to 5%), and 1,2-hexanediol (0.00005 to 10%).[13] According to FDA's VCRP data, there was no indication that the following remaining ingredients in this safety assessment were being used in cosmetic products in 2010: arachidyl glycol, cetyl glycol, hexacosyl glycol, lauryl glycol, myristyl glycol, octacosanyl glycol, stearyl glycol, decylene glycol, 1,2-butanediol, C14-18 glycol, C18-30 glycol, and C20-30 glycol.

Personal care products containing these ingredients may be applied to the skin, nails, or hair, or, incidentally, may come in contact with eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin, nails, or hair for variable periods following application. Daily or occasional use may extend over many years.

Noncosmetic Use

Cetyl Glycol

Some colloidal nanoparticles of Sm-Co alloys are made in octyl ether using samarium acetylacetonate and dicobalt octacarbonyl as precursors in a mixture of 1,2-hexadecanediol (cetyl glycol), oleic acid, and trioctylphospine oxide.[14]

Stearyl Glycol

Stearyl Glycol has been used as a surfactant (in octanol/water microemulsion) in a transdermal delivery system for the drug, 8-methoxsalen. [15]

Caprylyl Glycol

Study results support the notion that treatment of glutaraldehyde-treated tissue with a short-chain alcohol (ethanolic buffered solution) and long-chain alcohol (caprylyl glycol) combination will reduce both extractable phospholipids and the propensity for *in vivo* calcification. The use of glutaraldehyde-treated biological tissue in heart valve substitutes is an important option in the treatment of heart valve disease; however, the durability of these devices is limited, in part, because of tissue calcification. [16]

1,2-Butanediol

The Environmental Protection Agency (EPA) lists 1,2-Butanediol as one of the reactive compounds in aerosol coatings (i.e., aerosol spray paints) that contributes to ozone (O_3) formation. It is listed as having a reactivity factor of 2.21 g O_3/g 1,2-butanediol. Reactivity factor is defined as a measure of the change in mass of ozone formed by adding a gram of a volatile organic compound (VOC) to the ambient atmosphere. This listing of compounds, such as 1,2-butanediol, is in keeping with EPA's proposal to amend the aerosol coatings reactivity rule by adding compounds and associated reactivity factors based on petitions that were received. EPA has concluded that a national rule based on the relative reactivity approach achieves more reduction in ozone formation than would be achieved by a mass-based approach for this specific product category. States have previously promulgated rules for aerosol spray paints based upon reductions of VOC by mass.[17]

Butanediol (1,2- or 1,3- not specified)

Esterified butylene glycol (formed with reconstituted oils from triglycerides or fatty acids derived from the oils) is among the chemicals used in the production of resinous and polymeric coatings that may be safely used as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food. Also, esterified butylene glycol (formed with fatty triglycerides and marine oils, and the fatty acids and alcohols derived from them) is among the chemicals permitted for use in the formulation of defoaming agents that may be safely used in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food. [18]

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Information on the metabolism, distribution, and excretion of 1,2-butanediol following i.v. dosing indicate that, in rabbits, this chemical is metabolized slowly and excreted in the urine either as the glucuronide or unchanged; there was no evidence of tissue accumulation. Metabolites were not identified in the urine of rabbits fed 1,2-butanediol in the diet. In the absence of percutaneous absorption data, octanol/water partition coefficients (logP values) for most of the ingredients in this safety assessment are presented in a graph of logP versus 1,2-glycol chain length (Figure 2). Propylene Glycol is metabolized to lactate in mammals.

1,2-Butanediol

1,2-Butanediol was infused i.v. into rabbits at a dose of 1 g/kg body weight. Metabolism was described as slow, and 1,2-butanediol was excreted in the urine either as the glucuronide or unchanged.[19] Accumulation in the tissues was not observed. Metabolites were not isolated from the urine of rabbits fed 1,2-butanediol at a dose of 0.2 g/kg body weight.

Propylene Glycol

> The original 1994 CIR final safety assessment reported that, in mammals, the 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.
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Percutaneous Absorption

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.

Propylene Glycol

> 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. [20] Over a 24-h period, the cumulative penetration of PG was 57.1% of the applied amount.
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

> The dermal absorption of PG was determined in the outermost layers of skin using TED-FTIR spectroscopy.[21] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Skin Penetration Enhancement

The skin penetration enhancement effect of caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol has been demonstrated in vitro. Skin penetration of the following was enhanced: ^{3}H-corticosterone, ^{3}H-triethanolamine, and dihydrovenanthramide D. 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.

Caprylyl Glycol, Decylene Glycol, and 1,2-Hexanediol

Warner et al.[10] studied ^{3}H-corticosterone (CS) and ^{3}H-triethanolamine flux (TEA) enhancement across full-thickness hairless mouse (SKH-HR1 strain) skin in the presence of 1,2-octanediol (caprylyl glycol), 1,2-decanediol (decylene glycol), and 1,2-hexanediol, each in phosphate buffered saline (PBS). Permeability experiments were performed using a two–chamber diffusion cell, and results are presented in Table 4. Each of the 3 chemicals enhanced the skin penetration of CS and TEA in a concentration-dependent manner.

Pentylene Glycol and 1,2-Butanediol

In a study by Heuschkel et al.,[22] the influence of pentylene glycol and 1,2-butanediol on the skin penetration of the drug, dihydrovenavenanthramide D (DHAvD, 0.2% in hydrophilic cream) across full thickness human skin (from breast, females) was investigated using Franz-type diffusion cells. Relative amounts of DHAvD in different skin compartments (stratum corneum, viable epidermis, and dermis) following penetration from a hydrophilic cream and from a hydrophilic cream containing a 4% pentylene glycol/1,2-butanediol mixture were compared. Within 30 min, the amount of DHAvD that penetrated into the viable skin layers doubled in the presence of the glycol mixture. After 300 min, 12% of the applied dose was detected in the viable epidermis and dermis after application of DHAvD in hydrophilic cream, compared to 41% after application in the cream with the glycol mixture.

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.[20]

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

ANIMAL TOXICOLOGY

Acute Inhalation Toxicity

1,2-Butanediol

According to a data summary available from Dow Chemical Company, there were no obvious toxic effects in rats exposed for 7 h to an atmosphere saturated with 1,2-butanediol.[19] Further details relating to this study were not available.

Acute Oral Toxicity

Oral toxicity data on Caprylyl glycol, propylene glycol, and other 1,2-glycols for which data are available suggest that death (rats) would occur at relatively high doses (LD50 range: 2200 to > 20,000 mg/kg). Reportedly, high (unspecified) oral doses of 1,2-butanediol caused narcosis, dilation of the blood vessels, and kidney damage in rats.

Caprylyl Glycol

The acute oral toxicity of caprylyl glycol was evaluated using male and female rats (number and strain not stated).[23] Doses of ≥ 464 mg/kg caused sedation and ataxia. Specifically, loss of muscle tone and dyspnea were observed at a dose of 1000 mg/kg, and lateral position, coma, and death were observed at a dose of 1470 mg/kg. Deaths occurred within 2 h post-administration; at necropsy, pale parenchymal organs were observed in 3160 and 4640 mg/kg dose groups. Surviving animals recovered within 24 h, and 215 mg/kg was the nontoxic dose in this study. LD50 values of 2240 (males) and 2200 (females) were reported.

In another study (OECD 423 test procedure) involving rats, the LD50 for caprylyl glycol was > 2500 mg/kg.[24,24]

Stearyl Glycol

An LD50 of > 5,000 mg/kg was reported for rats dosed orally with stearyl glycol.[25]

Pentylene Glycol (1,2-Pentanediol)

The following acute oral LD50 values have been reported for pentylene glycol: 1.2700 E + 04 mg/kg (rats); 7,400 mg/kg (mice); 3,700 mg/kg (rabbits); and 5,200 mg/kg (guinea pigs).[25]

1,2-Butanediol

An acute oral LD50 of 4,192 mg/kg was reported for 1,2-butanediol in a study involving female Swiss albino mice/ICR.[26] Study details were not provided.

According to a data summary available from Dow Chemical Company, the acute oral LD50 for 1,2-butanediol in rats was 16 g/kg body weight.[27] Also, high (unspecified) doses caused narcosis in rats (often leading to death in a few hours), dilation of the blood vessels, and kidney damage.

1,2-Butanediol administered orally to rats (ethanol-dependent) at a dose of 2.74 g/kg did not induce any overt toxic effects.[19]

C15-18 Glycol

The acute oral toxicity of C15-18 glycol was evaluated using adult male Sprague-Dawley rats, and an LD50 of > 20.0 g/kg body weight was reported.[5]

Propylene Glycol

> The 24 h oral LD50 for PG was 22.8 g/kg body weight in a study involving 5 female Fischer rats. The lowest recorded 24 h oral lethal dose in this study was 20.9 g/kg body weight. Oral LD50 values (rats) of up to 27 g/kg body weight have been reported in other studies.
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Acute Dermal Toxicity

Decylene Glycol

In an acute dermal toxicity study involving rats, the LD50 for decylene glycol (SymClariol®) was > 2,000 mg/kg.[24]

1,2-Butanediol

According to a data summary provided by Dow Chemical Company, prolonged application of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects.[19] Details relating to the test procedure were not provided; however, it was presumed that neat material was tested.

Propylene Glycol

The dermal LD50 for PG was > 11.2 g/kg in mice and was 13 g/kg in rats.
From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Acute Intraperitoneal Toxicity

The available data suggest that 1,2-Butanediol (LD50s up to 5990 mg/kg) and pentylene glycol (TDLo = 3,510 mg/kg) are not significant acute i.p. toxicants. However, muscle incoordination was observed in rats at an i.p. dose of ~ 2.94 g/kg. In an i.p. dosing study in which ED_3 values for caprylyl glycol (1,2-octanediol), pentylene glycol (1,2-pentanediol), and 1,2-butanediol were compared, caprylyl glycol had the lowest ED_3 value (1.5 mmole/kg), suggesting that its intoxication potency (i.e., ability to induce ataxia) was greatest. Mortalities were observed in mice at the highest i.p. dose of PG (10,400 mg/kg).

Caprylyl Glycol, Pentylene Glycol, and 1,2-Butanediol

In a report by Shoemaker,[28] the intoxicating potency of alcohols, some of which were straight-chain primary alcohols and straight-chain diols, was determined. Data on the following 3 diols reviewed in this safety assessment were included: caprylyl glycol (1,2-octanediol), pentylene glycol (1,2-pentanediol), and 1,2-butanediol. Doses of each alcohol were injected (intraperitoneally [i.p.]) into male Sprague-Dawley rats, and intoxicating scores were recorded based on the following rating scale: 0 (normal) to 7 (death).

An ED_3 value for each chemical was determined. The ED_3 was defined as the dose (mmole/kg body weight) required to obtain a score of 3 (ataxia) on the intoxication rating scale (0 to 7 [death]). The following ED_3 values were reported: 1.5 mmole/kg (caprylyl glycol), 256.0 mmole/kg (pentylene glycol), and 32.6 mmole/kg (1,2-butanediol).[28]

Groups of 6 adult female, ICR Swiss albino mice were injected i.p. with increasing doses of 1,2-butanediol (geometric factor of 1.2) in distilled water (injection volume = 0.01 ml/g body weight). Mean LD50 values and 95% confidence limits were calculated from cumulative mortality curves at 24 h and 144 h. The following values were reported for 1,2-butanediol: 24 h LD50 of 66.5 mmol/kg (~5.99 g/kg) and 144 h LD50 of 46.5 mmol/kg (~ 4.19 mg/kg).[29]

Muscle incoordination was observed in rats at an i.p. dose of ~ 2.94 g/kg.[19]

Pentylene Glycol (1,2-Pentanediol)

An i.p. TDLo of 3,510 mg/kg has been reported for pentylene glycol in rats.[25]

Propylene Glycol

Following i.p. dosing with PG (5 ml/kg), none of the 5 female C3H mice died, but peritonitis was observed at necropsy. In other studies, i.p. LD 50 values up to 13.7 ml/kg (rats) and 11.2 g/kg (mice) have been reported.
From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

An acute study was performed in which female ICR mice were dosed i.p. with 2600, 5200, or 10400 mg/kg PG.[30] 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.
From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Other Acute Parenteral Toxicity Studies

Propylene Glycol

Acute i.v. LD50's of 6.2 ml/kg (rats) and 6.4 ml/kg (mice) have been reported for PG. In other parenteral toxicity studies, acute i.m. LD50 (20 g/kg - rats) and acute s.c. LD50 (18.5 g/kg – mice) values have been reported.
From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Repeated Dose Oral and Parenteral Toxicity

An NOAEL of 100 mg/kg/day was reported for rats in a 28-day oral toxicity study on SymClariol® (decylene glycol). Short-term oral administration of 1,2-butanediol to rats (males [42 days]; females [day 14 before mating to day 3 of lactation] yielded an NOAEL of 200 mg/kg/day. In rats fed 1,2-butanediol at concentrations of 5% to 40% in the diet for 8 weeks, death was not noted at 5% in the diet (~2.9 g/kg/day), but dietary concentrations ≥ 10% were fatal. Large (unspecified) doses of 1,2-butanediol did not cause irritation of the gastrointestinal tract in rats. Repeated applications of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects. All mice survived in a short-term study in which 10% PG was administered 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. Similarly, cats survived dosing 12% PG in the diet for 5 weeks and 41% PG in the diet for 22 days. Intrravenous dosing with PG over a 2-week period resulted in little toxicity in rats.

Decylene Glycol

SymClariol® (decylene glycol) was administered by gavage to rats (OECD 407 protocol) at doses of 100, 300, and 1000 mg/kg body weight in a 28-day study. An NOAEL of 100 mg/kg body weight was reported.

1,2-Butanediol

In an 8-week oral study, groups of rats were fed 1,2-butanediol at concentrations ranging from 5 to 40% in the diet (one dose level per group).[19] Tooooooolhere were no mortalities at the lowest dose (~ 2.9 g/kg body weight/day); however, doses ≥ 10% were classified as fatal. The following signs of toxicity were noted at the highest dose of 22 g/kg/day: weight loss, fatigue, reduced responsiveness, diarrhea, and rapid, shallow breathing. No abnormalities were observed in tissues of major organs from 2 rats at each of the 5 dose levels.

The following study is actually a combined repeated dose/reproductive and developmental toxicity study, and results relating to reproductive and developmental toxicity appear in that section later in the report text.[31] Groups of Crj-CD(SD) rats (10 males, 10 females) were dosed orally, by gavage, with aqueous 1,2-butanediol at doses of 40, 200, or 1,000 mg/kg/day. Males were dosed daily for 42 days, and females were dosed from day 14 before mating to day 3 of lactation. Control rats (10 males, 10 females) were dosed with distilled water.

None of the animals died, and there were no differences in histopathological findings or the following parameters between test and control animals: body weight, feed consumption, hematology parameters, clinical chemistry parameters, and organ weights. However, transient hypolocomotion and hypopnea (slight clinical signs) were observed in females that received 1,000 mg/kg doses. No observable effect levels (NOELs) for repeat dose toxicity were 1,000 mg/kg/day (males) and 200 mg/kg/day (females). The no observable adverse effect level (NOAEL) was 200 mg/kg body weight/day in this study. [31] The estimated dose of low concern (EDLC) for this study was calculated as 0.2 mg/kg/day.[7]

According to a summary of data provided by Dow Chemical Company, the administration of large (unspecified) doses of 1,2-butanediol to rats caused irritation of the gastrointestinal tract.[19]

According to a data summary provided by Dow Chemical Company, repeated applications of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects.[19] Details relating to the test procedure were not provided; however, it is presumed that neat material was tested.

Propylene Glycol

> Little or no toxicity was observed in short-term oral tests on PG inolving dogs and cats**.** Dogs received 3.0 ml/kg doses of undiluted PG over a 3- day period, and cats received 12% PG in the diet for 5 weeks and 41% PG in the diet for 22 days. Short-term i.v. dosing with PG resulted in little toxicity in rats. Groups of rats received i.v. infusions of PG/ethanol/water (5:1:4) over a 2-week period.
>
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

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.[32] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Subchronic Inhalation Toxicity

Subchronic inhalation data reported some effects due to PG administration, but these effects were inconsistent and without dose-response trends. Rats were exposed (nose-only) to PG at concentrations up to 22 mg/liter of air for 13 weeks.

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.[33] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Subchronic and Chronic Oral Toxicity

A TDLo of 2,450mg/kg was reported for pentylene glycol in rats dosed orally over a 28-week period. In subchronic oral toxicity studies involving rats, PG (50,000 ppm in diet) given in feed for 15 wks did not produce any lesions. The same was true for dogs that received 5% or 10% PG in drinking water in subchronic studies. Toxic effects were not observed in PG chronic feeding studies involving rats or dogs.

Pentylene Glycol

Pentylene glycol was administered orally to rats, intermittently over a 28-week period. A TDLo of 2,450mg/kg was reported.[25]

Propylene Glycol

No toxic effects were seen in a subchronic oral toxicity studies in which rats were fed 50,000 ppm PG in the diet for 15 weeks, and dogs received 5% PG in drinking water for 9 months and 10% PG in drinking water for 6 months. Similarly, no toxic effects were reported when rats or dogs were given feed containing PG in chronic studies. Rats received up to 50,000 ppm PG in the diet for 104 weeks, and, in another study, dogs received 2 g/kg PG in the diet for 104 weeks.[1]

From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Cytotoxicity

The cytotoxicity of cetyl glycol (130 µg/ml), lauryl glycol (99 µM), and pentylene glycol (5%) has been demonstrated in vitro. Cetyl glycol had a cytocidal effect on Ehrlich ascites carcinoma cells, lauryl glycol had a hemolytic effect on human erythrocytes, and pentylene glycol induced apoptosis in a human promyeolcytic leukemia cell line. Propylene glycol was moderately cytotoxic to human fibroblasts and keratinocytes in vitro.

Cetyl Glycol

In an antitumor activity test, 1,2-hexadecanediol (cetyl glycol) was injected intraperitoneally (i.p.) into 8 inbred C57BL/6 mice in which Ehrlich ascites carcinoma (EAC) cells had been implanted. Doses of 80/mg/kg/day were injected for 10 consecutive days. The survival of mice was monitored over a 2-month period. Compared to control mice, dosing with cetyl glycol prolonged the lifespan of animals more than 2.7-fold. Antitumor effects were described as marked, in that 4 of 8 mice

injected were alive, with scarce tumor proliferation, at 60 days. Cetyl glycol (130 μg/ml) was found to have a cytocidal effect (irreversible cell degeneration) on cultured EAC cells.[34]

Lauryl Glycol

Osorio e Castro et al.[35] studied hemolysis rates (at 37ºC) of human erythrocytes induced by C_2 and C_8-C_{14} straight chain 1-alkanols, 1,2-alkanediols, and the corresponding benzilidene derivatives (benzaldehyde acetals). The most active compound was 1-dodecanol (50% hemolysis at 15 μM), followed by 1,2-dodecanedol (lauryl glycol, 50% hemolysis at 99 μM) and the C_{10} benzylidene acetal (50% hemolysis at 151 μM).

Pentylene Glycol

Anselmi et al.[36] conducted an *in vitro* DNA fragmentation assay (human promyelocytic leukemia cell line [HL60]) to investigate the apoptosis- and necrosis-inducing potential of brief, 10 min applications of the preservative, pentylene glycol (between 0.01 and 5% [usual concentration as a preservative]). Cells treated with phosphate buffered saline served as controls. The percentage of apoptotic cells was quantified by analysis of DNA content. Pentylene glycol induced apoptosis only at a concentration of 5%. Externalization of phosphatidyl serine, a hallmark of apoptosis, was concomitant with the subdiploid DNA peak in HL60 cells treated with pentylene glycol.

Propylene Glycol

> 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.[37] 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.[37] 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.
>
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Ocular Irritation

Based on Draize test results, lauryl glycol has been classified as a severe ocular irritant. Undiluted 1,2-butanediol , but not 10% aqueous, induced ocular irritation in rabbits. Undiluted SymClariol® (decylene glycol) induced corrosion when instilled into the eyes of rabbits. In an in vitro ocular irritation assay (HET-CAM), 1% SymClariol® in neutral oil and caprylyl glycol (1% and 3%) in neutral oil were classified as non-irritants; however, a 50:50 (w/w) mixture of caprylyl glycol and 1,2-hexanediol was classified as a severe ocular irritant when evaluated at a concentration of 1% aqueous (effective concentration per ingredient = 0.5%) in the same assay. Together, the results of a neutral red release (NPR) assay, the HET-CAM assay, and the reconstituted human epithelial culture (REC) assay indicated that a lash gel serum containing 3% pentylene glycol might be a slight ocular irritant. In other studies, undiluted PG was, at most, a slight ocular irritant.

Caprylyl Glycol

In an *in vitro* assay (hen's egg test on the chorioallantoic membrane [HET-CAM]) for evaluating ocular irritation potential, caprylyl glycol was classified as a non-irritant at test concentrations of 1% and 3% in neutral oil.[38]

Caprylyl Glycol and 1,2-Hexanediol

A 50:50 (w/w) mixture of 1,2-hexanediol and caprylyl glycol (Symdiol® 68) was also tested in the HET-CAM assay. The mixture was classified as a severe eye irritant at a test concentration of 1% aqueous (effective concentration per ingredient = 0.5%).[39]

Lauryl Glycol

According to Worth and Cronin,[40] the European Union has classified 1,2-dodecanediol (lauryl glycol) as a severe ocular irritant. The European classification system has allowed 2 classes of acute eye toxicity, R36 for moderate irritants and R41 for severe irritants, and the Draize eye test has been used for the identification of R41 chemicals. Actual Draize test results for lauryl glycol were not included. This classification of lauryl glycol as a severe ocular irritant is included in a study by the preceding authors to explore the possibility of distinguishing between eye irritants and non-irritants by using *in vitro* endpoints of the HET-CAM assay and the neutral red uptake (NRU) test.

According to one of the prediction models for eye irritation potential, a chemical is more likely to be an eye irritant if its log (TH10) value is low (i.e., if a 10% solution of the chemical produces rapid hemorrhaging of the chorioallantoic membrane) and if its log (IC 50) value is low (i.e., if the chemical is cytotoxic to 3T3 cells). TH10 is defined as the mean detection time for hemorrhage in the vascularized chorioallantoic membrane of embryonated chicken eggs. The IC50 is defined as the concentration of test chemical (mg/ml) resulting in 50% inhibition of neutral red uptake in 3T3 cells. The TH10 and IC50 values for lauryl glycol were 171.0 and 0.02, respectively.[40] Using a logarithm calculator, log 0.02 = -1.70 and log 171.0 = 2.23.

Decylene Glycol

In an ocular irritation study (OECD 405 protocol) involving rabbits, SymClariol® (decylene glycol) induced corrosion when tested at a concentration of 100%. Additionally, the ocular irritation potential of 1% SymClariol® in neutral oil was evaluated in the HET-CAM assay, and results were negative.[24]

Pentylene Glycol

The ocular irritation potential of a lash gel serum containing 3% pentylene glycol was evaluated using the following in vitro assays: neutral red release (NPR) assay using rabbit cornea fibroblasts, HET-CAM, and the reconstituted human epithelial culture (REC) assay.[41] In the NPR assay, the undiluted product and dilutions (in hydrophilic or lipophilic substance) ranging from 0.1% to 60% were tested. Sodium dodecyl sulfate served as the positive control. The test product concentration that gave rise to the release of 50% neutral red dye (NR_{50}) was used as an endpoint to reflect cytotoxicity. Data were expressed as a percentage of cytotoxicity, compared to the negative control (dilution 0%), and the NR_{50} was calculated by interpolation from the curve representing the percentage of viability versus the concentration of test product. An NR50 of > 50% (slightly cytotoxic) was reported for the lash gel serum.

In the HET-CAM assay, the undiluted product (0.3 ml) was applied to the chorioallantoic membrane and classified as moderately irritating. In the REC assay, the product (neat or diluted) was applied to the apical surface of the epithelial culture. Hexadecylpyridinum bromide solution in saline and saline solution served as positive and negative controls, respectively. Results were expressed as a percentage of cytoxicity, compared to the negative control. The product was classified as slightly cytotoxic. Together, the results for the 3 in vitro assays indicate that the lash gel serum might be a slight ocular irritant, with a Draize score that might range from 0 to 15. The conclusion for this study (slight ocular irritant) is from a global assessment conducted by the International Research and Development Center that was based on results of the 3 methods used, because no single alternative method can predict ocular irritation with a sufficient level of safety.[41]

1,2-Butanediol

According to a summary of data provided by Dow Chemical Company, undiluted 1,2-butanediol was irritating to the eyes of rabbits, but was a non-irritant when tested as a 10% aqueous solution. [19]

Propylene Glycol

> PG (0.1 ml, pH 8.8) was a slight ocular irritant in rabbits in one study, but PG (0.1 ml, pH unknown) did not induce ocular irritation in another study involving rabbits.
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

> The ocular irritation potential of PG was determined using groups of 6 male and female New Zealand white albino rabbits.[42] 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.
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Skin Irritation and Sensitization

In the maximization test, results were negative for caprylyl glycol at a challenge concentration of 50% in petrolatum. Undiluted SymClariol® (decylene glycol)was classified as a moderate skin irritant in rabbits, but did not induce sensitization in the guinea pig maximization test at challenge concentrations of 2% and 5% in arachis oil or in the mouse local lymph node assay at concentrations of 5% to 50% in acetone/olive oil (4:1). Repeated applications of 1,2-butylene glycol to the skin of rabbits did not result in skin irritation, and results were negative for 1,2-hexanediol (10% to 100%) in the mouse local lymph node assay for evaluating sensitization potential . Dermal irritation/sensitization studies on PG were reported in the 1994 CIR final safety assessment and the amended final safety assessment. Both mild and no skin irritation were observed following the application of undiluted PG in animal studies. The application of 50% PG resulted in skin irritation/dermal inflammation. PG induced reactions ranging from no sensitization to mild sensitization.

Caprylyl Glycol

The skin sensitization potential of caprylyl glycol was evaluated in the guinea pig maximization test (OECD 406 protocol) using 20 animals. During intradermal and topical induction, caprylyl glycol was applied at concentrations of 5% (in peanut oil) and 50% (in petrolatum). The challenge concentration was 50% in petrolatum. Sensitization was not observed in any of the animals tested.[38]

Decylene Glycol

In a skin irritation study (OECD 404 protocol) involving rabbits, 100% SymClariol® (decylene glycol) was classified as a moderate skin irritant (PII = 3.2). SymClariol® was evaluated at the following concentrations in the guinea pig maximization test: 1% in arachis oil (intradermal induction), 5% in arachis oil (topical induction), and 2% and 5% in arachis oil (challenge). Sensitization was not observed in any of the 19 guinea pigs tested.[24]

The skin sensitization potential of SymClariol® was also evaluated at the following test concentrations in the mouse local lymph node assay: 5%, 10%, 25%, and 50% in acetone/olive oil (4:1). Sensitization was not associated with any of the concentrations tested.[24]

1,2-Butanediol

According to a summary of data provided by Dow Chemical Company, 1,2-butanediol did not induce skin irritation in rabbits, following prolonged and repeated application.[19] Details regarding the test procedure were not provided; however, it was presumed that neat material was used.

1,2-Hexanediol

The sensitization potential of 1,2-hexanediol was evaluated at concentrations of 10%, 50%, and 100% in acetone/olive (3:1) using the mouse local lymph node assay (OECD 429 protocol). Study results were indicative of no skin sensitization.[43]

Propylene Glycol

> 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.
>
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

> The dermal irritation potential of 100% PG was evaluated with male hairless SKH1 hr/hr mice.[44] 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).
>
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

An NOAEL of 1,000 mg/kg for reproductive/developmental toxicity has been reported for 1,2-butanediol in rats dosed orally. In a prenatal reproductive toxicity study involving rats dosed orally with 1,2-hexanediol , an NOEL of 300 mg/kg was reported. In other studies, no significant adverse reproductive or developmental effects in oral studies when evaluated in mice at concentrations 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. Embryonic development was reduced or inhibited completely in cultures of mouse zygotes exposed to 3.0 or 6.0 M PG, respectively. A study examining induction of cytogenetic aberrations in mice reported an increase in the frequency of premature centromere separation (PCS) with 1300-5200 mg/kg PG. In zygotes from PG-dosed mice, hyperploidy was increased.

1,2-Butanediol

The test procedure for the combined repeated dose and reproductive/developmental toxicity study (Crj-CD(SD) rats) and results relating to oral toxicity are included in the Short-Term Oral Toxicity section earlier in the report text. All of the animals were killed on day 4 of lactation. Neither effects on reproduction (copulation, implantation, pregnancy, parturition, or lactation) nor developmental toxicity effects on offspring were observed. The NOAEL was 1,000 mg/kg for parental animals and the F_1 generation.[31] The estimated dose of low concern (EDCL) for this study was calculated as 10 mg/kg/day.[7]

1,2-Hexanediol

1,2-hexanediol was administered orally (by gavage) to rats at doses of 30, 100, and 300 mg/kg body weight in a prenatal developmental toxicity study (OECD 414 protocol). An NOEL of 300 mg/kg was reported.[43]

Propylene Glycol

A continuous breeding reproduction study was conducted using COBS Crl:CD-1 (ICR)BR outbred Swiss albino mice (6 weeks old).[46] The continuous breeding phase of the study (task II) was begun after the dose-setting study (task I) and involved 3 experimental groups (40 mice per group) and a control group of 80 mice. Experimental and control groups contained an equal number of male and female mice. The 3 experimental groups were given the following doses (in feed or water), respectively, during a 7-day pre-mating period: 1.0% propylene glycol (daily dose of 1.82 g/kg), 2.5% propylene glycol (daily dose of 4.80 g/kg), and 5.0% propylene glycol (daily dose of 10.10 g/kg). Task 3 (crossover mating trial, not

performed) was to have been performed only if significant effects on fertility were observed, to determine whether F_0 males or females were more sensitive to these effects.

To perform an offspring assessment of reproductive function (task 4) following exposure to propylene glycol, the dam (from phase II) was dosed through weaning and F_1 mice were dosed until mating occurred at 74 ± 10 days of age. Mating pairs consisted of male and female offspring from the same treatment group (20/group/sex); F_2 litters were examined. In the continuous breeding phase (task II), there were no significant changes ($p < 0.05$) in mean live pup weight per litter between the control group and any of the treatment groups. In task IV (offspring assessment of reproductive function), only the high-dose group (5% propylene glycol) was involved. There were no significant differences ($p < 0.05$) between control and experimental groups with respect to the following observations in task IV: mating index, fertility index, mean number of live pups per litter, proportion of pups born alive, and sex of pups born alive.[46]

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

The reproductive and developmental effects of PG were evaluated using mice, rats, rabbits, and hamsters.[47] 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, respectively. 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, respectively. 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.[47]

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

PG was used as a vehicle in a reproductive and behavioral development study.[48] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Embryonic development was reduced or inhibited completely in cultures of mouse zygotes exposed to 3.0 or 6.0 M PG, respectively.

From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Female ICR mice were used to determine whether PG induced cytogenetic aberrations in mouse metaphase II (MII) oocytes that predispose zygotes to aneuploidy.[30] Groups of mice were first given an i.p. injection of 7.5 IU hCG 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 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 undosed males immediately after being given hCG; the females were dosed i.p. with 1300, 2600, or 5200 mg/kg PG 3 h after hCG administration. 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.[30]

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

GENOTOXICITY

SymClariol® (decylene glycol) was non-genotoxic in the Ames test. 1*,2-Butatnediol was not genotoxic in assays involving bacterial cells (doses up to 5,000µg/plate) or mammalian cells (doses up to 0.9 mg/ml). In the 1994 CIR final safety assessment, PG was not mutagenic in bacterial assays, but positive and negative results were reported in assays involving mammalian cells*.

Decylene Glycol

In the Ames test (OECD 471 protocol), SymClariol® (decylene glycol) was classified as non-mutagenic. Test concentrations were not stated.

1,2-Butanediol

1.2-Butanediol was not mutagenic to *Salmonella typhimurium* strains TA100, TA98, TA97, and TA102 at doses up to 5,000 µg/plate with or without metabolic activation. The test substance also induced neither chromosomal aberrations nor polyploidy in Chinese hamster CHL cells at doses up to 0.9 mg/ml either with or without metabolic activation.[49]

Propylene Glycol

> 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).
>
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

CARCINOGENICITY

Propylene Glycol

PG was not carcinogenic in a chronic study in which rats were given ≤50,000 ppm PG in the diet for 2 years (feeding schedule not included). 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.

From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

CLINICAL ASSESSMENT OF SAFETY

Skin Penetration Enhancement

Combined exposure to PG and oleic acid synergistically enhanced the dermal penetration of both compounds.

Propylene Glycol

PG penetration is enhanced by the addition of fatty acids, such as oleic acid.[50] 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. [51] 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 that oleic acid accumulates in a deeper layer after the tape stripping.[51]

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Predictive Testing - Irritation and Sensitization

A 1,2-hexanediol/caprylyl glycol preservative mixture tested at concentrations up to 15% did not induce sensitization. Decylene glycol (20%) did not induce skin irritation/sensitization when applied to intact skin; however, decylene glycol (1%) had low skin irritation potential when applied to scarified skin. Results were negative for skin irritation/sensitization in RIPTs on products containing 1,2-glycols at concentrations ranging from 0.112% pentylene glycol to 0.5% caprylyl glycol or 1,2-hexanediol. In an in-use test of a products containing 0.15% 1,2-hexanediol, neither skin irritation nor sensitization was observed. PG was a slight skin irritant, but not a sensitizer, in human subjects. Deodorants containing PG induced skin irritation and reactions ranging from + to 2+ were reported in skin sensitization studies on similar products. Addition of PG to an isopropanol vehicle enhanced the irritant reactions of benzoic acid; maximal enhancement was seen with 5% PG.

Caprylyl Glycol and 1,2-Hexanediol

The skin irritation and sensitization potential of a lipstick containing 0.5% caprylyl glycol was evaluated in an RIPT using 105 healthy subjects (males and females). The product was applied to the upper back of each subject and application sites were covered with a semi-occlusive patch for 24 h. It was concluded that the product did not demonstrate a potential for eliciting skin irritation or sensitization.[52]

Levy et al.[53] studied the potential for delayed type IV dermal sensitivity following exposure to a new preservative system containing 1,2-hexanediol and caprylyl glycol. In a repeat insult patch test, a 15% mixture of 1,2-hexanediol and caprylyl glycol (equal parts of the 2 ingredients) in carbomer gel (total volume = 20 µl) was applied to each of 205 subjects (163 females, 42 males; 18 to 70 years old). The mixture was applied under 48 h occlusive patches (Finn chambers) during induction and challenge phases. Challenge application involved a new test site and reactions were scored at 48 and 72 h post-application according to the following scale: + (definite erythema without edema) to +++ (definite erythema, edema, and vesiculation). One of the subjects had a D reaction (damage to the epidermis: oozing, crusting, and/or superficial erosions) to the mixture; however, no reactions were observed in a subsequent 4-day repeat open application test. The reaction observed was indicative of irritation.

A cosmetic formulation containing the same preservation system (gel vehicle) at an actual use concentration (0.5%) was evaluated in an additional group of 224 subjects (176 females, 48 males; 19 to 70 years old) according to the same test procedure. None of the subjects had a delayed type IV dermal reaction.[53]

The skin sensitization potential of a 50:50 (w/w) mixture of 1,2-hexanediol and caprylyl glycol (Symdiol® 68) was evaluated in an RIPT involving 56 subjects. At a test concentration of 20% in gel (effective concentration per ingredient = 10%), the mixture did not induce skin sensitization in any of the subjects tested.[39]

A leg and foot gel containing 0.5% 1,2-hexanediol was applied to the upper back of each of 101 healthy subjects (males and females) in an RIPT. Each site was covered with a semi-occlusive patch that remained in place for 24 h. The product did not induce skin irritation or sensitization in this study.[54]

In an in-use safety evaluation for skin irritation potential, 28 subjects (males and females) were instructed to use a body wash containing 0.15% 1,2-hexanediol for a minimum of 3 times per week over a 30-day period. There was no evidence of erythema, edema, or dryness of application sites in any of the subjects, and it was concluded that the product did not demonstrate a potential for eliciting skin irritation or sensitization.[55]

Decylene Glycol

The skin irritation potential of SymClariol® (decylene glycol) was evaluated using 52 subjects in a 48h semi-occluded patch test. At a concentration of 20% in petrolatum, the test substance did not induce skin irritation. SymClariol® (1% in neutral oil) had low skin irritation potential when applied to scarified skin sites on 10 subjects. In an HRIPT, SymClariol® (20% in petrolatum) did not induce skin sensitization in any of the 55 subjects tested. [24]

In a facial stinging test, SymClariol® was classified as having very slight stinging potential when applied at concentrations of 1% and 2% (in neutral oil) in a group of 10 subjects.[24]

Pentylene Glycol

The skin irritation and sensitization potential of a foundation containing 0.112% pentylene glycol was evaluated in an RIPT using 101 subjects (males and females). A 1" x 1" semi-occlusive patch containing 0.2 g of the product was applied repeatedly (24 h applications) to the upper back. It was concluded that the product did not have a potential for inducing skin irritation or allergic contact sensitization.[56]

PG induced skin irritation reactions in normal subjects. Reactions were observed at concentrations as low as 10% in predictive 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.

From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

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.[71] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

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.[57] It has also been stated that subjective or sensory irritation sometimes occurs in volunteers after application of various concentrations of PG.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

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).[58] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

In another SIOPT, a deodorant formulation containing 68.06% PG was tested undiluted using 20 subjects (gender not specified).[59] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

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.[60] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Thirty-day use studies were completed with 26 male, 40 female, and 24 male subjects to evaluate the potential for deodorant sticks containing 35,[61] 65.2,[62] and 73%,[63] 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.[64]

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

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.[65] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

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.[66] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Another RIPT was completed with 99 subjects to determine the sensitization potential of a stick antiperspirant formulation containing 86% PG.[67] (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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Provocative Testing – Irritation and Sensitization

PG induced skin irritation reactions in patients at concentrations as low as 2%. Patients with chronic venous insufficiency (CVI) had sensitization reactions to PG, whereas contact dermatitis patients did not.

Propylene Glycol

PG induced skin irritation reactions in patients. Reactions were observed at concentrations as low as 2% in provocative tests.

From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Thirty-six patients with CVI were patch tested with 5% PG in petrolatum by application to the back for 2 days.[68] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

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.[69] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

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 (dose not given).[70] 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.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Retrospective Analysis

Propylene Glycol

The NACDG performed a number of retrospective analyses on various dermatological conditions, and data on the relevance of positive reactions to PG were presented. These studies are summarized in Table 5.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Case Reports

Positive reactions were observed in a patient patch tested with 0.5% and 5% 1,2-pentylene glycol, but not in the control group. A few case reports concerning PG and hand dermatitis or atopic dermatitis have been described, and positive reactions were reported.

Pentylene Glycol (1,2-Pentanediol)

A 68-year-old, non-atopic female developed facial dermatitis after using an eye cream that contained pentylene glycol (1,2-pentanediol), and patch test results were positive. Positive patch test reactions (+1) to 0.5% and 5% aqueous pentylene glycol were also reported. Except for one control subject with a follicular reaction to 5% pentylene glycol, reactions to 0.5% and 5.0% aqueous pentylene glycol were negative in a control group of 29 subjects.[72]

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.[73, 74]

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

SUMMARY

The sixteen 1,2-glycols included in this safety assessment function mostly as skin and hair conditioning agents and viscosity increasing agents in personal care products, and caprylyl glycol and pentylene glycol also function as preservatives. The following four 1,2-glycols were reported to FDA as being used: caprylyl glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol. The results of a Personal Care Products industry survey indicate that ingredient use concentrations have ranged from (lowest to highest) 0.00003% (caprylyl glycol) to 10% (1,2-hexanediol); the survey did not include use concentration data on C15-18 glycol. Use concentrations of pentylene glycol were also included in this survey.

Safety test data from the CIR safety assessment on propylene glycol have been reviewed and are relevant to the safety assessment of other 1,2-glycols included in this report, based on structural similarities.

The Environmental Protection Agency (EPA) lists 1,2-butanediol as one of the reactive compounds in aerosol coatings (i.e., aerosol spray paints) that contributes to ozone (O_3) formation. Esterified butanediol (1,2- or 1,3- not specified) is used in the production of resinous and polymeric coatings that comprise the food contact surface of packaged food products.

Stearyl glycol has been prepared via the reaction of 2-hydroxyoctadecanoic acid with lithium aluminum hydride in dry tetrahydrofuran, and the production of 1,2-butanediol is via a continuous reaction and distillation operation. The available impurities data indicate that 1,2-butanediol is $\geq$ 99% pure and also contains water, 1,4-butanediol, and 1-acetoxy-2-hydroxybutane.

Information on the metabolism, distribution, and excretion of 1,2-butanediol following i.v. dosing indicate that, in rabbits, this chemical is metabolized slowly and excreted in the urine either as the glucuronide or unchanged; there was no evidence of tissue accumulation. Metabolites were not identified in the urine of rabbits fed 1,2-butanediol in the diet. The available octanol/water partitition coefficients on 1,2-glycols were used to predict skin penetration in the absence of *in vitro* percutaneous absorption data.

The skin penetration enhancement effect of caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol has been demonstrated *in vitro*. Skin penetration of the following was enhanced: ^{3}H-corticosterone, ^{3}H-triethanolamine, and dihydrovenanthramide D.

There were no obvious toxic effects in rats exposed for 7 h to an atmosphere saturated with 1,2-butanediol. Acute oral toxicity data on caprylyl glycol and other 1,2-glycols for which data are available suggest that death would occur at relatively high doses (LD50 range: 2200 to > 20,000 mg/kg). Reportedly, high (unspecified) oral doses of 1,2-butanediol caused narcosis, dilation of the blood vessels, and kidney damage in rats. Overt toxic effects were not observed in ethanol-dependent rats dosed orally with 2.74 g/kg 1,2-butanediol.

The available data suggest that 1,2-butanediol (LD50s up to 5.99 g/kg) and pentylene glycol (TDLo = 3.51 g/kg) are not significant acute i.p. toxicants. However, muscle incoordination was observed in rats at an i.p. dose of ~ 2.94 g/kg. In an i.p. dosing study in which ED_3 values for caprylyl glycol (1,2-octanediol), pentylene glycol (1,2-pentanediol), and 1,2-butanediol were compared, caprylyl glycol had the lowest ED_3 value (1.5 mmole/kg), suggesting that its intoxication potency (i.e., ability to induce ataxia) was greatest. In an acute dermal toxicity study involving rats, the LD50 for decylene glycol (SymClariol®) was > 2,000 mg/kg. Prolonged application or repeated applications of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects.

An NOAEL of 100 mg/kg/day was reported for rats in a 28-day oral toxicity study on SymClariol® (decylene glycol). Short-term oral administration of 1,2-butanediol to rats yielded an NOAEL of 200 mg/kg/day. Reportedly, in another repeated dose study, the administration of large (unspecified) doses of 1,2-butanediol to rats, caused irritation of the gastrointestinal tract. Signs of poisoning were noted at the highest dose of 22 g/kg/day in rats receiving 1,2-butanediol in the diet for up to 8 weeks; abnormalities were not observed in tissues from major organs. Intermittent oral administration of pentylene glycol to rats over a 28-week period yielded a TDLo of 2,450mg/kg. Cetyl glycol (130 µg/ml) had a cytocidal effect on Ehrlich ascites carcinoma cells, lauryl glycol (99 µM) had a hemolytic effect on human erythrocytes, and pentylene glycol (5%) induced apoptosis in a human promyeolcytic leukemia cell line *in vitro*.

Based on Draize test results, lauryl glycol has been classified as a severe ocular irritant. Undiluted 1,2-butanediol , but not 10% aqueous, induced ocular irritation in rabbits. Undiluted SymClariol® (decylene glycol) induced corrosion when instilled into the eyes of rabbits. In an in vitro ocular irritation assay (HET-CAM), 1% SymClariol® in neutral oil and caprylyl glycol (1% and 3%) in neutral oil were classified as non-irritants; however, a 50:50 (w/w) mixture of caprylyl glycol and 1,2-hexanediol was classified as a severe ocular irritant when evaluated at a concentration of 1% aqueous (effective concentration per ingredient = 0.5%) in the same assay. Together, the results of a neutral red release (NPR) assay, the HET-CAM assay, and the reconstituted human epithelial culture (REC) assay indicated that a lash gel serum containing 3% pentylene glycol might be a slight ocular irritant.

In the maximization test, results were negative for caprylyl glycol at a challenge concentration of 50% in petrolatum. Undiluted SymClariol® (decylene glycol) was classified as a moderate skin irritant in rabbits, but did not induce sensitization in the guinea pig maximization test at challenge concentrations of 2% and 5% in arachis oil or in the mouse local lymph node assay at concentrations of 5% to 50% in acetone/olive oil (4:1). Repeated applications of 1,2-butylene glycol to the skin of rabbits did not result in skin irritation, and results were negative for 1,2-hexanediol (10% to 100%) in the mouse local lymph node assay for evaluating sensitization potential.

An NOAEL of 1,000 mg/kg for reproductive/developmental toxicity has been reported for 1,2-butanediol in rats dosed orally. In a prenatal reproductive toxicity study involving rats, an NOEL of 300 mg/kg was reported for 1,2-hexanediol.

SymClariol® (decylene glycol) was non-genotoxic in the Ames test. 1,2-Butanediol was not genotoxic in assays involving bacterial cells (doses up to 5,000µg/plate) or mammalian cells (doses up to 0.9 mg/ml). Marked antitumor effects of cetyl glycol were observed in mice *in vivo* following i.p. doses of 80 mg/kg/day. Cetyl glycol (130 µg/ml) was found to have a cytocidal effect (irreversible cell degeneration) on cultured EAC cells.

Results were negative for skin irritation and sensitization potential in RIPTs in which 105 subjects were patch tested with a lipstick containing 0.5% caprylyl glycol and 101 subjects were patch tested with a leg and foot gel containing 0.5% 1,2-hexanediol. An in-use test of a body wash containing 0.15% 1,2-hexanediol did not result in skin irritation or sensitization reactions in 28 subjects. 1,2-hexanediol/caprylyl glycol mixture (in preservative system) did not induce sensitization at a concentration of 0.5% or 15% in an RIPT involving 205 human subjects. Skin sensitization also was not observed in another RIPT in which 56 subjects were tested with a 50:50 (w/w) mixture of 1,2-hexanediol and caprylyl glycol (Symdiol® 68; effective concentration per ingredient = 10%). SymClariol® (decylene glycol) did not induce skin irritation in 52 subjects or sensitization (RIPT) in 55 subjects patch tested at a concentration of 20% in petrolatum. However, SymClariol® (1% in neutral oil) had low skin irritation potential when applied to scarified skin in a group of 10 subject, and very slight stinging potential when tested at concentrations of 1% and 2% in neutral oil in 10 subjects. A foundation containing 0.112% pentylene glycol did not induce skin irritation or sensitization in an RIPT involving 101 subjects.Positive reactions were observed in a patient patch tested with 0.5% and 5% 1,2-pentylene glycol, but not in the control group. A few case reports concerning PG and hand dermatitis or atopic dermatitis have been described, and positive reactions were reported.

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.

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. The oral LD_{50} of PG was >21 g/ kg for rats. The dermal LD_{50} of PG was >11.2 g/kg for mice and was 13 g/kg for rats. Mortalities were observed in mice at the highest i.p. dose of PG (10,400 mg/kg). 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. Subchronic inhalation data reported some effects in rats 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 g/kg or 5 g/kg, respectively, PG.

Undiluted PG was, at most, a slight ocular irritant. Dermal irritation studies were reported in the 1994 CIR final safety assessment and in the amended final safety assessment. 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 assays using guinea pigs. In a study using guinea pigs, 0.5 ml PG was a weak sensitizer.

Oral administration of PG did not have any adverse reproductive or developmental effects when evaluated in mice at concentrations 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 study examining induction of cytogenetic aberrations in mice reported 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 base pair substitution assays, or in a micronucleus test or a hamster embryo cell transformation 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.

Combined exposure to PG and oleic acid synergistically enhanced the dermal penetration of both compounds. 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. A few case reports concerning PG and hand dermatitis or atopic dermatitis have been described, and positive reactions were reported.

DISCUSSION

The Expert Panel noted that caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol may act as penetration enhancers. Some cosmetic ingredients have been regarded as safe based on the fact that they do not penetrate the skin. If caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol enhance the penetration of such ingredients, then they should not exist together in formulation.

Table 1. Caprylyl Glycol and Other 1,2-Glycols[3]

Chemical Names/CAS Nos.	Functions in Cosmetics
Arachidyl Glycol 1,2-Eicosanediol; CAS No. 39825-93-9	Viscosity Increasing Agents - Aqueous; Viscosity Increasing Agents - Nonaqueous
Cetyl Glycol 1,2-Dihydroxyhexadecane; 1,2-Hexadecanediol; 1,2-Hexadecylene Glycol; 2-Hydroxycetyl Alcohol; CAS No. 6920-24-7	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Aqueous; Viscosity Increasing Agents - Nonaqueous
Hexacosyl Glycol	Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Nonaqueous
Lauryl Glycol 1,2-Dihydroxydodecane; 1,2-Dodecanediol; 1,2-Dodecylene Glycol; CAS No. 1119-87-5	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient
Myristyl Glycol 1,2-Tetradecanediol; CAS No. 21129-09-9	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient; Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous
Octacosanyl glycol 1,2-Octacosanediol; CAS No. 97338-11-9	Emulsion Stabilizers; Viscosity Increasing Agents - Nonaqueous
Stearyl Glycol 1,2-Dihydroxyoctadecane; 1,2-Octadecanediol; CAS No. 20294-76-2	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Nonaqueous
Caprylyl Glycol Capryl Glycol; 1,2-Dihydroxyoctane; 1,2-Octanediol; 1,2-Octylene Glycol; CAS No. 1117-86-8	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient; preservative
Decylene Glycol 1,2-Decanediol; CAS No. 1119-86-4	Skin-Conditioning Agents - Miscellaneous
Pentylene Glycol 1,2-Dihydroxypentane; 1,2-Pentanediol; CAS No. 5343-92-0	Skin-Conditioning Agents - Miscellaneous; Solvents; preservative
1,2-Butanediol 1,2-Butylene Glycol; 1,2-Dihydroxybutane; CAS No. 584-03-2	Skin-Conditioning Agents - Humectant; Solvents; Viscosity Decreasing Agents
1,2-Hexanediol 1,2-Dihydroxyhexane; CAS No. 6920-22-5	Solvents
C14-18 Glycol Ethylene Glycol Fatty Acid Ester (2)	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
C15-18 Glycol Alkylene (15-18) Glycol; Cetyl Stearyl Vicinal Glycol; Glycols, C15-18; CAS Nos. 70750-40-2 and 92128-52-4	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
C18-30 Glycol Ethylene Glycol Fatty Acid Ester (1)	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
C20-30 Glycol Alkylene (20-30) Glycol	Emulsion Stabilizers; Skin-Conditioning Agents - Occlusive

Table 2. Chemical and Physical Properties

Property	Values	Reference
Arachidyl Glycol		
Molecular weight	314.55	ACD/Labs[75]
Molar volume	354.0 ± 3.0 cm^3/mole (20°C, 760 Torr)	″
Density	0.888 ± 0.6 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.000000063 g/l (25°C)	″
Mass solubility	0.000000063 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.00000000020 mol/l (25°C)	″
Molar solubility	0.00000000020 mol/l (pH 7, 25°C)	″
Melting point	84.3 to 84.8°C	″
Boiling point	435.2 ± 18.0°C (760 Torr)	″
Flash point	183.7 ± 15.8°C	″
Enthalpy of vaporization	79.83 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	2.11E-09 Torr	″
pKA	14.19 ± 0.20 (25°C)	″
logP	7.692 ± 0.216 (25°C)	″
Cetyl glycol		
Molecular weight	258.44	ACD/Labs[75]
Molar volume	288.0 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.897 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.000067 g/l (25°C)	″
Mass solubility	0.000067 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.00000026 mol/l (25°C)	″
Molar solubility	0.00000026 mol/l (pH 7, 25°C)	″
Melting point	75 to 76°C (not calculated)	Bryun[76]
Boiling point	356.1 ± 10.0°C (760 Torr)	ACD/Labs[75]
Flash point	151.9 ± 13.6°C	″
Enthalpy of vaporization	69.61 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.69E-06 Torr (25°C)	″
pKA	14.19 ± 0.20 (25°C)	″
logP	5.567 ± 0.216 (25°C)	″
Lauryl glycol		
Molecular weight	202.33	ACD/Labs[75]
Molar volume	222.0 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.911 ± 0.06 g/cm3 (20°C, 760 Torr)	″
Refractive index	1.4558 (20°C, λ = 589.3 nm)	″
Mass intrinsic solubility	0.028 g/l (25°C)	″
Mass solubility	0.028 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.00014 mol/l (25°C)	″
Molar solubility	0.00014 mol/l (pH7, 25°C)	″
Melting point	60 to 61°C (not calculated)	Swern[77]
Boiling point	179 to 181°C (4 Torr) – not calculated; 304.3 ± 10°C (760 Torr)	″
Flash point	134.3 ± 13.6 °C	″
Enthalpy of vaporization	63.17 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	8.40E-05 Torr	″
pKA	14.19 ± 0.20 (25°C)	″
logP	3.441 ± 0.216 (25°C)	″
Myristyl glycol		
Molecular weight	230.39	ACD/Labs[75]

Table 2. Chemical and Physical Properties

Property	Values	Reference
Molar volume	255.0 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.903 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.0015 g/l (25°C)	ACD/Labs[75]
Mass solubility	0.0015 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.0000067 mol/l (25°C)	″
Molar solubility	0.0000067 mol/l (pH 7, 25°C)	″
Melting point	68 to 68.5 °C	″
Boiling point	152 to 154 °C (0.2 Torr); 333.1 ± 10.0°C (760 Torr)	″
Flash point	143.8 ± 13.6 °C	″
Enthalpy of vaporization	66.48 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.16E-05 Torr (25°C)	″
pKA	14.19 ± 0.20 (25°C)	″
logP	0.4504 ± 0.216 (25°C)	″
Octacosanyl Glycol		
Molecular weight	426.76	ACD/Labs[75]
Molar volume	486.1 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.877 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.0000032 g/l (25°C)	″
Mass solubility	0.0000032 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.0000000076 mol/l (25°C)	″
Molar solubility	0.0000000076 mol/l (pH 7, 25°C)	″
Boiling point	536.3 ± 23.0°C (760 Torr)	″
Flash point	210.9 ± 17.2°C	″
Enthalpy of vaporization	93.49 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	9.74E-14 Torr (25°C)	″
pKA	14.19 ± 0.20 (25°C)	″
logP	11.943 ± 0.217 (25°C)	″
Stearyl Glycol		
Molecular weight	286.49	ACD/Labs[75]
Molar volume	321.0 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.892 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.0000023 g/l (25°C)	″
Mass solubility	0.0000023 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.0000000080 mol/l (25°C)	″
Molar solubility	0.0000000081 mol/l (pH 7, 25°C)	″
Melting point	79 to 79.5°C (not calculated)	Niemann[78]
Boiling point	377.2 ± 10.0°C (760 Torr)	ACD/Labs[75]
Flash point	157.6 ± 13.6°C	″
Enthalpy of vaporization	72.30 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	3.09E-07 Torr (25°C)	″
pKA	14.19 ± 0.20 (25°C)	″
logP	6.629 ± 0.216 (25°C)	″
Caprylyl Glycol		
Molecular weight	146.23	ACD/Labs[75]
Molar volume	155.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.937 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	4.2 g/l (25°C)	″
Mass solubility	4.4 g/l (pH 7, 25°C)	″

Table 2. Chemical and Physical Properties

Property	Values	Reference
Molar intrinsic solubility	0.029 mol/l (25°C)	″
Molar solubility	0.030 mol/l (pH 7, 25°C)	″
Melting point	36 to 37°C (not calculated)	Fringuelli[79]
Boiling point	137 to 139°C (not calculated); 243.0 ± 8.0°C (760 Torr)	Mugdan[80]
Flash point	109.1 ± 13.0°C	ACD/Labs[75]
Enthalpy of vaporization	55.78 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	5.59E-03 Torr	″
pKA	14.31 ± 0.10 (25°C)	″
logP	1.316 ± 0.215 (25°C)	″
Decylene Glycol		
Molecular weight	174.28	STN[9]
Molar volume	188.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.922 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.40 g/l (25°C)	″
Mass solubility	0.40 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.0023 mol/l (25°C)	″
Molar solubility	0.0023 mol/l (pH 7, 25°C)	″
Melting point	48-49°C	Swern[77]
Boiling point	93 to 96°C (0.5 Torr) - not calculated; 255.0 ± 0.0°C (760 Torr)	Orito[81]
Flash point	122.4 ± 13.0°C	ACD/Labs[75]
Enthalpy of vaporization	57.21 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	2.54E-03 Torr (25°C)	″
pKA	14.21 ± 0.20 (25°C)	″
logP	2.378 ± 0.216 (25°C)	″
Pentylene Glycol		
Molecular weight	104.15	ACD/Labs[75]
Molar volume	106.4 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.9723 g/cm^3 (20°C) – not calculated; 0.978 ± 0.06 g/cm^3 (20°C, 760 Torr)	Clendenning[82]
Refractive index	1.4400 (20°C, λ = 589.3 nm) – not calculated	Emmons[83]
Mass intrinsic solubility	95 g/l (25°C)	ACD/Labs[75]
Mass solubility	95 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.91 mol/l (25°C)	″
Molar solubility	0.91 mol/l (25°C)	″
Boiling point	78 to 80°C (0.3 Torr) – not calculated ; 206.0 ± 0.0°C (760 Torr)	Clendenning[82]; Emmons[83]
Flash point	104.4 ± 0.0°C	ACD/Labs[75]
Enthalpy of vaporization	51.45 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	5.75E-02 Torr (25°C)	″
pKA	14.22 ± 0.20 (25°C)	″
logP	-0.278 ± 0.215 (25°C)	″
1,2-Butanediol		
Molecular weight	90.12	ACD/Labs[75]
Molar volume	89.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	1.0205 g/cm^3 (20°C) – not calculated; 1.001 ± 0.06 g/cm^3 (20°C)	Mamedov[84]; Tishchenko[85]
Refractive index	1.4380 (20°C, λ = 589.3 nm)	ACD/Labs[75]

Table 2. Chemical and Physical Properties

Property	Values	Reference
Mass intrinsic solubility	230 g/l (25°C)	″
Solubility	Very soluble in water	NIOSH[11]
Mass solubility	230 g/l (pH 7, 25°C)	ACD/Labs[75]
Molar intrinsic solubility	2.55 mol/l (25°C)	″
Molar solubility	2.55 mol/l (pH 7, 25°C)	″
Melting point	-50°C and -114°C (not calculated)	STN[9]
Boiling point	132 to 133°C (760 Torr) – not calculated; 190.3 ± 8.0°C (760 Torr)	Clendenning[82]; Hill[86]
Flash point	93.3 ± 0.0°C	ACD/Labs[75]
Enthalpy of vaporization	49.64 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.48E-01 Torr 10 (20ºC)	″ NIOSH[11]
pKA	14.27 ± 0.20 (25°C)	STN[9]
logP	-0.810 ± 0.215 (25°C)	″
Stability	Stable in neutral, acidic, or alkaline solutions	OECD[7]
Half life	≥ 1 year (25ºC; pH: 4, 7, and 9)	″
1,2-Hexanediol		
Molecular weight	118.17	ACD/Labs[75]
Molar volume	122.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.961 ± 0.06 g/cm^3 (20°C)	″
Refractive index	1.4518 (25°C, λ = 589.3 nm) – not calculated	Zelinski[87]
Mass intrinsic solubility	37 g/l (25°C)	ACD/Labs[75]
Mass solubility	37 g/l (pH7, 25°C)	″
Molar intrinsic solubility	0.31 mol/l (25°C)	″
Molar solubility	0.31 mol/l (pH 7, 25°C)	″
Melting point		″
Boiling point	112 to 113°C (12 Torr) – not calculated; 223.5 ± 0.0°C (760 Torr)	Lapporte[88]
Flash point	95.8 ± 13.0°C	″
Enthalpy of vaporization	53.48 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.94E-02 Torr	″
pKA	14.22 ± 0.20 (25°C)	″
logP	0.253 ± 0.215 (25°C)	″

Table 3. Current Cosmetic Product Uses[12] and Concentrations of 1,2-Glycols[13]

Product category	2010 uses (total number of products in category)	2010 concentrations (%)
caprylyl glycol		
Baby products		
Shampoos	2 (57)	-
Lotions, oils, powders, and creams	3 (151)	0.6
Other	6 (149)	-
Bath Products		
Oils, Tablets, and Salts	7 (338)	-
Bubble Baths	3 (176)	-
Soaps and Detergents	32 (1781)	0.0004 to 1
Other	6 (227)	-
Eye makeup		
Eyebrow pencil	1 (153)	0.5
Eyeliner	27 (834)	0.5 to 0.7
Eye shadow	57 (1343)	0.3 to 5
Eye lotion	49 (260)	0.3 to 1
Eye makeup remover	5 (133)	0.3
Mascara	64 (528)	0.3 to 0.7
Other	31 (412)	0.8
Fragrance products		
Cologne and toilet waters	-	0.5
Perfumes	-	0.2 to 0.3
Powders (dusting and talcum, excluding aftershave talc)	6 (237)	0.3
Other	12 (641)	0.3 to 0.5
Noncoloring hair care products		
Conditioners	19 (1313)	0.002 to 1
Rinses	2 (34)	-
Shampoos	11 (1487)	0.0002 to 0.7
Tonics, dressings, etc.	26 (1321)	0.01 to 0.8
Wave sets	2 (60)	
Other	10 (838)	2
Hair coloring products		
Dyes and colors (all types requiring caution statements and patch tests)	-	0.3 to 0.5
Other	1 (168)	0.002 to 0.5
Makeup		
Blushers	33 (471)	0.3 to 1
Face powders	59 (724)	0.6 to 1
Foundations	36 (624)	0.2 to 1
Leg and body paints	1 (29)	
Lipstick	218 (1,883)	0.3 to 3
Makeup bases	12 (2045)	0.5 to 1
Rouges	2 (107)	-
Other	34 (536)	0.2 to 0.6
Nail care products		
Basecoats and undercoats	1 (69)	0.0004
Cuticle softeners	2 (30)	
Creams and Lotions	1 (15)	-
Polish and Enamel	1 (351)	0.0004 to 0.5
Other	1 (137)	0.0005 to 0.5
Personal Cleanliness Products		
Deodorants (underarm)	36 (623)	0.03 to 2
Other	49 (925)	0.3 to 0.7
Shaving products		
Aftershave lotion	15(381)	0.2 to 0.5
Preshave lotions (all types)	-	0.0008 to 0.5

Table 3. Current Cosmetic Product Uses[12] and Concentrations of 1,2-Glycols[13]

Product category	2010 uses (total number of products in category)	2010 concentrations (%)
Shaving cream	7 (128)	0.001 to 0.4
Other	6 (126)	0.4
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	91 (1528)	0.0003 to 1
Depilatories	-	0.5
Face and neck lotions	157 (1652)	0.2 to 1
Body and hand lotions	151 (1875)	0.02 to 1
Body and hand sprays	-	0.0003 to 0.8
Foot powders and sprays	2 (46)	-
Moisturizers	269 (2750)	0.2 to 1
Moisturizing sprays	-	0.3
Night creams and lotions	53 (386)	0.5 to 1
Paste masks (mud packs)	34 (462)	0.3
Skin fresheners	8 (267)	0.00003 to 0.4
Other	77 (1446)	0.2 to 1
Suntan products		
Gels, creams, and liquids	3 (106)	0.6 to 2
Indoor tanning preparations	16 (247)	0.5 to 1
Other	4 (61)	0.3 to 2
Total uses/ranges for caprylyl glycol	1761	0.00003 to 5
Pentylene glycol		
Bath products		
Other	1 (227)	-
Soaps and detergents	19 (1781)	1 to 3
Eye makeup		
Eyeliner	10 (834)	1 to 2
Eye shadow	17 (1343)	-
Eye lotion	35 (260)	0.005 to 4
Eye makeup remover	5 (133)	1 to 3
Mascara	11 (528)	2 to 3
Other	18 (412)	-
Fragrance products		
Cologne and toilet waters	1 (1426)	-
Other	2 (641)	1
Noncoloring hair care products		
Conditioners	1 (1313)	0.001
Shampoos	2 (1487)	0.001
Tonics, dressings, etc.	8 (1321)	-
Other	1 (838)	-
Makeup		
Blushers	1 (471)	-
Face powders	13 (724)	2
Foundations	24 (624)	1 to 4
Leg and body paints	1 (29)	
Lipstick	6 (2045)	-
Makeup bases	2 (126)	-
Rouges	1 (107)	
Makeup fixatives	3 (49)	-
Other	4 (536)	0.5 to 3
Nail care products		
Cuticle softeners	-	4
Other	-	5
Personal hygiene products		
Deodorants (underarm)	3 (623)	0.2
Other	6 (925)	0.001 to 5

Table 3. Current Cosmetic Product Uses[12] and Concentrations of 1,2-Glycols[13]

Product category	2010 uses (total number of products in category)	2010 concentrations (%)
Shaving products		
Aftershave lotion	2 (381)	-
Other	6 (126)	-
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	44 (1528)	0.003 to 3
Face and neck lotions	134 (1652)	0.5 to 5
Body and hand lotions	52 (1875)	0.005 to 3
Body and hand sprays	-	2
Foot powders and sprays	1 (46)	-
Moisturizers	141 (2750)	0.7 to 5
Night creams and lotions	21 (386)	2 to 4
Paste masks (mud packs)	13 (462)	1 to 4
Skin fresheners	12 (267)	-
Other	74 (1446)	2 to 5
Suntan products		
Gels, creams, and liquids	1 (106)	5
Indoor tanning preparations	13 (247)	3
Other	1 (61)	-
Total uses/ranges for pentylene glycol	710	0.001 to 5
1,2-hexanediol		
Baby products		
Shampoos	1 (57)	-
Lotions, oils, powders, and creams	2 (151)	-
Bath products		
Oils, tablets, and salts	1 (338)	0.2
Soaps and detergents	5 (1781)	0.0004
Other	1 (227)	-
Eye makeup		
Eyeliner	1 (834)	-
Eye shadow	-	0.3 to 0.6
Eye lotion	6 (260)	0.3
Eye makeup remover	2 (133)	0.4
Mascara	16 (528)	0.5 to 0.7
Other	3 (412)	-
Fragrance products		
Cologne and toilet waters	-	10
Other	1 (641)	-
Noncoloring hair products		
Shampoos	1 (1487)	0.0003
Tonics, dressings, etc.	2 (1321)	0.3
Makeup		
Blushers	-	0.3
Face powders	1 (724)	0.3
Foundations	2 (624)	0.2 to 0.8
Leg and body paints	1 (29)	
Lipstick	16 (2045)	0.3
Makeup bases	1 (126)	0.2
Other	2 (536)	0.5
Nail care products		
Cuticle softeners	1 (30)	-
Other	-	0.4
Personal hygiene products		
Deodorants (underarm)	3 (623)	-
Other	12 (925)	0.3

Table 3. Current Cosmetic Product Uses[12] and Concentrations of 1,2-Glycols[13]

Product category	2010 uses (total number of products in category)	2010 concentrations (%)
Shaving products		
Aftershave lotion	4 (381)	0.5
Other	1 (126)	0.4
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	16 (1528)	0.00005 to 0.6
Face and neck lotions	20 (1652)	0.3 to 0.6
Body and hand lotions	8 (1875)	0.3 to 0.6
Moisturizers	27 (2750)	0.4 to 0.5
Night creams and lotions	5 (386)	-
Paste masks (mud packs)	3 (462)	-
Skin fresheners	1 (267)	-
Other	5 (1446)	0.2 to 0.6
Suntan products		
Gels, creams, and liquids	1 (106)	0.3 to 0.5
Indoor tanning preparations	1 (247)	-
Total uses/ranges for 1,2-hexanediol	173	0.00005 to 10
C15-18 glycol		
Makeup		
Other	1 (536)	-
Total uses/ranges for C15-18 glycol	1	

Table 4. Corticosterone and TEA Permeability Coefficients in the Presence of Permeation Enhancers[10]

Enhancer	Enhancer Concentration (M)	Permeability Coefficient of CS[α] (cm/s x 10^7)	Permeability Coefficient of TEA[α] (cm/s x 10^8)
PBS – control		2.2 ± 0.8	1.35 ± 0.65
1,2-octanediol	0.005	6.2 ± 1.1	
	0.0104	7.4 ± 1.4	4.2 ± 1.3
	0.02	30 ± 3	12 ± 8
	0.024	27 ± 9	20 ± 5
	0.035	110 ± 10	
1,2-decanediol	0.0006	5 ± 1	
	0.001	11 ± 3	4.7 ± 2.1
	0.00141	28 ± 7	
	0.00192	80 ± 20	7.1 ± 0.7
	0.0024	110 ± 1	63 ± 16
1,2-hexanediol	0.09	6.5 ± 2.7	
	0.145	13 ± 3	2 ± 1
	0.25	23 ± 5	
	0.35	65 ± 23	9.2 ± 4.1

[α]Mean ± SD (n = 3)

Figure 2. Octanol/Water Partitioning Coefficient (log P)

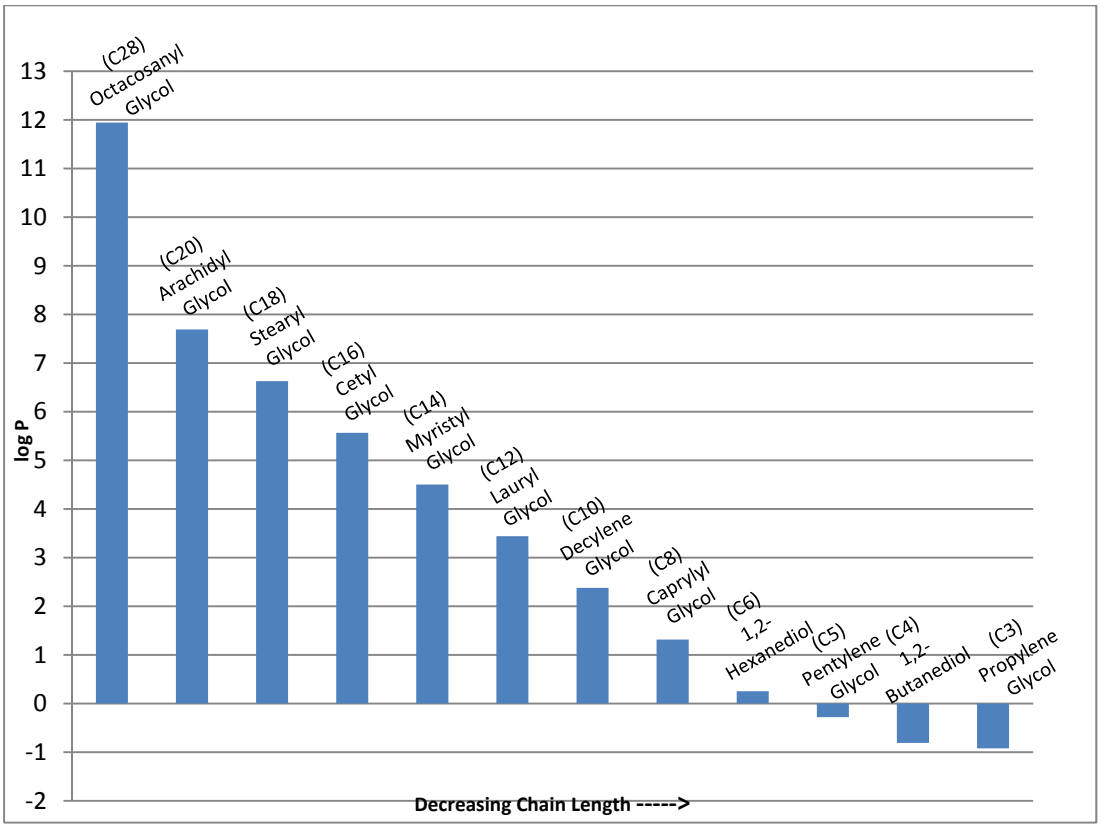
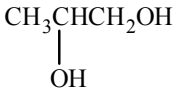


Table 5. Retrospective analyses with propylene glycol

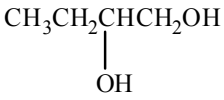
No. of patients	Years studied	% PG	Methods	Findings
not given	1984-1996	10 aq.	data were collected from NACDG-reported studies; the SPIN for each allergen was calculated as the proportion of the population allergic by the weighted clinician-assessed likelihood of relevance of the reaction	the SPIN rank for PG has changed over time: 23 in 1984-1985; 40 in 1992-1994; 41 in 1994-1996[89]
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[90]
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[91]
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[92]
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[93]

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

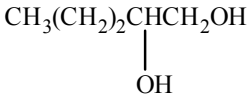
Figure 1. Formulas of 1,2-Glycols



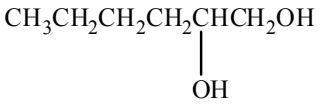
Propylene Glycol



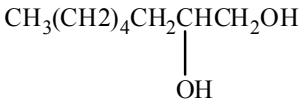
1,2-Butanediol



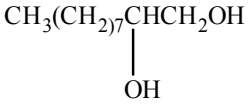
Pentylene Glycol



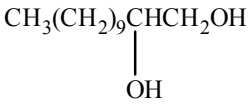
1,2-Hexanediol



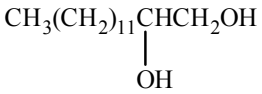
Caprylyl Glycol



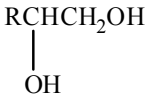
Decylene Glycol



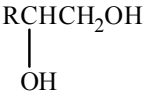
Lauryl Glycol



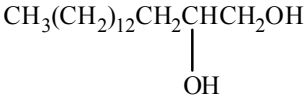
Myristyl Glycol



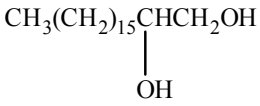
C14-18 Glycol
(wherein R is C12-C16)



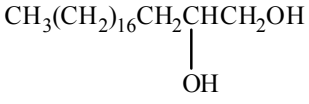
C15-18 Glycol
(wherein R is C13-C16)



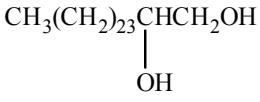
Cetyl Glycol



Stearyl Glycol

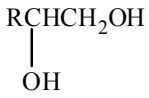


Arachidyl Glycol

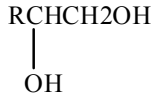


Hexacosyl Glycol

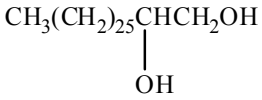
Figure 1. Formulas of 1,2-Glycols



C18-30 Glycol
(wherein R is C16-C28)



C20-30 Glycol
(wherein R is C18-C28



Octacosanyl Glycol

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DATA

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: September 16, 2010

SUBJECT: Unpublished data on products containing 1,2-glycols

Clinical Research Laboratories, Inc. 2009. Repeated insult patch test of a leg and foot gel containing 0.5% 1,2-Hexanediol. CRL Study Number: CRL34109-1.

Clinical Research Laboratories, Inc. 2009. In-use safety evaluation to determine the dermal irritation potential of a cosmetic product or toiletry (body wash containing 0.15% 1,2-Hexanediol). CRL Study Number: CRL50709.

Clinical Research Laboratories, Inc. 2009. Repeated insult patch test of a lipstick containing 0.5% Caprylyl Glycol. CRL Study Number: CRL37609-3.

International Research and Development Center. 2010. Assessment of the eye irritating potential of a cosmetic product through alternative methods to the Draize test (lash gel serum containing 3% Pentylene Glycol). Report Ref: CTOX/10002.

Consumer Product Testing Co. 2008. Repeated insult patch test of a foundation containing 0.112% Pentylene Glycol. Experiment Reference Number: C08-1978.01.

Clinical
Research
Laboratories, Inc.

Final Report

Repeated Insult Patch Test

CLIENT:

ATTENTION: Claims Substantiation Analyst

TEST MATERIAL: Leg and Foot Gel
Containing 0.5% 1,2-Hexanediol

CRL STUDY NUMBER: CRL34109-1

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
President/Medical Director

Michael J. Muscatiello, Ph.D.
Executive Vice President/COO

George J. Neumaier, M.D.
Diplomate American Board
of Dermatology

REPORT DATE: June 1, 2009

371 Hoes Lane • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520

Clinical
Research
Laboratories, Inc.

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: CRL34109-1

Start Date: April 13, 2009

Completion Date: May 22, 2009

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted, as indicated below.

Karen Hayley
Signature of QA Auditor

June 1, 2009
Date

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material.

INVESTIGATIVE SITE

Clinical Research Laboratories, Inc.
371 Hoes Lane
Piscataway, New Jersey 08854
732-981-1616

TEST MATERIAL

The following test material was provided by :. and was received by Clinical Research Laboratories, Inc. on April 3, 2009:

Test Material	Test Condition	Patch Type
Leg and Foot Gel	Test as received	Semi-occlusive*

The test material was coded with the following CRL identification number:

CRL34109-1

STUDY DATES

This study was initiated on April 13, 2009 and was completed on May 22, 2009.

* Semi-occlusive Strip (Brady Medical, Mesquite,TX)

PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix I). Subjects who met the following criteria were impaneled:

- Male and female panelists between the ages of 18 and 70;
- Subjects who have completed a Panelist Profile/Medical History;
- Subjects who are in general good health as determined by a Panelist Profile/Medical History;
- Subjects who do not exhibit any skin diseases that might be confused with a skin reaction from the test material;
- Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;
- Subjects willing to sign an Informed Consent Form in conformance with 21 CFR Part 50: "Protection of Human Subjects";
- Subjects who have completed a HIPAA Authorization Form in conformance with 45 CFR Parts 160 and 164;
- Females who are not pregnant or lactating;
- Subjects who demonstrate dependability and intelligence in following directions;
- Subjects who are not currently using any systemic or topical corticosteroids, anti-inflammatory drugs or antihistamines;
- Subjects who do not exhibit skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.

TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scoring Scale

0 No visible skin reaction
± Barely perceptible erythema
1+ Mild erythema
2+ Well defined erythema
3+ Erythema and edema
4+ Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.

RESULTS

This study was initiated with 112 subjects. Eleven subjects discontinued study participation for reasons unrelated to the test material. A total of 101 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

CONCLUSION

Based on the test population of 101 subjects and under the conditions of this study, the test material identified as Leg and Foot Gel did not demonstrate a potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.

TABLE I

Summary of Dermal Scores

Test Material:	Leg and Foot Gel

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	DISCONTINUED		
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Leg and Foot Gel

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	DISCONTINUED										
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	DISCONTINUED											
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	DISCONTINUED										
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	DISCONTINUED							
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	DISCONTINUED											
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	DISCONTINUED											
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Leg and Foot Gel

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	DISCONTINUED		
61	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0	0	0	0
63	0	DISCONTINUED										
64	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Leg and Foot Gel

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	±	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Leg and Foot Gel 3											
Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
101	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0
104	0	DISCONTINUED										
105	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0
110	0	0	0	0	0	0	0	0	0	DISCONTINUED		
111	0	0	0	0	0	0	0	0	0	0	0	0
112	0	0	0	0	0	0	0	0	0	0	0	0

Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
1	MS	18675	69	F
2	KB	24000	61	F
3	AB	23860	63	M
4	FL	18275	52	M
5	LS	20205	66	F
6	HS	24646	49	F
7	WA	14950	51	F
8	GP	24017	39	F
9	KW	16112	54	M
10	DP	23728	38	M
11	ES	18566	46	M
12	KH	15618	60	F
13	MC	20467	41	M
14	LH	23724	49	F
15	JA	01057	58	F
16	LU	15838	61	M
17	ED	14488	57	F
18	AM	18310	53	M
19	AJ	14956	48	F
20	NP	18496	32	F
21	TP	20918	24	F
22	CP	22751	57	F
23	LA	21135	26	F
24	RA	09722	46	F
25	MJ	24194	44	F
26	WS	17503	61	F
27	VT	24473	49	F
28	BK	24743	49	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
29	ER	24265	54	F
30	RD	21017	47	M
31	TM	22343	26	F
32	MM	22344	51	F
33	DC	19990	51	F
34	SR	23160	28	F
35	BY	24296	62	F
36	JM	13991	68	F
37	KR	17395	28	F
38	DC	23486	59	M
39	SS	23451	59	F
40	MM	18694	39	F
41	SO	11316	65	F
42	SC	23058	46	F
43	AP	23481	40	F
44	FC	23784	50	M
45	LN	24351	42	F
46	RW	19993	62	M
47	KW	23127	50	F
48	AR	19595	23	F
49	JS	23688	45	F
50	ED	04355	70	F
51	MH	21487	26	M
52	LW	18134	31	F
53	LK	19317	59	F
54	AN	23619	42	M
55	AJ	23767	59	M
56	JO	08352	59	F

Appendix I
(Continued)

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
57	JK	14141	69	F
58	BM	00054	55	F
59	EJ	18712	51	F
60	KM	14519	42	F
61	JD	19635	26	F
62	MC	23416	20	M
63	JG	25036	21	M
64	DP	24464	38	F
65	FT	24002	32	F
66	JR	15859	35	F
67	JR	18151	62	M
68	TR	18677	53	F
69	BB	04876	59	F
70	JB	07118	63	F
71	KC	09142	54	F
72	SH	21327	44	F
73	KS	24067	50	F
74	RS	05543	43	M
75	FK	04033	60	M
76	AC	23207	30	F
77	JM	20081	58	M
78	MH	11093	51	F
79	LM	24462	25	M
80	JB	12170	65	F
81	JS	02800	53	F
82	HP	18497	54	F
83	JM	08354	59	M
84	TS	23518	42	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
85	MD	24381	27	F
86	SC	20528	26	F
87	LR	22519	44	F
88	AA	20915	31	F
89	CG	20751	46	F
90	AR	23884	29	F
91	KG	17907	31	F
92	BT	13184	62	F
93	BZ	06424	66	F
94	DL	23982	55	M
95	JZ	23306	69	F
96	JH	23464	62	F
97	WG	18828	62	F
98	AR	19479	25	F
99	CA	00159	59	F
100	VR	21842	60	F
101	GM	19064	35	F
102	HZ	10052	64	F
103	CG	24297	28	F
104	HA	24771	26	F
105	YR	23984	49	F
106	QW	13551	40	F
107	MP	06524	69	F
108	TH	08056	50	F
109	LZ	08758	44	F
110	LH	13288	66	F
111	BA	22252	62	F
112	BP	24412	46	F

Clinical
Research
Laboratories, Inc.

Final Report

**In-Use Safety Evaluation to
Determine the Dermal Irritation Potential of a
Cosmetic Product or Toiletry**

CLIENT:

ATTENTION: **Claims Substantiation Analyst**

TEST MATERIAL: **Unisex Body Wash** containing 0.15% 1,2-Hexanediol

CRL STUDY NUMBER: **CRL50709**

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
President/Medical Director

Michael J. Muscatiello, Ph.D.
Executive Vice President/COO

REPORT DATE: **July 10, 2009**

371 Hoes Lane • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520

Clinical Research Laboratories, Inc.

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: CRL50709

Start Date: May 28, 2009

Completion Date: June 26, 2009

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted, as indicated below.

Signature of QA Auditor

07-10-09
Date

FINAL REPORT

In-Use Safety Evaluation to Determine the Dermal Irritation Potential of a Cosmetic Product or Toiletry

PURPOSE

The purpose of this study was to evaluate the dermal irritation potential of Unisex Body Wash -1, under controlled use conditions, following a four-week use period.

INVESTIGATOR

Clinical Research Laboratories, Inc.
371 Hoes Lane
Piscataway, New Jersey 08854
732-981-1616

SPONSOR

TEST MATERIAL

The following test material was provided by ic. and was received by Clinical Research Laboratories, Inc. on May 22, 2009:

Unisex Body Wash

STUDY DATES

This study was initiated on May 28, 2009 and was completed on June 26, 2009.

STUDY POPULATION

A total of 28 male and female subjects, ranging in age from to 18 to 68 years old and in generally good health, were selected for the study (Subject Demographics – Appendix I). Subjects who met all of the inclusion criteria and none of the exclusion criteria were impaneled for this study.

Subject Inclusion Criteria

a. Subject is male or female between 18 and 70 years of age;

b. Subject is free from any dermal disorders which may affect test results;

c. Subject exhibits no erythema or edema of the test sites, and no greater than mild dryness, at the baseline examination;

d. Subject has signed an Informed Consent Form in compliance with 21CFR Part 50: "Protection of Human Subjects";

e. Subject is a regular user of cosmetic, personal care or toiletry products;

f. Subject is willing to refrain from shaving test sites within 24 hours of evaluation;

g. Subject has completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;

h. Subject is dependable and able to follow directions;

i. Subject is in generally good health and has a current Panelist Profile/Medical History Form on file;

j. Subject agrees not to introduce any new cosmetic or personal care products, other than the assigned test material, during the course of the study.

Subject Exclusion Criteria

a. Subject reports being pregnant or nursing;

b. Subject has received treatment with sympathomimetics, antihistamines, vasoconstrictors, non-steroidal anti-inflammatory agents, and/or systemic or topical corticosteroids within one week prior to initiation of the study;

c. Subject has known allergies to cosmetics or toiletries;

d. Subject has participated in a dermal study within one week of study initiation;

e. Subject has participated in an investigational systemic drug study within two weeks of study initiation;

f. Subject has a history of acute or chronic dermatologic, medical, and/or physical conditions which would preclude application of the test material and/or could influence the outcome of the study.

STUDY EVALUATIONS

Safety Assessments – Dermal Evaluations

The test sites of each subject were examined for signs of irritation including erythema, edema, and dryness. Any observed irritation was graded and the results recorded on the dermal examination score sheet using the following scoring scales:

Erythema	Edema	Dryness
1 = None	1 = None	1 = None
2 = Mild	2 = Mild	2 = Mild
3 = Moderate	3 = Moderate	3 = Moderate
4 = Severe	4 = Severe	4 = Severe

STUDY EXECUTION

Informed Consent

At the Baseline Visit, the study procedures were explained to all subjects intending to participate. All subjects were completely informed about the pertinent details and purpose of the study, according to the Informed Consent guidelines. A written Informed Consent was read, understood, and signed by each subject. Each subject was given a copy of the signed Informed Consent Form.

Subject Identification

All subjects were initially identified by a permanent CRL identification number. Once the subject met qualification criteria, a study subject number was assigned at the Baseline Visit. This permanent subject number was assigned in sequence as subjects were enrolled in the study.

Product Use

Each subject was given a copy of the Sponsor's use directions and panelist instructions. Each subject was instructed to use the test material according to the following instructions:

Apply a small amount (approximately the size of a quarter) to wet hand, and/or body. Work into lather, and then rinse clean. The product should be used for a minimum of three times a week for a period of 30 days.

Subjects were instructed to replace their usual body wash with the provided test material. Other than the assigned test material, no new toiletries or personal care products were to be introduced by the panelists during the study.

STUDY EXECUTION (Continued)

Baseline Visit

All subjects reported to CRL for the Baseline Visit. The test sites of each subject were examined and evaluated for evidence of irritation (erythema, edema and dryness) as described in the *Study Evaluations* section of this report. After acceptance onto the study, subjects were assigned sequential subject numbers in the order of qualification and were issued the identically numbered test product. Subjects were given verbal and written instructions outlining study requirements and restrictions and a Daily Diary to note each use of the assigned product.

Final Visit

After the approximately four-week use period, each subject was given a dermal examination as described in the *Study Evaluations* section of this report. The Daily Diaries were reviewed and collected along with test products at the conclusion of the study.

TEST RESULTS

A total of 28 subjects completed the study. Dermal examination results appear in Table I and Table II.

Daily Diaries

There were no comments recorded on the Daily Diary that were related to reactions or symptoms perceived during use of the test material.

CONCLUSION

The dermal evaluation of Unisex Body Wash [redacted] over a four-week use period revealed no evidence of erythema, edema, or dryness of the test sites under conditions of the study. In this test population, the test material identified as Unisex Body Wash [redacted] does not demonstrate a potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.

Table I

Dermal Examination Results

Torso						
Subject Number	Baseline			Final		
	Erythema	Edema	Dryness	Erythema	Edema	Dryness
1	1	1	1	1	1	1
2	1	1	1	1	1	1
3	1	1	1	1	1	1
4	1	1	1	1	1	1
5	1	1	1	1	1	1
6	1	1	1	1	1	1
7	1	1	1	1	1	1
8	1	1	1	1	1	1
9	1	1	1	1	1	1
10	1	1	1	1	1	1
11	1	1	1	1	1	1
12	1	1	1	1	1	1
13	1	1	1	1	1	1
14	1	1	1	1	1	1
15	1	1	1	1	1	1
16	1	1	1	1	1	1
17	1	1	1	1	1	1
18	1	1	1	1	1	1
19	1	1	1	1	1	1
20	1	1	1	1	1	1
21	1	1	1	1	1	1
22	1	1	1	1	1	1
23	1	1	1	1	1	1
24	1	1	1	1	1	1
25	1	1	1	1	1	1
26	1	1	1	1	1	1
27	1	1	1	1	1	1
28	1	1	1	1	1	1

Dermal Scoring Scale: (Erythema, Edema, Dryness)
1 = None
2 = Mild
3 = Moderate
4 = Severe

Table II

Dermal Examination Results

Subject Number	Baseline Examination						Final Examination					
	Left Arm			Right Arm			Left Arm			Right Arm		
	Erythema	Edema	Dryness	Erythema	Edema	Dryness	Erythema	Edema	Dryness	Erythema	Edema	Dryness
1	1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1	1	1	1	1
5	1	1	1	1	1	1	1	1	1	1	1	1
6	1	1	1	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1
8	1	1	1	1	1	1	1	1	1	1	1	1
9	1	1	1	1	1	1	1	1	1	1	1	1
10	1	1	1	1	1	1	1	1	1	1	1	1
11	1	1	1	1	1	1	1	1	1	1	1	1
12	1	1	1	1	1	1	1	1	1	1	1	1
13	1	1	1	1	1	1	1	1	1	1	1	1
14	1	1	1	1	1	1	1	1	1	1	1	1
15	1	1	1	1	1	1	1	1	1	1	1	1
16	1	1	1	1	1	1	1	1	1	1	1	1
17	1	1	1	1	1	1	1	1	1	1	1	1
18	1	1	1	1	1	1	1	1	1	1	1	1
19	1	1	1	1	1	1	1	1	1	1	1	1
20	1	1	1	1	1	1	1	1	1	1	1	1
21	1	1	1	1	1	1	1	1	1	1	1	1
22	1	1	1	1	1	1	1	1	1	1	1	1
23	1	1	1	1	1	1	1	1	1	1	1	1
24	1	1	1	1	1	1	1	1	1	1	1	1
25	1	1	1	1	1	1	1	1	1	1	1	1
26	1	1	1	1	1	1	1	1	1	1	1	1
27	1	1	1	1	1	1	1	1	1	1	1	1
28	1	1	1	1	1	1	1	1	1	1	1	1

Dermal Scoring Scale: (Erythema, Edema, Dryness)
1 = None
2 = Mild
3 = Moderate
4 = Severe

Table II
(Continued)

Dermal Examination Results

Subject Number	Baseline Examination						Final Examina on					
	Left Leg			Right Leg			Left Leg			Right Leg		
	Erythema	Edema	Dryness	Erythema	Edema	Dryness	Erythema	Edema	Dryness	Erythema	Edema	Dryness
1	1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1	1	1	1	1
5	1	1	1	1	1	1	1	1	1	1	1	1
6	1	1	1	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1	1	1	1	1
8	1	1	1	1	1	1	1	1	1	1	1	1
9	1	1	1	1	1	1	1	1	1	1	1	1
10	1	1	1	1	1	1	1	1	1	1	1	1
11	1	1	1	1	1	1	1	1	1	1	1	1
12	1	1	1	1	1	1	1	1	1	1	1	1
13	1	1	1	1	1	1	1	1	1	1	1	1
14	1	1	1	1	1	1	1	1	1	1	1	1
15	1	1	1	1	1	1	1	1	1	1	1	1
16	1	1	1	1	1	1	1	1	1	1	1	1
17	1	1	1	1	1	1	1	1	1	1	1	1
18	1	1	1	1	1	1	1	1	1	1	1	1
19	1	1	1	1	1	1	1	1	1	1	1	1
20	1	1	1	1	1	1	1	1	1	1	1	1
21	1	1	1	1	1	1	1	1	1	1	1	1
22	1	1	1	1	1	1	1	1	1	1	1	1
23	1	1	1	1	1	1	1	1	1	1	1	1
24	1	1	1	1	1	1	1	1	1	1	1	1
25	1	1	1	1	1	1	1	1	1	1	1	1
26	1	1	1	1	1	1	1	1	1	1	1	1
27	1	1	1	1	1	1	1	1	1	1	1	1
28	1	1	1	1	1	1	1	1	1	1	1	1

Dermal Scoring Scale: (Erythema, Edema, Dryness)
1 = None
2 = Mild
3 = Moderate
4 = Severe

Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
1	RC	24401	29	M
2	SK	23111	47	F
3	GL	20066	45	M
4	SM	25342	44	M
5	SS	25113	38	M
6	DM	16746	49	F
7	DR	11074	54	F
8	LF	11640	38	F
9	AP	23481	40	F
10	LS	02796	49	F
11	RG	24650	45	F
12	FJ	19966	26	M
13	RW	23459	22	F
14	LM	25352	19	F
15	AN	23619	42	M
16	LB	21158	68	F
17	DL	00579	48	F
18	JG	19733	33	F
19	MW	21485	22	M
20	BP	21488	60	F
21	KP	18217	23	F
22	AA	25043	18	F
23	DR	25148	20	M
24	AJ	21188	22	M
25	CE	16142	35	M
26	KW	02212	22	F
27	SB	14185	35	F
28	CM	00741	64	F

Appendix II

Test Material Assignment

Subject Numbe	Subject Initials	CRL ID #	CRL Test Material I entification
1	RC	24401	CRL50709-1
2	SK	23111	CRL50709-2
3	GL	20066	CRL50709-3
4	SM	25342	CRL50709-4
5	SS	25113	CRL50709-5
6	DM	16746	CRL50709-6
7	DR	11074	CRL50709-7
8	LF	11640	CRL50709-8
9	AP	23481	CRL50709-9
10	LS	02796	CRL50709-10
11	RG	24650	CRL50709-11
12	FJ	19966	CRL50709-12
13	RW	23459	CRL50709-13
14	LM	25352	CRL50709-14
15	AN	23619	CRL50709-15
16	LB	21158	CRL50709-16
17	DL	00579	CRL50709-17
18	JG	19733	CRL50709-18
19	MW	21485	CRL50709-19
20	BP	21488	CRL50709-20
21	KP	18217	CRL50709-21
22	AA	25043	CRL50709-22
23	DR	25148	CRL50709-23
24	AJ	21188	CRL50709-24
25	CE	16142	CRL50709-25
26	KW	02212	CRL50709-26
27	SB	14185	CRL50709-27
28	CM	00741	CRL50709-28

Clinical
Research
Laboratories, Inc.

Final Report

Repeated Insult Patch Test

CLIENT:

ATTENTION: Claims Substantiation Analyst

TEST MATERIAL: Lipstick containing 0.5% Caprylyl Glycol

CRL STUDY NUMBER: CRL37609-3

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
President/Medical Director

Michael J. Mustatiello, Ph.D.
Executive Vice President/COO

George J. Neumaier, M.D.
Diplomate American Board
of Dermatology

REPORT DATE: June 19, 2009

371 Hoes Lane • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520

Clinical
Research
Laboratories, Inc.

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: CRL37609-3

Start Date: April 27, 2009

Completion Date: June 12, 2009

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted, as indicated below.

Karen Hayley
Signature of QA Auditor

June 19, 2009
Date

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material.

INVESTIGATIVE SITE

Clinical Research Laboratories, Inc.
371 Hoes Lane
Piscataway, New Jersey 08854
732-981-1616

TEST MATERIAL

The following test material was provided by and was received by Clinical Research Laboratories, Inc. on April 10, 2009:

Test Material	Test Condition	Patch Type
Lipstick	Test as Received	Semi-occlusive*

The test material was coded with the following CRL identification number:

CRL37609-3

STUDY DATES

This study was initiated on April 27, 2009 and was completed on June 12, 2009.

* Semi-occlusive Strip (Brady Medical, Mesquite,TX)

PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix I). Subjects who met the following criteria were impaneled:

- Male and female panelists between the ages of 18 and 70;
- Subjects who have completed a Panelist Profile/Medical History;
- Subjects who are in general good health as determined by a Panelist Profile/Medical History;
- Subjects who do not exhibit any skin diseases that might be confused with a skin reaction from the test material;
- Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;
- Subjects willing to sign an Informed Consent Form in conformance with 21 CFR Part 50: "Protection of Human Subjects";
- Subjects who have completed a HIPAA Authorization Form in conformance with 45 CFR Parts 160 and 164;
- Females who are not pregnant or lactating;
- Subjects who demonstrate dependability and intelligence in following directions;
- Subjects who are not currently using any systemic or topical corticosteroids, anti-inflammatory drugs or antihistamines;
- Subjects who do not exhibit skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.

TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scoring Scale

0 No visible skin reaction
± Barely perceptible erythema
1+ Mild erythema
2+ Well defined erythema
3+ Erythema and edema
4+ Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.

RESULTS

This study was initiated with 118 subjects. Thirteen subjects discontinued study participation for reasons unrelated to the test material. A total of 105 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

CONCLUSION

Based on the test population of 105 subjects and under the conditions of this study, the test material identified as Lipstick did not demonstrate a potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.

TABLE I

Summary of Dermal Scores

Test Material:	Lipstick

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	DISCONTINUED											
6R	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	DISCONTINUED											
11R	0	0	0	0	0	0	0	0	0	0	0	X*
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	DISCONTINUED					
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	X	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0

R = Subject number was reassigned due to early discontinuation.
X = Subject Absent
*No reaction was observed at the 96 hour reading.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Lipstick											
Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
26	0	DISCONTINUED										
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	DISCONTINUED											
37R	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	DISCONTINUED											
39R	DISCONTINUED											
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0

R = Subject number was reassigned due to early discontinuation.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Lipstick

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0	0	0	0
62	0	DISCONTINUED										
62R	0	0	0	0	0	0	0	0	0	0	0	0
63	DISCONTINUED											
63R	0	0	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	DISCONTINUED											

R = Subject number was reassigned due to early discontinuation.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Lipstick

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	DISCONTINUED					
78	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	DISCONTINUED											
91	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Lipstick

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
101	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0
110	0	0	0	0	0	0	0	0	0	0	0	0
111	0	0	0	0	0	0	DISCONTINUED					
112	0	0	0	0	0	0	0	0	0	0	0	0

Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
1	JS	25062	51	F
2	AF	25055	42	F
3	SW	25166	18	F
4	LS	25019	54	F
5	AC	24968	18	F
6	BR	25049	35	M
6R	DT	24320	24	F
7	KL	25144	52	F
8	CC	25057	62	F
9	CB	25054	40	F
10	DL	25052	35	F
11	TM	25035	18	F
11R	BD	14500	34	F
12	BB	24594	39	M
13	DM	25189	19	M
14	JP	25013	44	M
15	ZS	24979	36	F
16	DR	25148	20	M
17	AA	25043	18	F
18	JB	25201	29	F
19	AP	15450	28	F
20	SJ	24667	19	F
21	SP	25202	21	M
22	GC	25174	31	M
23	TS	25117	18	M
24	BB	19594	25	M
25	SS	24983	36	F
26	SM	24996	21	F
27	NR	25177	59	F
28	KR	25178	66	M

Subject Number	Subject Initials	CRL ID #	Age	Sex
29	KC	25162	41	F
30	DL	25050	38	F
31	JF	25203	30	M
32	LD	25151	21	F
33	MD	25047	18	M
34	EC	24826	36	F
35	JD	24855	49	F
36	JL	25169	43	M
37	HT	25023	29	M
37R	GO	14807	48	F
38	TD	25176	45	F
39	TH	25175	55	M
39R	LD	24566	18	M
40	CD	25061	40	F
41	RK	16842	25	M
42	FK	21304	21	M
43	KS	25108	44	F
44	KT	25180	58	F
45	MS	25107	42	M
46	SP	25056	36	F
47	MK	24784	57	F
48	TD	24785	39	F
49	DD	08478	54	F
50	KS	25187	57	F
51	TT	24709	58	F
52	DS	25155	32	F
53	DS	25053	40	F
54	EC	25204	43	F
55	DB	06701	43	F
56	BM	25149	18	M

INTERNATIONAL RESEARCH & DEVELOPMENT CENTER
MONACO

Assessment of the Eye Irritating Potential of a Cosmetic Product through Alternative Methods to the Draize Test

Test Product: [redacted] **Lash** [redacted] **Gel Serum** Containing 3% Pentylene Glycol

Reference: [redacted]

Report Date: 10 March 2010
Report Ref: CTOX/10002

CONCLUSION:

Taking into account the responses of the 3 alternative methods used, we consider that the estimated Draize classification of the test product might be "slightly irritant" with Draize score which might range from 0 to 15.

According to our experience and with respect to the type of product tested (make-up product), we consider that this product is as well tolerated as products belonging to the same category.

According to the estimated Draize score, the following [redacted] US warning may be proposed:

"No Statement"

Olivier DOUCET Pharm. D., Ph. D.
European Registered Toxicologist
Director of Skin Research Dpt

TABLE CONTENT

1- INTRODUCTION

There is a need to evaluate the eye irritation potential of cosmetic products for purposes of consumer safety and regulatory requirements. For the time being, the Draize rabbit eye test is practically the only method for determining ocular irritation, which is acceptable to various regulatory groups.

For the last few years, a clear desire, based on both ethical and scientific grounds, has been arising to replace the use of animals, in cosmetic product testing. In that respect, a wide number of *in vitro* or *ex vivo* assays have been proposed worldwide as alternatives to the Draize test. Despite the tremendous efforts concentrated either by the Cosmetic Toiletries and Fragrances Association (CTFA) or the European Community (EC) and British Home Office (BHO), none of these alternative methods have been successfully validated.
However, in some particular fields such as eye irritation, it is clear that under the increasing pressure of consumer associations, regulatory agencies tend to be more and more favorable to the use of these methods for safety assessment. For instance, the French government recently registered the Hen's Egg Test on Chorio-Allantoïc Membrane (HET-CAM) and the Neutral Red Release (NRR) assay as official test methods for determining the irritating potential of cosmetic products (Journal Officiel de la République Française, 26/12/96, Annexe IV; 30/12/99, Annexe VI).

The aim of this study was to predict the eye irritation potential of formulated products. For that purpose, we developed a particular « *in vitro* » approach, which combines several alternative methods. Indeed, many international studies have clearly demonstrated the interest of combining at least 2 or 3 alternative methods when assessing eye irritation through *in vitro* tests.

Taking into account both the results obtained during the last international validation studies (Balls et al., 1995; Gettings et al., 1990; Gettings et al. 1994; Gettings et al., 1996) and the recent advances in the use of *in vitro* models we selected as «relevant» alternative methods the 3 following *in vitro* tests:

- the Neutral Red Release (NRR) assay
- the Hen's Egg Test on the Chorio-Allantoic Membrane (HET-CAM)
- the Reconstituted Human Epithelial Culture (REC) assay

The combination of these different *in vitro* methods allows the assessment of different end-points and thus explores various types of mechanisms (cytotoxicity, acute vascular effect, toxicokinetic, transepithelial absorption,...) which are generally considered as taking part in the eye irritation phenomena (Rougier et al., 1994).

The conclusion of the study results from a global assessment, systematically based on the responses of the 3 methods used, since none single alternative method can predict eye irritation with a sufficient level of safety.

2- TECHNICAL INFORMATIONS

2-1 Product characteristics

The product [redacted] Lash [redacted] Gel Serum, [redacted] was received from the sponso[redacted] [redacted]on the 15 February 2010.
The test product, identified as a make-up product, is a translucent colorless gel, having a pH of 6.0 at 22.9°C.

Upon receipt, it was stored at room temperature in the Cell Toxicology Laboratory. An aliquot of the test product was stored in a specific room of the Skin Research Dpt. According to the internal Skin Research procedures, it will be kept there for a minimum period of 3 years.

2-2 Testing facilities

The test were performed in the Cell Toxicology Laboratory of Skin Research Dpt - International Research & Development Center - Lancaster Group - 2, rue de la Lüjernetta, Monaco.

2-3 Data storage

All the data relative to the study will be stored in the premises of the Skin Research Dpt for a period of 10 years.

2-4 Authentication of the study

I, the undersigned Olivier DOUCET, Director of the Study, certify that this study has been carried out in the premises of the Skin Research Dpt of Lancaster Group - COTY International Research Development Center and according to our internal standard protocol under the responsibility of Mylène LANVIN and Technical Investigators of the Laboratory.

Olivier DOUCET Pharm. D., Ph. D.
European Registered Toxicologist
Director of Skin Research Dpt

I, the undersigned Mylène LANVIN, Responsible for the Study, certify that this study has been performed under my supervising in accordance with our internal standard protocol.

Mylène LANVIN
Research Assistant
Head of Safety & Regulatory Affairs

We, the undersigned Carine LINOSSIER and Elisabeth MARTINS, Technical Investigators, certify that all the observations and numerical data presented in this document are an accurate reflection of the results obtained during this study.

Carine LINOSSIER
Technical Investigator
Safety & Regulatory Affairs

Elisabeth MARTINS
Technical Investigator
Safety & Regulatory Affairs

3- ALTERNATIVE METHODS USED

3-1 The Neutral Red Release (NRR) assay

Principle of the method

The NRR assay with rabbit cornea cells (SIRC) is a short-term monolayer culture test system in which cells are first exposed to Neutral Red dye (NR) then to the test material. According to the toxicity of the product, the cells are damaged and release their neutral red dye. The neutral red contained in surviving cells was extract with a revelation solution and spectrophotometrically measured. The test product concentration that gives rise to the release of 50% NR dye (NR_{50}) is used as endpoint to reflect the cytotoxicity of the test product.

Two stages can be necessary to assess the NR_{50} of a test product. The first stage allows the estimation of the NR_{50} whereas the second stage permit to accurately assess the final score.

Materials

Chemicals: Sodium Dodecyl Sulfate (SDS) and Sodium Chloride (NaCl) were purchased from Sigma Chemical Co. (St Louis, MO, USA). Neutral red dye was supplied by Fluka AG (Buchs, CH). Modified Eagle's Medium (MEM), fœtal calf serum, antibiotics (penicillin/streptomycin 5000UI/5000µg/ml and fungizon amphotericin B 250µg/ml), MEM Non Essential Amino Acids (NEAA) and Phosphate-Buffered Saline (PBS) were supplied by Invitrogen (Cergy-Pontoise, France). Before using, fœtal calf serum was maintained in a bain-marie at 56°C during 30 minutes in order to obtain a "modified" fœtal calf serum.

Rabbit cornea SIRC cells: Rabbit cornea fibroblasts SIRC (ATCC n°CCL60) were bought in the United States at ATCC (American Type Culture Collection Rockville, Maryland, USA) through a French supplier (CERDIC, Sophia Antipolis, France). Cells were cultured according to the internal procedures of our laboratory for freezing, unfreezing and subculturing. Briefly, cells were maintained in medium MEM supplemented with 2% antibiotics and 1% MEM Non Essential Amino Acids. This completed medium was extemporaneously supplemented with 10% of "modified" fœtal calf serum. Cells were incubated in a humidified atmosphere at 37°C, 5% CO_2.

Experimental procedure

Cell seeding: For treatment, cells were seeded in all the wells of 24-well plates. The plates were incubated for 24 hours at 37°C, 5% CO_2.

Application of the neutral red dye: The NRR assay was carried out according to the principle of the colorimetric test described by Borenfreund and Puerner (1984, 1985). After incubation, 1 ml of neutral red solution test, centrifuged before using, was added to each well of the plates. The plates were incubated for 3 hours at 37°C, 5% CO_2.

Test product dilutions: According to the physico-chemical characteristics of the test product, the dilutions were performed extemporaneously in an hydrophilic (w/v) or a lipophilic substance (w/w). During the first stage, the product was tested diluted at 0%; 5%; 15%; 25%; 35% and 50%.
According to this preliminary results, some dilutions were selected for the second stage. The principle is given in the following Table 1.

Table 1: Dilutions to be selected for the second stage

Stage n°1 NR50 (%)	**Stage n°2 Dilutions to be tested (%)**		
< 4	0.1	1	5
≥ 4 and ≤ 6	1	5	10
> 6 and < 13	5	10	15
≥ 13 and ≤ 17	10	15	20
> 17 and < 23	15	20	25
≥ 23 and ≤ 27	20	25	30
> 27 and < 33	25	30	35
≥ 33 and ≤ 37	30	35	40
> 37 and < 46	35	40	50
≥ 46 and ≤ 50	40	50	60
> 50	Slight cytotoxicity / Unnecessary Stage n°2		

Test product application: After incubation for 3 hours, the neutral red solution was removed and 1 ml of complete culture medium was added in each well of the plate. The plate was maintained at room temperature for 30 minutes. Then each well was rinsed with 2 ml of PBS and 500 µl of each test product dilution were added in the same time in two wells of the plate. After a 55-second contact (or 25 seconds for the positive control), each well was rinsed with PBS. The plate was gently stirring throughout contact time.

Revelation of the cytotoxicity: An ethanol/acetic acid/distilled water solution was then added to each well. The plates were gently stirring during about 15 minutes until having an homogeneous coloration. 200 µl of the resulting solutions were put, in duplicate, in the wells of a 96-well plate.

Reading: The optical densities (O.D.) were read at 540 nm by using a multi-well spectrophotometer. The ethanol/acetic acid/distilled water solution served as "blank".

Control solution application: The positive control (Sodium Dodecyl Sulfate = SDS) was tested diluted at 0%; 0.01%; 0.05%; 0.2% and 0.25%. The dilutions were performed in 0.9% sodium chloride solution. The dilution 0% which represents the negative control was applied to the cells during 55 seconds whereas the dilutions 0.01%; 0.05%; 0.2% and 0.25% were applied during only 25 seconds.

Test scoring: Data were expressed as a percentage of cytotoxicity, compared to the negative control (dilution 0%). The NR_{50} was calculated by interpolation from the curve representing the percentage of viability versus the concentration of test product.

The cytotoxicity of the product was obtained from the NR_{50} according to the scale presented in Table 2.

Table 2: Cytotoxicity scale from the NR_{50} endpoint

NR_{50} (%)	**% of death observed at the dilution 50%**	**Classification**	**COTY Conclusion**
> 50	≤ 20	Negligible cytotoxicity (PNI)	Slightly cytotoxic (SI)
	> 20 and < 50	Not very important cytotoxicity (SI)	
> 25 and ≤ 50		Moderate cytotoxicity (MI)	Moderately cytotoxic (MI)
≤ 25		Important Cytotoxicity (I)	Cytotoxic (I)

The conformity of the study was checked by using a positive control. According to the internal procedure, this study complied if the NR_{50} of the positive control ranged from 0.118% to 0.162%.

3-2 The Hen's Egg Test on the Chorio-Allantoic Membrane (HET-CAM)

Principle of the method

The Het-Cam is an *in vitro* method used to evaluate the irritant potential of a test material (J.O.R.F., 26/12/96, Annexe IV). The test procedure is based on the assessment by a trained person of the immediate effects following application of test product to the chorioallantoic membrane of 10-day-old fertile eggs. The determination of the Het-Cam score, according to the scale described by Luepke (1985, 1986), allows the assessment of the irritating potential of the test product.

Materials

Chemicals: Sodium Dodecyl Sulfate (SDS) and Sodium Chloride (NaCl) were purchased from Sigma Chemical Co. (St Louis, MO, USA).

Hen's eggs: Fresh fertile White Leghorn hen's eggs, weighing 50-65 g, were supplied by Couvoir du Cerveloup (Vourey, France).

Experimental procedure

Upon their arrival, all the defective eggs and eggs which weight is not ranged from 50 to 65 g, were eliminated. The hen's eggs were incubated at 15°C during at least 48 hours. Then, they were placed, on their long axis, in a rotating incubator under a temperature of 37.5°C ± 1°C; 60% ± 5% relative humidity (Union FrancoSuisse, Evreux, France) for 10 days. The eggshell was removed around the airspace. After a 5 ml saline solution (NaCl 0.9% with distilled water) application and the removal of the inner shell membrane, the vascular chorioallantoic membrane (CAM) was exposed to the air.

Test product application: Four eggs are treated with 0.3 ml of the product, tested neat or diluted according to the type of product. Previously maintained at a temperature of 37.5°C, the test product was applied onto the surface of the CAM. After a 20-second contact, the membrane was gently rinsed off by using 5 ml (10 ml or more if necessary) of saline solution kept at 37.5°C.

Investigator observations: Observations were achieved by using a specific lamp KL1500 electronic (SCHOTT, France) emitting a cold and white light. Blood vessels and albumen were continuously observed by a trained person for a 5-minute period. Irritant effects, such as hyperhaemia, haemorrhage and coagulation (opacity and/or thrombosis), were scored according to their occurrence within the test period.

Control solutions application: Two eggs treated with a sodium dodecyl sulfate solution in saline solution (SDS solution) served as positive control while at least 2 eggs treated with saline solution were used as negative control.
If the test product was diluted in mineral oil, 2 eggs were treated with this lipophilic diluant to check its Het-Cam score.

The irritating effect of the test product (if any) was quantified according to the scoring system described in the French regulation (J.O.R.F., 26/12/96, Annexe IV) presented in Table 3.

Table 3: Het-Cam scoring system according to Luepke's scale

Vascular effect	Time (t)		
	$0 < t \leq 30$ s.	30 s. $< t \leq 2$ min.	2 min. $< t \leq 5$ min
Hyperhaemia	5	3	1
Haemorrhage	7	5	3
Coagulation	9	7	5

For each parameter (Hyperhaemia, Haemorrhage, Coagulation) the individual scores obtained from the 4 eggs were averaged. The sum of these 3 values gave the so called "Het-Cam score" of the test product on a scale ranging from 0 to 21.

The magnitude of the eye irritating potential of the test product was then calculated according to the classification developed by Luepke (1985, 1986) and described in the French regulations (J.O.R.F., 26/12/96, Annexe IV), see Table 4.

Table 4: Test product classification

Het-Cam score	Classification	COTY Conclusion
Score < 1	Practically non irritant	Slightly irritant (SI)
1 ≤ Score < 5	Slightly irritant	
5 ≤ Score < 9	Moderately irritant	Moderately irritant (MI)
Score ≥ 9	Irritant	Irritant (I)

The conformity of the study is checked by using controls. According to the internal procedure, the study complied if the Het-Cam score for the positive control ranged from 14 to 18 and the Het-Cam score for the negative control ranged from 0 to 1.

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3-3 The Reconstituted human Epithelial Culture (REC) assay

Principle of the method

The REC assay is a cytotoxicity test based on a time course approach. The formulated product is applied onto three-dimensional reconstituted human epithelial cultures, having the feature of the epithelial part of the cornea. The quantification of the test product cytotoxicity is performed through a colorimetric assay: the MTT test (Mosmann, 1983). The determination of a simplified mean cytotoxicity index (SMCI) is used to quantify the time course toxicity for the applied substance, according to the procedure described by Doucet et al. (1998).

Materials

Chemicals: Hexadecylpyridinium Bromide (CPB) and 3-(4, 5-dimethylthiazol-2-yl) 2, 5-diphenyltetrazolium bromide (MTT) were purchased from Sigma Chemical Co. (St Louis, MO, USA). Isopropanol was supplied by Carlo Erba (Milan, Italy) and Phosphate–Buffered Saline (PBS, saline solution) by Invitrogen (Cergy-Pontoise, France). Modified culture medium (MCDB 153) was supplied by SkinEthic Laboratories (Nice, France).

Reconstituted human Epithelial Cultures (REC): Reconstituted human epithelial cultures were supplied by SkinEthic Laboratories (Nice, France). They were obtained by culturing transformed human keratinocytes (TR146 cell line) derived from squamous carcinoma (Regnier et al., 1987; Rupniak et al., 1985).

Experimental procedure

Test product application: The product was tested neat or diluted according to the type of product. Test sample was directly applied onto the apical surface of the epithelial culture. Product was gently spread with a brush. Cultures were treated with the test product in duplicate. The cultures were transferred to a 24-well culture dish, each well containing fresh medium MCDB 153. They were incubated at 37°C, 5%CO_2 / 95% air atmosphere for 1 hour, 3 hours and 24 hours. After each exposure time, cultures were washed with PBS, and the MTT assay (Mosmann, 1983) was performed. After incubation in MTT reagent, the formazan crystals were extracted by isopropanol. Optical densities were read at 570 nm, by using a spectrophotometer (isopropanol served as "blank").

Control solutions application: For each time, 2 cultures treated with an hexadecylpyridinium bromide solution in saline (CPB solution) served as positive control while 2 cultures treated with saline solution were used as negative control.
If the test product was diluted in mineral oil, 2 cultures treated with this lipophilic diluant were used also as negative control.

The results were expressed as a percentage of cytotoxicity compared with the negative control. The time course of toxicity for the applied product was expressed as a cumulative simplified mean cytotoxicity index (SMCI) calculated over 24 hours, as follows:

$$SMCI = \frac{(\%cyt.\ 1h) + (\%cyt.\ 3h/3) + (\%cyt.\ 24h/24)}{3}$$

with: %cyt. 1h = % of cytotoxicity of the test product after 1 hour.
%cyt. 3h = % of cytotoxicity of the test product after 3 hours.
%cyt. 24h = % of cytotoxicity of the test product after 24 hours.

The cytotoxicity of the product was determined according to the classification presented in Table 5.

Table 5: Cytotoxicity scale from the SMCI endpoint

SMCI	Cytotoxicity
< 7.5	Slightly cytotoxic
7.5 ≤ and < 15	Moderately cytotoxic
≥ 15	Cytotoxic

The conformity of the study is checked by using a positive control. According to the internal procedure, the study complies only when the SMCI of the positive control lies within the confidence internal range.

The product classification in terms of eye irritation results from a global assessment based on the responses of the 3 *in vitro* methods used. The following Table 6 reflects this multi-technical approach and gives information about the proposed safety classification of the test product. This latter is extrapolated from the results of the 3 alternative methods and presented as an estimated Draize classification. Based on this, an attempt is made for issuing some specific US warnings.

Table 6 : Table of concordance between the *in vitro* scores and the estimated Draize classification for skin care products, sun care products, alcoholic products and make-up products.

Test Method	*In Vitro Threshold*	*Estimated European Draize Classification*	*U.S. Warning*
REC Assay Het-Cam NRR Assay	Score < 7.5 Score < 9 Score > 50	Slightly Irritant (Draize score : 0 - 15)	No statement
REC Assay Het-Cam NRR Assay	7.5 <= Score < 15 Score < 9 25 < Score <= 50	Moderately Irritant (Draize score : 15.1 - 30)	Avoid contact with eyes. If contact occurs, flush with water.
REC Assay Het-Cam NRR Assay	15 <= Score < 24.5 Score >= 9 Score <= 25	Irritant (Draize score : 30.1 - 50)	This product may cause irritation. Avoid contact with eyes. If contact occurs, flush with plenty of water. If irritation persists, consult a physician.
REC Assay Het-Cam NRR Assay	Score >= 24.5 Score >= 9 Score <= 25	Strongly Irritant (Draize score : 50.1 - 110)	Determination of appropriate warning statements. Suitability to market the product has to be considered.

4- RESULTS AND CONCLUSIONS

4-1 NRR assay

4-1-1 Summary

The Neutral Red Release (NRR) assay conducted on rabbit cornea fibroblasts (SIRC) is an *in vitro* method currently used to assess the cytotoxicity of a test product after a short contact time of the test substance with the cells by measuring the neutral red release from pre-loaded cells (Brantom et al., 1997; Reader et al., 1989). The cytotoxicity is revealed by the concentration of test product (NR_{50}) which inhibited of 50% the cell survival and growth.
In this study, the procedure used was adapted from the protocol described in French regulation as official method for the assessment of the irritating potential of formulated cosmetic products (J.O.R.F., 30/12/99, Annexe VI).
Under the experimental conditions used, an NR_{50} superior to 50% was obtained for the product [redacted] Lash [redacted] Gel Serum, [redacted] From this result, the test product was considered slightly cytotoxic.

4-1-2 Results

Stage 1
The first stage of this study was initiated in the premises of the International Research & Development Center - Lancaster Group on the 22 February 2010 and was completed on the 23 February 2010.

The test produc[redacted] Lash [redacted] Gel Serum was tested diluted at 0%; 5%; 15%; 25%; 35% and 50% in saline solution.

The optical densities and the percentages of viability obtained for the test product and the positive control are presented in Tables 7 and 8 respectively. The graphic assessment of the NR_{50} for the test product and the positive control were presented in Fig. 1 and 2 respectively.

Table 7: Optical densities (O.D.) and cytotoxicity (%) obtained for the test product and the negative control (representing the 0% dilution) during the stage n°1

(O.D.) and cytotoxicity (%) obtained for the test product and the negative control						
Product dilution (%)	**0**	**5**	**15**	**25**	**35**	**50**
Well 1	0.773	0.764	0.783	0.782	0.759	0.647
Well 2	0.761	0.777	0.778	0.770	0.741	0.648
Well 3	0.780	-	-	-	-	-
Well 4	0.769	-	-	-	-	-
Mean	0.771	0.771	0.781	0.776	0.750	0.648
SD	0.008	0.009	0.004	0.008	0.013	0.001
Cytotoxicity (%)	**0.00**	**0.03**	**0.00**	**0.00**	**2.69**	**15.99**

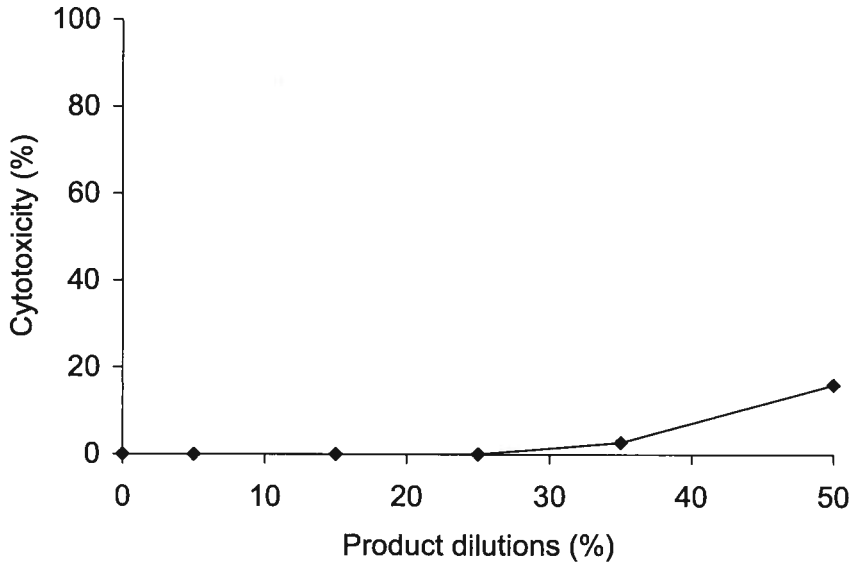

Fig. 1: Assessment of the NR_{50} for the test product

NR_{50} > 50%

Table 8: Optical densities (O.D.) and cytotoxicity (%) obtained for the positive control and the negative control (representing the 0% dilution) during the stage n°1

(O.D.) and cytotoxicity (%) obtained for the positive control and the negative control					
Product dilution (%)	**0**	**0.01**	**0.05**	**0.2**	**0.25**
Well 1	0.791	0.765	0.608	0.115	0.097
Well 2	0.787	0.781	0.620	0.125	0.091
Well 3	0.790	-	-	-	-
Well 4		-	-	-	-
Mean	0.789	0.773	0.614	0.120	0.094
SD	0.002	0.011	0.008	0.007	0.004
Cytotoxicity (%)	**0.00**	**2.07**	**22.21**	**84.80**	**88.09**

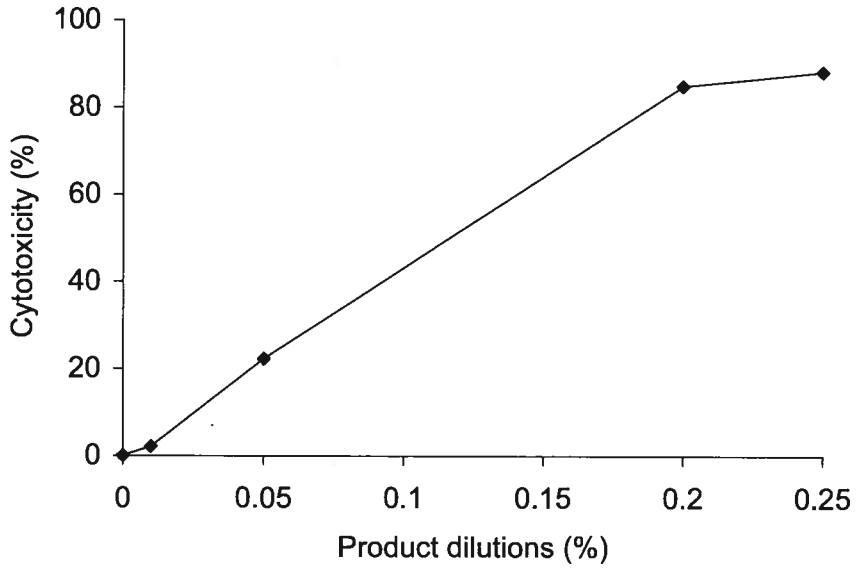

Fig. 2: Assessment of the NR_{50} for the positive control

NR_{50} = 0.129%

Stage 2

According to table 2 and to the results obtained during the first stage of this study, it was not necessary to perform the stage 2.

4-1-3 Conclusion

Under the experimental conditions used, the NR_{50} of the product [redacted] Lash [redacted] Gel Serum was superior to 50%. From this result, the test product may be considered slightly cytotoxic.

According to our experience and with respect to the type of product tested (make-up product), we consider that this product is as well tolerated as products belonging to the same category.

4-2 HET-CAM

4-2-1 Summary

The Hen's Egg Test-Chorioallantoic Membrane (Het-Cam) is an *in vitro* method currently used to assess the eye irritating potential of a test product (Balls et al., 1995; Gettings et al., 1994). The test procedure is based on the evaluation of immediate effects following application of the test substance onto the surface of the chorioallantoic membrane of 10-day-old fertile hen's eggs.
In this study, the protocol used was adapted from Luepke (Luepke, 1985; Luepke and Kemper, 1986) and was performed according to the method described by the French regulation (J.O.R.F., 26/12/96, Annexe IV). The Het-Cam score of the product [redacted] Lash [redacted] Gel Serum, [redacted] was determined after application to the chorioallantoic membrane of 0.3 ml of neat test material.
Under the experimental conditions used, the Het-Cam score of the test product was 7.0. Consequently, this product may be classified as moderately irritant when applied neat to the hen's egg chorioallantoïc membrane.

4-2-2 Results

This study was initiated in the premises of the International Research & Development Center – Lancaster Group on the 25 February 2010 and was completed on the 26 February 2010.

Date of arrival of the eggs: 08 February 2010
Date of incubation at 15°C: 08 February 2010
Date of incubation at 37.5°C: 15 & 16 February 2010

The individual results obtained for the test product, tested neat, the positive and the negative controls are respectively presented in Tables 9, 10 and 11.

Test product: [redacted] Lash [redacted] Gel Serum, [redacted]

Table 9: Individual egg scores obtained for the test product

Egg N°	Hyperhaemia	Haemorrhage	Coagulation
1	3	3	0
2	3	3	0
3	3	5	0
4	3	5	0
Mean	3.0	4.0	0

Mean Score = 7.0 Classification: Moderately irritant

Remarks:

Positive control: SDS solution in saline

Table 10: Individual egg scores obtained for the positive control

Egg N°	Hyperhaemia	Haemorrhage	Coagulation
1	5	7	5
2	5	5	5
Mean	5.0	6.0	5.0

Mean Score = 16.0

Negative control: saline solution

Table 11: Individual egg scores obtained for the negative control

Egg N°	Hyperhaemia	Haemorrhage	Coagulation
1	0	0	0
2	0	0	0
Mean	0	0	0

Mean Score = 0

4-2-3 Conclusion

Under the experimental conditions used, the Het-Cam score of the product [redacted] Lash [redacted] Gel Serum was 7.0. From this result, the test product may be considered moderately irritant when applied neat to the hen's egg CAM.

According to our experience and with respect to the type of product tested (make-up product), we consider that this product is as well tolerated as products belonging to the same category.

4-3 REC assay

4-3-1 Summary

The Reconstituted human Epithelial Culture (REC) assay is an *in vitro* method used to assess the cytotoxicity of a test product through a three-dimensional epithelial model. After application of the test product, the cytotoxicity is evaluated by a rapid colorimetric test: the MTT test, according to the protocol described by Mosmann (1983).
In this study, the protocol used was adapted from the test procedure described by Doucet et al. (1998). The time course of toxicity for the applied product, expressed as a cumulative simplified mean cytotoxicity index (SMCI) was used as endpoint.
Under the experimental conditions used, a SMCI of 5.61 was calculated. From this result, the product [redacted] Lash [redacted] Gel Serum, [redacted] was considered slightly cytotoxic when applied neat onto the reconstituted epithelial cultures.

4-3-2 Results

This study was initiated in the premises of the International Research & Development Center – Lancaster Group on the 24 February 2010 and was completed on the 25 February 2010.

Cell cultures

Date of arrival:	24 February 2010	Date of expiry:	01 March 2010
Batch n°:	10022B0203	Age of the culture:	7 days

The REC score, expressed as a simplified mean cytotoxicity index (SMCI), obtained for the product, tested neat is presented in Table 12.

Table 12: REC score (SMCI) and cytotoxic potential obtained for the test product

Test Product	SMCI	Cytotoxicity / Classification
[redacted] Lash [redacted] Gel Serum [redacted]	5.61	Slightly cytotoxic

4-3-3 Conclusion

Under the experimental conditions used, the SMCI of the test product [redacted] Lash [redacted] Gel Serum was 5.61. From this result, the test product may be considered slightly cytotoxic when applied neat onto reconstituted human epithelial cultures.

According to our experience and with respect to the type of product tested (make-up product), we consider that this product is as well tolerated as products belonging to the same category.

5- FINAL ASSESSMENT

The aim of this study was to predict the eye irritation potential of formulated products by using a particular « *in vitro* » approach, which combines several alternative methods:

- the Neutral Red Release (NRR) assay
- the Hen's Egg Test on the Chorio-Allantoic Membrane (HET-CAM)
- the Reconstituted Human Epithelial Culture (REC) assay

For the tested product, [redacted] Lash [redacted] Gel Serum, [redacted] the following results and classifications were obtained:

NRR assay:	NR_{50} > 50%	slightly cytotoxic
HET-CAM:	Score = 7.0	moderately irritant
REC assay:	SMCI = 5.61	slightly cytotoxic

Taking into account the responses of these 3 methods, we consider that the estimated Draize classification of the test product might be **slightly irritant** with Draize score, which might range from 0 to 15.

According to our experience and with respect to the type of product tested (make-up product), we consider that this product is as well tolerated as products belonging to the same category.

According to the estimated Draize score, the following [redacted] US warning may be proposed:

"No Statement"

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Consumer Product Testing Co.

EST. 1975

FINAL REPORT

CLIENT: [redacted]

ATTENTION: [redacted]

TEST: Repeated Insult Patch Test
Protocol No.: 1.01

TEST MATERIAL: FOUNDATION [redacted]
containing 0.112% Pentylene Glycol

EXPERIMENT REFERENCE NUMBER: C08-1978.01

Richard R. Eisenberg, M.D.
Board Certified Dermatologist

Joy Frank, R.N.
Executive Vice President, Clinical Evaluations

Report Date: 6/13/08

This report is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the report nor the name of these Laboratories nor any member of its staff, may be used in connection with the advertising or sale of any product or process without written authorization.

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

Consumer Product Testing Co.
EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: C08-1978.01

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of clinical laboratory studies. These studies have been performed with adherence to the applicable ICH Guideline E6 for Good Clinical Practice and requirements provided for in 21 CFR parts 50 and 56 and in accordance to standard operating procedures and applicable protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study. All data pertinent to this study will be stored in the Consumer Product Testing Company archive, unless specified otherwise, in writing by the Sponsor.

Quality Assurance personnel involved:

Quality Assurance — Date 6/13/08

The representative signature of the Quality Assurance Unit signifies that this study has been performed in accordance with standard operating procedures and study protocol as well as government regulations regarding such procedures and protocols.

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234
Clinical • Toxicology • Analytical Chemistry • Microbiology

Objective: To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.

Participants: One hundred sixteen (116) qualified subjects, male and female, ranging in age from 16 to 79 years, were selected for this evaluation. One hundred one (101) subjects completed this study. It was noted that Subject #22 Panel 20080165 was recruited in error, since she exceeded the desired age range. Her data are presented for completeness, but were not included in the final results. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

a. Male and female subjects, age 16[a] and over.
b. Absence of any visible skin disease which might be confused with a skin reaction from the test material.
c. Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.
d. Completion of a Medical History form and the understanding and signing of an Informed Consent form.
e. Considered reliable and capable of following directions.

Exclusion Criteria:

a. Ill health.
b. Under a doctor's care or taking medication(s) which could influence the outcome of the study.
c. Females who are pregnant or nursing.
d. A history of adverse reactions to cosmetics or other personal care products.

Test Material: FOUNDATION [redacted]

Study Schedule:

Panel #	Initiation Date	Completion Date
20080158	April 14, 2008	May 22, 2008
20080165	April 21, 2008	May 30, 2008

[a]With parental or guardian consent

Methodology:

The upper back between the scapulae served as the treatment area. Approximately 0.2 g of the test material, or an amount sufficient to cover the contact surface, was applied to the 1" x 1" absorbent pad portion of a clear adhesive dressing. This was then applied to the appropriate treatment site to form a semi-occlusive patch.

Induction Phase:

Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period.

With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications were discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted.

Rest periods consisted of twenty-four hours following each Tuesday and Thursday removal, and forty-eight hours following each Saturday removal.

Challenge Phase:

Approximately two (2) weeks after the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic twenty-four and seventy-two hours post-application.

Methodology (continued):

Evaluation Criteria (Erythema and additional Dermal Sequelae):

0	=	No visible skin reaction	E	=	Edema
0.5 / +	=	Barely perceptible	D	=	Dryness
1	=	Mild	S	=	Staining
2	=	Moderate	P	=	Papules
3	=	Marked	V	=	Vesicles
4	=	Severe	B	=	Bullae
			U	=	Ulceration
			Sp	=	Spreading

Erythema was scored numerically according to this key. If present, additional Dermal Sequelae were indicated by the appropriate letter code and a numerical value for severity.

Results:

The results of each participant are appended (Table 1).

Observations remained within normal limits throughout the test interval.

Subject demographics are presented in Table 2.

Summary:

Under the conditions of this study, test material, FOUNDATION [redacted] did not indicate a potential for dermal irritation or allergic contact sensitization.

Table 1
Panel #20080158

Individual Results

FOUNDATION [redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	+	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	-	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	-	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	DID NOT COMPLETE STUDY											
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	DID NOT COMPLETE STUDY							
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
- = Subject not present for supervised removal

Table 1
(continued)
Panel #20080158

Individual Results

FOUNDATION [redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	DNC
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	----------DID NOT COMPLETE STUDY----------											
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	----------DID NOT COMPLETE STUDY----------											
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	----------DID NOT COMPLETE STUDY----------											
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
DNC = Did not complete study

Table 1
(continued)
Panel #20080165

Individual Results

FOUNDATION [redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	DID NOT COMPLETE STUDY										
9	DID NOT COMPLETE STUDY											
10	0	DID NOT COMPLETE STUDY										
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	DID NOT COMPLETE STUDY			
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch

Table 1
(continued)
Panel #20080165

Individual Results

FOUNDATION [redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	DID NOT COMPLETE STUDY							
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	—DNC—	
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	DID NOT COMPLETE STUDY											
56	DID NOT COMPLETE STUDY											

24* = Supervised removal of 1st Induction and Challenge Patch
DNC = Did not complete study

Table 2
Panel #20080158

Subject Data

Subject Number	Initials	Age	Sex
1	BS	61	F
2	AC	41	M
3	RT	68	M
4	LT	67	F
5	DB	46	F
6	RM	44	M
7	GG	58	F
8	MA	20	M
9	GC	43	F
10	WC	41	M
11	DC	50	F
12	JG	47	F
13	JP	79	F
14	WM	39	F
15	RR	65	F
16	GD	69	F
17	GC	50	F
18	LO	49	F
19	NN	19	F
20	KC	37	F
21	JG	45	M
22	MM	34	F
23	GB	62	F
24	JT	77	M
25	DW	40	F
26	BL	55	F
27	JH	53	M
28	KC	44	F
29	PF	72	F
30	MT	33	F

Table 2
(continued)
Panel #20080158

Subject Data

Subject Number	Initials	Age	Sex
31	FR	47	M
32	JM	28	F
33	JR	30	F
34	JR	62	F
35	JF	42	F
36	BG	26	F
37	NR	33	F
38	CG	16	F
39	MM	72	F
40	IT	24	F
41	AA	34	M
42	JS	21	F
43	RS	66	F
44	NM	28	F
45	JC	30	M
46	LP	49	F
47	JM	44	F
48	EF	49	M
49	MM	29	F
50	PJ	44	F
51	ML	45	M
52	JS	46	F
53	CL	64	F
54	CF	61	M
55	DF	41	F
56	SF	56	F
57	WA	37	M
58	JJ	52	M
59	GA	35	F
60	PR	46	F

Table 2
(continued)
Panel #20080165

Subject Data

Subject Number	Initials	Age	Sex
1	HC	63	F
2	OC	31	F
3	DD	39	F
4	KT	22	F
5	AG	68	F
6	JD	60	M
7	KC	16	F
8	MS	39	F
9	HC	29	M
10	DB	40	M
11	DG	38	F
12	NC	67	F
13	GC	45	M
14	AD	57	M
15	AT	41	F
16	KC	56	F
17	VB	20	F
18	JD	77	F
19	MH	63	F
20	GP	74	F
21	DG	52	F
22	ES	80	F
23	AA	41	F
24	BM	61	F
25	IH	60	F
26	CW	24	F
27	MM	22	F
28	JC	39	F
29	DC	33	F

Table 2
(continued)
Panel #20080165

Subject Data

Subject Number	Initials	Age	Sex
30	CW	77	F
31	MM	41	F
32	RO	69	F
33	FD	58	M
34	DD	52	F
35	LL	52	F
36	PL	49	M
37	AV	76	F
38	BB	40	F
39	GS	51	F
40	LR	48	F
41	JC	35	M
42	JC	67	M
43	MR	74	F
44	MC	50	F
45	MP	37	F
46	TM	50	M
47	EI	36	F
48	ET	58	F
49	JM	56	M
50	JV	26	F
51	AB	17	F
52	MG	57	F
53	CF	44	F
54	MR	60	F
55	RR	37	M
56	MN	42	F

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. 8/23/10
Industry Liaison to the CIR Expert Panel

DATE: August 23, 2010

SUBJECT: Comments on the Draft Report on Caprylyl Glycol Prepared for the August 30-31, 2010 CIR Expert Panel Meeting

p.2 - It would be helpful if the two sentences on UV absorption were presented together (1 is in the Chemical and Physical Properties section, the other is in the Analytical Methods section).
p.7, 20 - "pentylene glycol (1,2-propanediol)" needs to be corrected (should be 1,2-pentanediol) in several places
p.12 - The mouse study using concentrations ≤5% Propylene Glycol is mentioned in the summary of the Reproductive and Developmental Toxicity section, but this study does not appear to be mentioned in the section itself.
p.13 - Should "eCG" in the first paragraph be "hCG" (as in the second paragraph)?
p.14 - In the summary of the Carcinogenicity section, please indicate how often the mice were treated with Propylene Glycol.
p.18-19 - As information on Propylene Glycol is summarized throughout this report, is the additional summary of Propylene Glycol data at the end of the report necessary?
p.19 - In the Summary, it would be helpful to indicate that the Council use survey included uses of Pentylene Glycol.
p.19 - In the second paragraph of the Summary, please change "should be considered relevant" to "are relevant" (otherwise the information on Propylene Glycol should not be in the report).
p.19 - Please state the compounds for which dermal penetration was enhanced.

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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: Personal Care Products Council Task Force on Caprylyl Glycol and Related Compounds

DATE: October 28, 2010

SUBJECT: Request to Remove Ingredients From the Report

Based on the data included in the report, the Council Task Force on Caprylyl Glycol recommends that the Caprylyl Glycol report only include ingredients with 4 to 12 carbons (1,2-Butanediol, Pentylene Glycol, 1,2-Hexanediol, Caprylyl Glycol, Decylene Glycol and Lauryl Glycol). The Task Force recommends that the larger compounds (Myristyl Glycol, Cetyl Glycol, Stearyl Glycol, Arachidyl Glycol, Hexacosyl Glycol, Octacosanyl Glycol, C14-18 Glycol, C15-18 Glycol, C18-30 Glycol, C20-30 Glycol), for which only one use was reported (C15-18 Glycol), be removed from the report.

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