BLUE

Caprylyl Glycol

CIR EXPERT PANEL MEETING

JUNE 27-28, 2011

Administrative

Cosmetic Ingredient Review
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June 3, 2011

Memorandum

To: CIR Expert Panel

From: Wilbur Johnson, Jr.
Manager/Lead Specialist

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

At the December 13-14, 2010 CIR Expert Panel meeting, the Panel issued a tentative report with a conclusion stating that these ingredients are safe in the present practices of use and concentration. Technical comments on this report were received from the Council after the tentative report was formally announced, and have been addressed. The report has also been revised to include ingredient frequency of use data provided by FDA this year.

A copy of the draft final report on these ingredients is included along with the following: CIR report history, Minutes from the June, August, and December 2010 Panel meetings, Literature search strategy, Data profile, and the Council's technical comments on the tentative report. The Expert Panel needs to determine whether a final report on the safety of 1,2-glycols should be issued.

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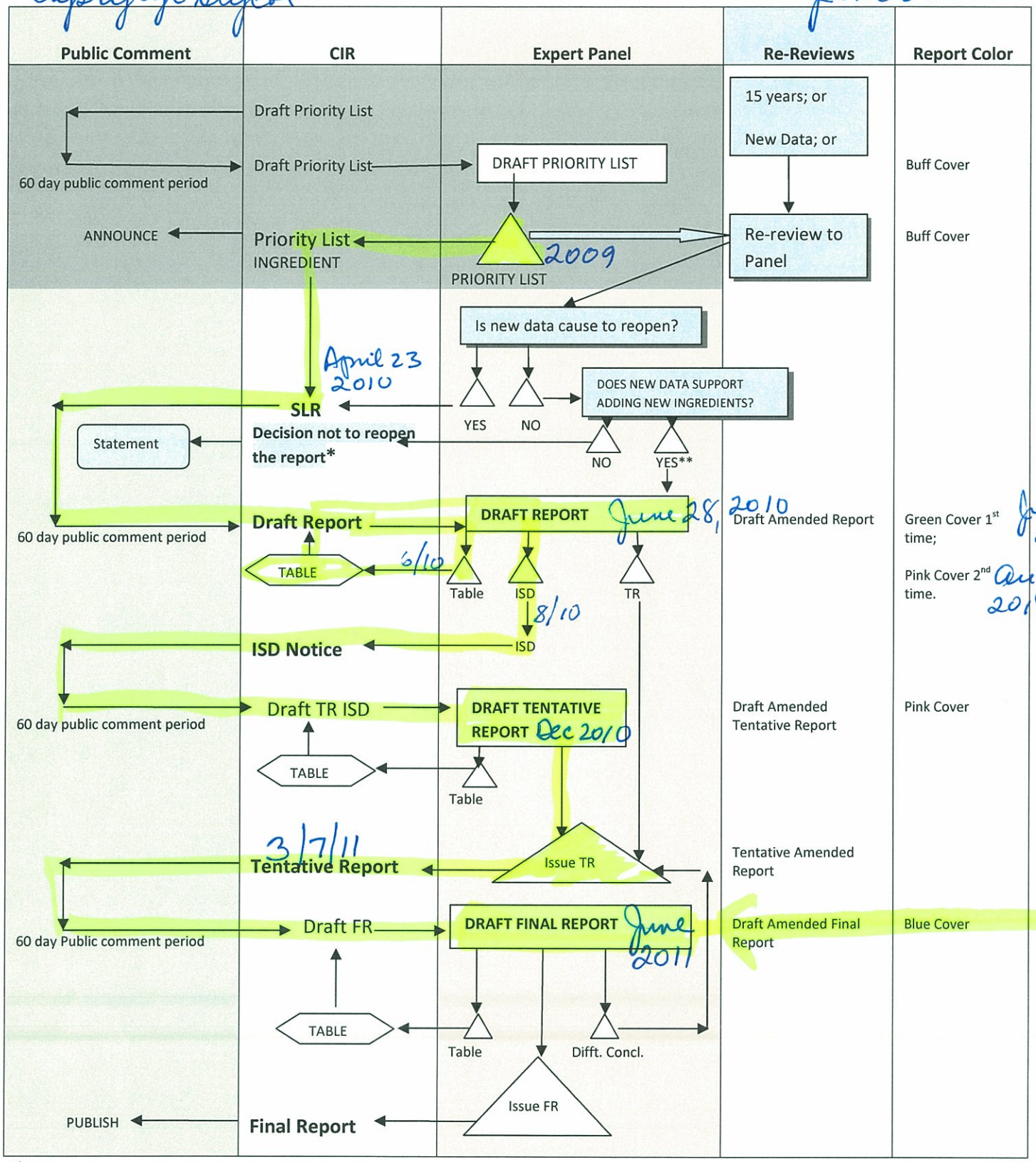
SAFETY ASSESSMENT FLOW CHART

Caprylyl Glycol

June 2011



*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 were provided by the Council.

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, updated use concentration data on caprylyl glycol was received on October 1, and 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. The new data have been added to the safety assessment.

The 1,2-glycols function mostly as skin and hair conditioning agents and viscosity increasing agents in cosmetics; caprylyl glycol and pentylene glycol also function as preservatives. Concern was expressed that the lipophilicity of 1,2-glycols with greater than 12 carbons in the chain may alter the dermal penetration of these ingredients and that the available metabolic modeling may not be relevant. The Panel reached a consensus, however, that there were ample data demonstrating that the lower chain length 1,2-glycols penetrate the skin readily and that repeat dose systemic toxicity data are available demonstrating the safety of these ingredients. It was agreed that the available data on these are sufficient, and similar structural activity relationships, biologic functions, and cosmetic product usage, suggest that the available data may be extrapolated to support the safety of the entire group.

Accordingly, the Panel reached the tentative conclusion that the 16 ingredients in the report are safe in the present practices of use and concentration. It was also determined that, were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group. A tentative report with this conclusion was issued by the Expert Panel and made available for public comment on March 7, 2011. Technical comments on the tentative report, received from the Council, have been addressed.

4th Review, Belsito and Marks Teams/Panel: June 27-28, 2011

The draft final report will be reviewed by the Expert Panel at this meeting.

Literature Search on Caprylyl Glycol and Related Ingredients*

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
Search updated on 5/10/11 using PubMed, Toxline, and SciFinder – 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

Literature Search on Caprylyl Glycol and Related Ingredients*

(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

Search Strings

″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″

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

Caprylyl Glycol Check List for June, 2011. 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

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 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 datain 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 -- 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.
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 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 whereyou 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 –
DR. EISENMANN: Well, primary uses of just (inaudible) compounds, there seems to be a little use of --
DR. HILL: Mm-hmm. I agree.

DR. 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.
DR. EISENMANN: I don't have it in yet.
DR. MARKS: Okay.
DR. 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.
DR. 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, thenthere will be a certain frequency of use. I guess it comes out of the VCRP, 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 downthe road?
DR. 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.
DR. 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).
DR. 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, 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, 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
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?"
DR. 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 inthe 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 goup 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. 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.
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.
DR. HILL: Well, then I'll be outvoted.
(Laughter)

DR. MARKS: Well, the other team may have a
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 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.
DR. 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.
DR. 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.
DR. 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.
DR. ANDERSEN: Small.
DR. HILL: If it's -- yes. And in this case, it is small.
DR. ANDERSEN: Hence, the empirical data
DR. HILL: Right.
DR. 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).
DR. 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 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.
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. 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. 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 thatthat 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, thatwas a robust discussion.

Day 1 of the June 28-29, 2010 CIR Expert Panel Meeting – Dr. Belsito's Team

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 But now we're not finding what the listof -- 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 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 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 sen out?

DR. BELSITO: No.
DR. ANSELL: The survey was initiated a 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 lis of chemicals was finalized versus when we could go out.
DR. BERGFELD: How much time do you need?
DR. ANSELL: Well, we'll we'll have to ask Carol. But she needs --
DR. BERGFELD: Did you h Did you have six months? Did you need 12 months?
DR. ANSELL: Oh, no, no. I think it's
DR. BERGFEL DR. ANSELL: No, we didn't have -- the
DR. BERGFELD: You had months? Six weeks?
DR. ANSELL: Yeah, I think she needs two to three months to pull this
that until this data is available for these documents, maybe the entire document shouldn't be
sent to the committee. Are we kind of wasti 6 time a little bit of reading this and the forgetting most of it and having to read it again in August, for example? Maybe the committee shouldn't receive the document unti suggestion.
DR. ANDERSEN: On the possibility that we would get lucky and the resp 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 an 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 actuallythis -- I think this will get better. Theexception to that will be if we have a great ideathat comes in at the 11th hour that here's anotheringredient that, guy, we just missed. It shouldhave been included. And, you know, we're 45 daysfrom the meeting and we call up Carol, wellthere's nothing she can do. I mean, she can makeanother request for data, but that doesn'tgenerate responsiveness in suppliers or formulators. So, there's always going to be thepotential that something is disjointed. But we can do better by establishing the family as earl 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 ofapplying pressure on industry to get the data in. So, thank you for doing that. Bu sometimes it just isn't going to work.
DR. BELSITO: Okay. So, we'll tryharder and we'll try and create our super familie in August with all the ingredients so that theindustry has a heads-up.
DR. BERGFELD: And you'll table this?
DR. BELSITO: Yeah, it's tabled.

Day 2 of the June 28-29, 2010 CIR Expert Panel Meeting

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 wo of them here. In addition, the data is quite scant but we felt that by including summaries o 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.

Minutes from the August 30-31, 2010 (116th) CIR Expert Panel Meeting – Dr. Belsito's Team

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.

Minutes from the August 30-31, 2010 (116th) CIR Expert Panel Meeting – Dr. Marks' Team

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.

Minutes from the August 30-31, 2010 (116th) CIR Expert Panel Meeting – Day 2

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.

Minutes from the December 13-14, 2010 (117th) CIR Expert Panel Meeting – Dr. Marks' Team

The next ingredients, the caprylyl group and that's the Pink Book. We have some more dermal penetration which I didn't get to look at and another document on the metabolism assessment of 2-1 glycol, C6 to C12. In August the pane issued an insufficient data announcement asking for dermal absorption data of caprylyl glycol or similar lipid solubles 1-2 glycols, hopefully on of you have looked at this, and if there i significant dermal absorption then we need the reproductive and developmental tox, we need 28-day dermal tox, and then lastly we felt we needed genotox data. What I had reviewed suggested there wasn't a significant amount of absorption. What does this say? Limited dermal penetration available. What did we receive this morning and what did that suggest?
DR. SLAGA: High dermal penetration.
DR. BERGFELD: High dermal penetration?
DR. ANSELL: Our report which came in wave two of the dermal penetration predicts 80 percent for the 1-2 hexane and caprylyl glycol would be absorbed -- 80 percent of hexane and caprylyl glycol and 40 percent of the decylene and laurylglycols. I will restate that. There is significant dermal absorption so that we obviously need 1 28-day dermal tox and the reproductive and developmental tox.
DR. KATZ: There is also another problem and Bob will probably comment more on thistomorrow. The study that was done, the dermal absorption study, was done incorrectly and it needs to be repeated. It was done as a full-thickness study and it should not have been so that the results are very misleading from the way the study was done. Again Bob will comment more on this tomorrow, but that was our suggestion that it needs to be redone. Also given what Jay just said, it probably even compounds and make things worse if we're talking about absorption because if you're getting absorption when the study was done incorrectly, there probably is even a bigger problem.
DR. MARKS: Is this the study that was handed out this morning you're talking about, Linda?
DR. KATZ: It was the study that was in the material that was sent to us previously.
DR. MARKS: Right. That's why I used the word suggested because I wasn't quite comfortable with interpreting it without Bob's input. The one this morning would suggest significant dermal penetration. Shall we move forward with the assumption that there is significant dermal absorption? Are there problems with the study that was given out this morning?
DR. BRESLAWEC: Linda, I'm sorry. Could you please repeat the specific study with which you have concerns?
DR. KATZ: The study that we had concerns with was the study that was sent in the material for review prior to this meeting. We have not had a chance to look at the material that was given this morning so that I can't comment and I'm sure Bob can't either.
DR. BRESLAWEC: Which study? The dermal penetration study?
DR. KATZ: The dermal penetration study that was part of the packet of material that was sent in preparation for this morning. It was done incorrectly. It was done as a full-thickness study and it should not have been so that I don't know is this study is a repeat of that study, the one that you present today because I've not had a chance to look at it and I'm not sure that Bob has either.
DR. SLAGA: As to the caprylyl glycol, I didn't think there was a real study. There was an enhancement study. Is that the one you're referring to?
DR. KATZ: Yes. It's one that's the 5-percent caprylyl glycol that was submitted. That one was done on full-thickness skin and it should not have been done that way. Again I can't comment on the material that was given out this morning because to be honest with you I haven't even read it so that I don't know what this morning's study looks like.
DR. HILL: I had a question about these. What is the source of these two documents that we have sitting here? Are these coming from CI panel staff?
DR. BRESLAWEC: This morning?
DR. HILL: There is one that says Metabolism Assessment for 1-2 Glycols and the one that says Dermal Penetration.
DR. BRESLAWEC: These comments were distributed by the council. Jay, do you want to address them? We have not seen them.
DR. KATZ: I think thought probably we may all be in agreement which is that you probably do need to go back and do the repro studies anyway because the data that was presented in the material is not adequate to be able to say that those don't need to be done.
DR. ANSELL: I don't think I can respond directly. I'll have to check across the hall in terms of who actually did the work. I think the point is that we do not disagree that the material is potentially absorbed 40 to 80 percent based on the calculations. However, we also provided in the second wave repro and a 28-day feeding stud so that I'm not sure that I would necessarily agree that the data isn't available to respond t the panel's request.
DR. MARKS: I think that's important so that we could move forward with what we received assuming that these ingredients are absorbed, the caprylyl glycol. So now the next question is th reproductive and developmental tox data that was presented in the second wave. For those of you who are not aware of that terminology, we received an email correspondence at the end of November with a large amount of data which are not in these books and that included, Jay, reproductive and developmental and also a 28-day dermal tox.
DR. HILL: Is there dermal tox here? I'm looking at oral tox.
DR. ANSELL: My note says it was oral.
DR. MARKS: Oral.
DR. HILL: The significance of that is rodents in particular aggressively glucuronidate sulfate and excrete in bile as compared to humans so that I'm not sure that oral is sufficient.
DR. MARKS: I agree. We asked for dermal. At this point let's go back to the reproductive and developmental tox. Were you comfortable that it was safe from that point of view?
DR. SHANK: I was for 1-2 hexanediol and caprylyl glycol is only two carbons longer so tha I thought the reproductive toxicity data satisfied our needs.
DR. MARKS: So that we still need the 28-day dermal tox so there would be an insufficient there. How about the genotox?
DR. SLAGA: The one study where it's mentioned, there are no details so that it's very difficult to interpret, and there wasn't any mammalian anyway. It would be nice to have some genotoxicity both bacterial and mammalian. Although the bacterial is mentioned, it gives no details about the study.
MR. JOHNSON: The mammalian genotoxicity study was included in the Wave 2 submission along with the skin penetration study. Are you referring to that in any way, Dr. Slaga?
DR. SLAGA: This is one study under the decylene glycol and there are no details about concentrations. This is not in the book.
DR. HILL: Back to what Dr. Shank was saying, that the problem with the repro tox is it seems to be all done orally and I am very skeptical if we're at oral route for things that are alcohols that are processed, like I say rodents, aggressively clear especially the more lipophilic they get by glucuronidation sulfation and billiary excretion much more so than humans, although I don't know for this particular class of compounds that we have that comparative data, but it to me calls into question those toxicology studies if we didn't do them dermally.
DR. MARKS: Ron Shank, would you comment since you thought the reproductive and development toxicity studies were okay or safe or would support a safe conclusion?
DR. SHANK: I considered that the oral study would achieve blood circulating levels of the compound much higher than a dermal study would and there was still no systemic toxicity so that I thought that was sufficient.
DR. HILL: Which is probably true given the doses which are high.
DR. MARKS: Tom, would you comment? You just looked at Wave 2 genotox data.
DR. SLAGA: The data is fine now.
DR. MARKS: The data is fine so that we can take that off insufficient. After our discussions at this point I think we can still proceed with an insufficient data but it assumed dermal absorption and no matter whatever the discussion tomorrow in terms of the dermal absorption, the only thing we need is the 28-day dermal tox. Is that correct?
DR. SHANK: I think the 28-day oral sufficient. I don't see that we need the 28-day dermal.
DR. MARKS: Ron Hill, do you want to comment on that because you're the one who was concerned about the oral? Ron Shank, I assume the same reasoning as the productive is that the blood levels would be high enough that if there were going to be a toxicologic signal it would occur with the oral study.
DR. SHANK: Yes for systemic toxicity.
DR. HILL: Let me look back at the data. Do we have now data on something larger than hexyl? This is which one that's in here in the second wave? Caprylyl. That's C8, but we're going to extrapolate up to C12. Does that raise any issues for anybody but me? I'm thinking about things like placental transport which may go up if we go from 8 to 12. By the way, there is a metabolic barrier in placenta which is pretty dissimilar depending on compound class between rodents and humans.
DR. MARKS: Are there comments?
DR. ANSELL: I wanted to point out that as part of the submission we have provided a metabolism assessment which predicts that the C6 through C12 follow common metabolic pathways using the Meteor Program.
DR. HILL: Although those are predicted, I'm not sure that that gives me an incredible comfort level because it's generating long-chain alphahydroxy acids.

DR. ANSELL: The predictions are accurate. The predictions are used to bridge the data. To the extent that we're accepting 8 but concerned about 12, if we demonstrate that they go through common metabolic pathways then the 12 should be acceptable.
DR. HILL: That I agree with.
DR. MARKS: Ron Hill, what action do you want to take?
DR. HILL: We're proposing that we need to have the dermal penetration study repeated at least. Right?
DR. MARKS: No. Ron Shank said that it was satisfactory. When we reviewed the data we would need if it penetrated, we have okay reproductive and developmental tox, we have okay 28-day oral which would be a substitute for the dermal tox, and we have genotox data, so that dermal penetration now becomes a moot subject as I interpret it. Is that correct, Ron and Tom? So I think we have enough to move forward with a safe conclusion and that would be issued as a tentative report, but there was another thing I wanted to address and we'll come back to that. Ron Hill, I'll let you think a minute. But am I interpreting, Ron Shank and Tom Slaga, that we could proceed with a safe no matter what the dermal absorption is, but we're assuming it is absorbed.
DR. SHANK: Yes, for me. We can assume it's safe as used.
DR. MARKS: Tom, I assume that's the same.
DR. SLAGA: It is.
DR. MARKS: I have comment in here, Jay. There was a request from the council to limit it with four to 12 carbon compounds and that would being the number of ingredients down significantly to six and that's the number of compounds that's the issue. Ron Shank, as I recall you brought up the issue of water soluble versus lipid soluble and could you extend if I recall correctly the longer carbon compounds greater than 12 there was an issue of lipid solubility and could you read across with this data. Jay, first, could you comment about the council's suggestion to limit the ingredients?
DR. ANSELL: In consideration of the concerns and in consideration of the fact that 15 or 18 aren't currently used products, we did think the group could be narrowed to eliminate the materials above 12.
DR. BRESLAWEC: Is the reason that you're asking that they be excluded because they 40 are not used or do you have a reason for why they don't belong as part of this group?
DR. ANSELL: I think the panel is raising that question as to whether they can be reasonably included because of whether they exceed the ability of the alternative assessment. And to the extent that they're not used, we concur with the panel that they may fall outside the scope of the data available.
DR. MARKS: Ron Shank?
DR. SHANK: I've long maintained that if they're not used and they're just not to be considered, that's fine. But in fact, for the last couple of years we've included many chemicals in a series even though they're not used. We say if they were used in the same way they would be safe. So now to say we're not going to include these because they're not used is not consistent with what we've done in the past.
DR. SLAGA: We also have in several reports referred to compounds that are not in use and we have a little statement
DR. ANSELL: No. I don't think th issue is whether they're used or not as the fundamental cut. I think the original question is has the universe of materials staff has included in this list appropriately grouped them and I think there's a concern on the part of the expert panel that there are materials in here which exceed the ability to reply upon the data and to that extent we concur with the panel that perhaps 15 through 18 do exceed appropriate grouping for this class of materials.
DR. SHANK: That's very different than saying exclude them because they're not used. You're excluding them because they don't fit in with the read-across.
DR. ANSELL: Absolutely.
DR. HILL: I was one of the people who expressed concern with how far we were extrapolating so that I would love to see those ingredients removed on that basis because my comfort level with that extrapolation goes way down above 12.
DR. BRESLAWEC: If the panel to be very clear about the reason why these are being excluded.
DR. MARKS: The two Rons, could you please respond to that? As I recollect, do I remember correctly, there was an issue of lipid versus aqueous solubility in terms of either including or excluding?
DR. HILL: Yes, that was the deal. We had a discussion that focused on the log P values last time and that we were relying heavily on propylene glycol data and propylene glycol is very dissimilar in terms of where we would expect it to distribute in tissues than a C12 glycol. And in particular because we do not have biotransformation data even though we now have a prediction, I don't know how good that prediction is and because metabolism by P450s is highly dependent on lipophilicity, I think we're already pushing the envelope in my estimation going out to C12 based on C8 data and without any idea of commonalities of biohandling we're pushing into the great unknown and the farther we push the greater the chances that something unusual will pop up. And particularly as we go into the realms of lipophilicity where we're going to get a lot of membrane incorporation as opposed to compounds that shouldn't much stick in membranes, I think we might expect some biological activities that we aren't seeing with the smaller molecules and we don't have any information about that.
DR. MARKS: Ron Shank?
DR. SHANK: I have nothing to add to that.
DR. MARKS: So that you concur that we should cut off?
DR. SHANK: I do.
DR. MARKS: And that would be all compounds that are C-12 or greater so that if we look on page 34 --
DR. HILL: Greater than C12. Not C12 or greater.
DR. BERGFELD: So that laurylglycol would be included but myristylglycol would not? Is that correct?
DR. HILL: Correct.
DR. MARKS: Tomorrow, Ron Hill, when we get into the discussion I'll ask you or Ron Shank whichever one of you want to comment as to why we want to delete those. Tomorrow we will move to issue a tentative report that the compounds less than and equal to C12 or delete those greater tha C12 in this report that we have before us are safe as used.
MR. JOHNSON: Dr. Marks, there is one question that I have regarding the 28-day oral toxicity study on decyleneglycol and the finding of squamous epithelial hyperplasia of the forestomach and whether or not there are any concerns relating to that finding.
DR. HILL: Where in the document is that referenced?
MR. JOHNSON: It's in the Wave 2 data submission at the repeated dose toxicity. It's the study on decyleneglycol.
DR. HILL: It was in Wave 2?
MR. JOHNSON: Yes.
DR. HILL: Yes, because I was looking here that there is some mention of some cellular effects with cetyl which is obviously a lot larger and that was one of the bases for my discomfort last time with trying to extrapolate too far. I didn't see this.
DR. SLAGA: You're referring to forestomach tumors? There are a number of studies of a number of compounds that do that in mice but they never related to a human.
DR. MARKS: So that, Tom, you are not concerned? If there are no further comments, we'll move this report forward to issuing a tentative report with a safe-as-used conclusion for those compounds that are C12 and less.

Minutes from the December 13-14, 2010 (117th) CIR Expert Panel Meeting – Dr. Belsito's Team

DR. BELSITO: Good. Well, that's done. Where do we go next? Caprylyl glycol. There was a handout -- a couple handouts on the 1, 2-glycols, mercifully that were pretty short. And one is dermal penetration predictions for 1, 2-glycols for C6 through C12. Okay. And these are calculated not real. And then the other is a metabolism assessment for C6 through C12 glycols.
Based on prediction, they're saying the default values for absorption for 24 hours are 80 percent for 1, 2- hexanediol and 1, 2-octanediol and 40 percent for the 1, 2- decandiol and 1, 2-dodecanediol. And the metabolism they predict would be c. hydroxylation and beta oxidation are the metabolic pathways for the longer chain compounds; that's the decanediol and dodecanediol than for the shorter chain compounds.
So I guess our insufficient data was dermal absorption on caprylyl glycol or a similar lipid soluble 1, 2-glycol. And we did get some data on the pigskin, but it was for the --
MS. EISENMANN: It was for C8.
DR. BELSITO: C8. Okay. But it was same animal, two spots on the same animal. So I guess the question --
MS. EISENMANN: For the in-vitro study.
DR. BELSITO: Right. But it was skin taken, two pieces of skin from the same pig.
MS. EISENMANN: I understand that. Yeah.
DR. BELSITO: Yeah.
MS. EISENMANN: It really is more of a preliminary study.
DR. BELSITO: Right.
MS. EISENMANN: And they were looking only at the cold compound.
DR. BELSITO: Right. And there didn't seem to be much in the way of absorption into the receptor fluid. It was mainly into the skin.
MR. BRONAUGH: Now I would have to add that to me it looks like there's absorption. It didn't go into the receptor fluid, but all the dermis was there.
DR. BELSITO: Right.
MR. BRONAUGH: And it was 80 percent of the material of the dermis. First of all, a study

should remove most of the dermis before they do it so that they consider it as an artificial reservoir penetration. If a chemical is soluble and there was (inaudible) into the receptor fluid.
But even if you don't do that, I think most people would agree that you have to -- if you have material in the dermis at the end of the in-vitro study, you have to conclude that as being percutaneously fluent.
UNIDENTIFIED SPEAKER: Yeah.
DR. BELSITO: Okay.
DR. LIEBLER: I made the same note in my copy of the report because you're right. I mean, it goes to the dermis, and it stops there because it's not going to be soluble in the aqueous buffe
2 under it.
3 MR. BRONAUGH: And in-vivo, Blood vessels come up right under the epidermis.
DR. BELSITO: Right.
MR. BRONAUGH: And the chemicals don't have to diffuse through the dermis.
DR. LIEBLER: Right.
DR. BELSITO: Okay. So then based upon that study and what we just got would be predicted in terms of absorption, what we must conclude is that it absorbed, and, therefore, we need reproductive and developmental in 28 day, which we do not have.
MS. EISENMANN: Well, you have an oral --
UNIDENTIFIED SPEAKER: Twenty-eight days.
MS. EISENMANN: -- reproductive on the 6, and we're hoping that because the modeling data shows that the 6 and the 8 tend to be similar, that it would be all right with the data on the 6. You had this before, but now there's a little more detail.
You also have the 28-day oral on 8 and 10, and the results of those two are very similar, though the main effect was irritation on the fore stomach. So if you don't have any other systemic effects, you're hoping that you'll be okay with that.
DR. BELSITO: Okay. So Dan, Paul in alphabetical order. Wilma, comments?
DR. BERGFELD: I don't have a comment on that one at all.
DR. BELSITO: So we have absorption, but we have an oral repro on the 8?
MS. EISENMANN: Six.
DR. BELSITO: Six and an oral 28-day on the --
MS. EISENMANN: Eight and ten. And the genotoxicity.
DR. BELSITO: Yeah. No. That's -- right. We have negative gene mutation, negative chromosome aberration. So I don't -- you know, that last point is just the repro and the dermal toxicity that we asked for addressed with the oral reproductive.
DR. KLAASSEN: It seems like that should be sufficient.
(Pause)
DR. LIEBLER: So it sounds like carcinogenesis is probably off the table because there's no genotox or mutagenicity. And the issue then is repro developmental, and we've got the hexanediol study that's on page 13 in the draft report with expanded information in wave 2.
DR. BELSITO: Mm-hmm.
DR. LIEBLER: And the question is whether we're willing to accept the C6 diol repro developmental negative data as indicative of the C8 diol reproductive developmental. On top of that, we do have propylene glycol data that is negative --
DR. BELSITO: Mm-hmm.
DR. LIEBLER: -- of repro developmental. So in my view, I think those two things together are acceptable.
DR. BELSITO: Okay. And then the 28-day dermal toxicity, it says the 28-day oral that we got more details on.
DR. SNYDER: We have a good (inaudible) there of 100 mg. So I would assume that could be facilitated into an argument about absorption, even if it is absorbed.
DR. BELSITO: Well, but then -- I mean, I remember with -- I'm blacking out what it was -- that Tom Slaga had an issue with possible effects on skin from chronic use. Was it -- it was the diesters. Remember, that was several years back.
MR. JOHNSON: Glycerol diesters?
DR. BELSITO: Yeah. The glycerol diesters that -- you know, so nothing happened internally, but what would happen in terms of skin effects of repeated application to skin. I mean, I don't know if that's an issue with the glycols. I'm just raising it, but, okay, there's no internal organ effect. Is there a potential skin effect?
DR. KLAASSEN: I don't think so, not to my mind.
DR. LIEBLER: You're talking about --
DR. BELSITO: Carcinogenesis.
DR. LIEBLER: -- a point Tom raised in review of other ingredients --
DR. BELSITO: Yeah. There was --
MR. JOHNSON: Yeah.
DR. BELSITO: There was --
DR. LIEBLER: -- several years ago?
DR. BELSITO: Yeah.
DR. LIEBLER: Okay.
DR. BELSITO: There was 1,2-diesters, right, glyceral diesters that, okay, nothing happened when they got inside, but he was concerned about effects in cutaneous carcinogenesis from application to the skin.
DR. LIEBLER: I'd need to know -- I need to hear more rationale.
DR. KLAASSEN: That was because second messengers and that sort of thing.
DR. BELSITO: Right.

DR. KLAASSEN: Where you wouldn't anticipate these --
DR. LIEBLER: Well, he might be thinking that these would behave as diacylglycerals, which are mediators are signaling.
DR. BELSITO: Right. That was the issue with the others, but I'm --
DR. LIEBLER: You're not --
DR. BELSITO: I'm just saying. Okay.
DR. KLAASSEN: Things you wouldn't anticipate.
DR. BELSITO: Just pointing things out.
DR. LIEBLER: Yep. That's fine.
DR. BELSITO: I'm not against Slaga at all.
DR. LIEBLER: I think we're okay. So these estimations for absorption, were these based on -- I haven't had a chance to review this since we just got this, this morning. But were these based on an animal model or a human model and then calculations?
DR. KLAASSEN: Let's ask Bob.
DR. BELSITO: Yes.
UNIDENTIFIED SPEAKER: Thanks, Bob.
MR. BRONAUGH: You know I don't remember all the details. I'm just seeing this I guess for the first time this morning, but it was -- let me take a look.
DR. KLAASSEN: Apparently they have a formula in their computer that takes into account molecular weight and partition coefficients.
MR. BRONAUGH: Well, it's the pod sky equation I think. It does take into account molecular weight and also partition coefficients. So it's a formula -- actually, most of the data is based on human data, but it's in-vitro data.
DR. LIEBLER: Now we've got these two little measurements of the pigskin where the glycol goes as far as the dermis and piles up in the dermis. So I think it's safe to assume that that is indicative of a high propensity for absorption, systemic absorption from dermal application.
And then we've got these model-based predictions that say 80 percent -- I'm assuming they're meaning 80 percent of any dose applied would be absorbed.
MR. BRONAUGH: That's what they're saying.
DR. LIEBLER: Yeah.
DR. KLAASSEN: That's quite a bit.
DR. LIEBLER: Well, that's the nice thing about models. You never -- often you never actually have your model really tested.
I think I'm comfortable with concluding, based on the model and the limited amount of data in the pig test systems, that there would be significant absorption.
DR. KLAASSEN: Right.
DR. LIEBLER: And I don't know what the number would be, but we probably don't really need a number.
DR. KLAASSEN: No.
DR. BELSITO: It's significantly absorbed. Okay. I mean, we have predictive tests and some evidence on a rather defective in-vitro method that didn't remove the dermis. But we know it piled up in the dermis, and the prediction would be sitting next to the blood vessel is the only way it's going to get out to eventually be absorbed. So now we know that.
So then we've agreed that the oil repro on the 1, 2-hexanediol is sufficient.
DR. SNYDER: Just reiterate that. So Ron Shanks' issue last time was that the propylene glycol and the butanediol and all those are water soluble and not lipid soluble, and we have no repro data on any of the lipid soluble ingredients. And so is this new data we have, is this just another water soluble ingredient? Or is does that cover that issue that Ron raised and that it is a lipid soluble? So was the hexanediol another water soluble?
MR. JOHNSON: No.
DR. BELSITO: No.
DR. LIEBLER: It's in the middle of the range really.
DR. SNYDER: That's going to be -- that's going to be the hurdle I think. So we're comfortable --
DR. BELSITO: Well, in his -- in the notes we have what he defined as water soluble.
DR. SNYDER: Well, he said he wanted -- yeah --
DR. BELSITO: He wanted C12 or something, right?
DR. SNYDER: He wanted the caprylyl glycol.
MS. EISENMANN: He wanted caprylyl glycol, but the model is just caprylyl and hexanediol or more similar than the other solvents.
DR. LIEBLER: Right. The model says the longer chain is going to have lower absorption. The models says, just on the first page of this model document, last sentence, "To 80 percent from 1, 2-hexanediol and 1, 2- oxtanediol," which is the caprylyl, and then 40 percent for the decanediol and dodecanediol. So C10 and C12 are predicted at 40 percent.
And I think we're not talking about limiting this to C4 through C12?
DR. BELSITO: No. We have to get --
DR. LIEBLER: We haven't gotten there yet?
DR. BELSITO: No.
DR. LIEBLER: Okay. All right. Well, that's the range that's discussed in this model --
MS. EISENMANN: Right.
DR. LIEBLER: -- essentially C6 through C12.

DR. BELSITO: Okay. So right now we're at the point where we've said safe as used. They're absorbed, but there is a negative oral repro; and there is a negative 28- day oral, and that we don't assume that these will have long-term effects on skin as we were with the 1, 2-diester, the (inaudible) glycerol in particular. So then --

UNIDENTIFIED SPEAKER: Negative gene.

DR. BELSITO: In the negative gene, right. So then we come to the fact that the FDA -- PCPC

Has requested that we change a little bit what we were looking at, and that's someplace in here under the data.

UNIDENTIFIED SPEAKER: Last page.

DR. BELSITO: Last page. Based on the data included in the report, the task force in caprylyl glycol recommended that the report only include ingredients with 4 to 12 carbons. The larger ones, myristyl, cetyl, stearyl, arachidyl, hexacosyl, octacosanol, C14-18, C15-18, 18-30, 20-30, and 15-18 be removed. And of note, of those to be removed, there's only one reported use, and that's for the C20-C30.

So I guess before we decide whether we want to remove them, what is the rationale to removing them?

DR. LIEBLER: Not because they're not in the dictionary.

MS. EISENMANN: No uses, and we don't have any data on them.

MS. BRESLAWEC: Well, I don't know that that in itself is a sufficient reason to remove something if we don't have data and doesn't have uses. I think there may be a scientific basis for removing these, and if there is, then the panel should --

DR. BELSITO: Right.

MS. BRESLAWEC: -- should articulate it. But just for no uses, no information, there's another path.

DR. BELSITO: I mean, I don't -- again, I would agree with Halyna. I don't -- I may be wrong. I don't see a scientific basis for not being able to just the jargon term "read-across" from the larger molecular weights. We also have one reported use for one of these larger ones. So it's not like we're swimming in the dark. We have a reported use for C15-18. So we do have sort of a concentration range so to speak for the larger ones. I would say keep them in.

Curt, Dan, Paul, Wilma?

DR. SNYDER: I agree. Keep them in unless there is some further justification.

DR. LIEBLER: I agree.

DR. KLAASSEN: I was wondering too why they were taken out.

DR. LIEBLER: The only question will probably be whether or not we have data to allow us to infer the absorption of the longer chain derivatives, and until this morning, we had nothing. As of this morning, we at least have this model. The modeling doesn't have much data to be matched up against. That's the only question.

So it's possible that our colleagues on the other team may have some doubts about the sufficiency of the data supporting the longer chain. I think if the model is correct, and the model is probably not too bad at worst, then it's simply going to say that the absorption of these longer chain derivatives is going to be progressively less as the chains get longer. And I think that I would be unlikely -- I would not think that that would affect any of the other endpoints that we're concerned about once you establish absorption.

So if C20 is absorbed at 2 percent or 5 percent relative to C8, which might be 40 percent, then the question becomes carcinogenicity, repro developmental, and all of the data that we have with the shorter chain compound suggests that it's not an issue with any of those. I don't think the chain length is going to make these suddenly carcinogenic or repro developmental toxins because the business end of the molecule is the glycol.

UNIDENTIFIED SPEAKER: Right. I agree.

DR. LIEBLER: Or we could make that case. It's possible that our colleagues wouldn't agree, and that's what we have meetings for.

DR. BELSITO: And a quick synopsis of that should go into the discussion as to why we kept those ingredients in there.

Other comments? Okay. Well, seeing none, let's try and tackle the isoparaffins before lunch.

Minutes from the December 13-14, 2010 (117th) CIR Expert Panel Meeting – Day 2

DR. MARKS: In August of this year, the expert panel issued an insufficient data announcement with these ingredients in the caprylyl glycol and other 1-2 glycols, which included reproduction development, dermal tox, and genotoxicity and dermal penetration. We found that these insufficient data needs were met and that we could issue a tentative report with a conclusion safe as used, but we would also limit the report to include only those that are less than or equal of C-12. Those that are greater than C-12 compounds we would delete from the report.

DR. BERGFELD: And that's a motion?

DR. MARKS: Yes, that's a motion. Safe as used.

DR. BERGFELD: Safe as used. Is there a second?

DR. BELSITO: (inaudible)

DR. BERGFELD: No. Any discussion?

DR. MARKS: We weren't sure why would want to delete the ones that are greater than C-12, and I'll let Dan and Paul address that.

DR. LIEBLER: So, for the C-12s I'd like to hear more rationale for why you'd want to delete those.

DR. SHANK: (inaudible)

DR. LIEBLER: For greater than C-12, pardon me.

DR. MARKS: Right, and I'll defer that to the two Rons on our team. I think it has to do to lipid versus aqueous solubility, but I'll let Ron and Ron discuss that.

DR. HILL: It is my belief that we don't have sound dermal penetration data that supports extrapolating to that extent. We have data out to C-10. We have data for C-8 and data for C-10 and I think we're already extrapolating when we go to C-12 without any data whatsoever and we don't have any -- and we're in a range of lipophilicity where I actually believe we will have at least penetration into the upper layers of skin where there could be biological effects exerted, there could be penetration through skin. And I don't think we have data -- well, there is no data in this report to suggest that it couldn't go all the way through the skin and be systemically available, and just there is no science on any of these propylene glycols above C-12. And so we had a communication from industry, basically, that they were good with deleting ingredients above that which to me suggested that perhaps they agree with that assessment and I think there's nothing in use on those glycols above that. So, on that basis, I'm comfortable with the report and I'm comfortable voting yes as long as we don't go past C-12. If we go past C-12, I have no comfort level because I think there's no science to support the safety.

DR. BERGFELD: Ron Shank, you wanted to comment?

DR. SHANK: I agree with that. That's fine.

DR. BERGFELD: Dan, you wanted to comment?

DR. MARKS: Well, John -- could we ask John to comment, John Bailey, because the council also asked this to be done.

DR. BAILEY: No, I think our Science and Support Committee, CIR Science and Support Committee, agreed that C-12 -- above C-12, you know, could be deleted, that the -- we were concerned that this was an inappropriate grouping, you know, because of the data that we had and so forth, so they were comfortable with extracting those. However, I mean, I would ask, if this is premised on dermal penetration, it seems to me that the degree of dermal penetration is going to go down as the molecular weights go up, so that's my view. You know, if that's different -- I think Ron Hill disagrees, you know, perhaps Bob Bronaugh is here, he could comment as someone who's very experienced in this area. So, you know, there is a degree of uncertainty and our group felt that it was okay to take these out.

DR. BERGFELD: Dan, do you want to continue?

DR. LIEBLER: Sure, I'll continue, then we may have a comment from somebody else. When I approached this yesterday I wasn't really certain about the question of how well the longer chain glycols would penetrate, so we had a pretty robust discussion of this and we also engaged Bob Bronaugh in our discussion.

What we had available to us was penetration data on, I believe, it's C-8 and then we have this modeling data, and we also had -- I think this was with the -- maybe I'm getting this mixed up with the alkyl benzoates. Is that the one with the very limited skin --

DR. BELSITO: (inaudible)

DR. LIEBLER: Yeah. Anyway, the primary thing we had on these longer chains was the modeling predictions which predicted that penetration of approximately 80 percent of the applied dose, presumably in human skin, with hexane and octane diols and 40 percent with the decane and dodecane diols. In other words, it's decreasing -- penetration decreasing with increasing chain length, which is, from my understanding from talking with Bob Bronaugh, the general characteristic of more lipophilic compounds with higher Kows.

So, with that in mind -- I actually don't share Ron's concern that these compounds will penetrate the skin to a greater extent, so if there -- there may be other rationale for not including these compounds, but the dermal penetration issue, I think, is not a valid reason not to include these.

DR. BERGFELD: Bob Bronaugh, do you want to make a comment? Can you come to the mic?

DR. HILL: And while you're coming to the mic, could I at least just ask you to distinguish between penetration all the way through the skin where there's systemic availability versus penetration into the upper layers of skin where there are metabolizing enzymes and such?

DR. BRONAUGH: Well, first I would say that you don't have to penetrate all the way through the skin to have systemic bioavailability. You just need to get out of the stratum -- I'm sorry, out of the epidermis into the upper dermal layers where the blood vessels are.

In terms of penetration and predictability, certainly as you get a higher logP, I cannot -- I can't remember what the logPs were of the C-10, C-12 compounds.

DR. HILL: I've got a table --

DR. BRONAUGH: Were they 8?

DR. HILL: Okay, so the C-10 logP is 2. The C-14 logP is 4.5 --

DR. BRONAUGH: Okay, well --

DR. HILL: And the molecular weights are below 300 still --

DR. BRONAUGH: Okay, well, that's -- the logPs of 2 and 4 are really ideal for penetration and the molecular weight of 300 is certainly not going to be a limiting factor.

DR. HILL: Now, grant you, they're long, floppy chains so the diffusion coefficients would be lower, that much --

DR. BRONAUGH: Right, but, you know, I think there's definitely a possibility that those longer chain compounds could penetrate. And with regard to the shorter chain compound, the one we had data on, the C-8, clearly that's 80 percent of the material in the dermis. I think most people would agree that that compound is penetrating as well. And, in fact, most people would not have all the dermis tissue in the diffusion cell, you really want to remove most of it with a dermatome or something so that material can partition into the receptor fluid. That would be my take on it.

DR. HILL: And the other issue I had in particular was that all we have is predicted metabolism data and in this particular case, I'm sorry, but I have very limited stock in those predictions. I think in the absence of solid data and showing bio-transformation to alphahydroxy acids which could be of some interest, that within the range where we have similar lipophilicities, similar penetration issues, I was still comfortable, but --

DR. BRONAUGH: Yeah, definitely a possibility of metabolism, certainly.

DR. BERGFELD: Thank you. Any other comments? Paul?

DR. SNYDER: I guess -- so the basis is the dermal penetration and the fact that these are not used, otherwise why wouldn't we go insufficient for the greater than C-12s for dermal penetration data?

DR. MARKS: I would say it's not because they're not used. We aren't going to arrive at a safety assessment whether it's used or not used, it's on other characteristics, which, again, I'll let the two Rons address why they're concerned.

DR. BERGFELD: Ron Shank, we haven't heard from you. Maybe you'd comment on that, and then Ron Hill?

DR. SHANK: Well, I thought we were asked by the Liaison Committee to not include these and since they're not used and there's no data on them, no biological data on them, why not go ahead with that?

DR. BERGFELD: Ron Hill, do you have a comment or not?

DR. HILL: No, other than just if we can't simply remove those ingredients, does that leave us with an insufficient data for those if we're saying sufficient to support the safety through C-12 and then I would be asserting insufficient to support the safety above C-12? Is that what the conclusion would end up being?

DR. BERGFELD: Alan, you want to comment?

DR. ANDERSEN: Well, if I carry through the concerns about absent data then if they are left in the report I would expect, once you finally vote, that the panel would have insufficient data for a number of those.

But that is your call in terms of the data's sufficiency, but there is nothing fundamentally wrong with declaring that a number of ingredients in this report have insufficient data.

DR. BERGFELD: If I could make a comment. We have a couple options, I think, one to just exclude them at this point in time, and just do a limited assessment, or two, to include them and have part of them be insufficient. Is that correct? All right, Don?

DR. BELSITO: Well, first of all, we do have a use for C-15, 18 glycol. There's one reported use. Second, we have timelines for insufficient data. This is a pink report. I would prefer not to remove them, to go ahead, and I'll cede to the other team although I'm not quite certain that their arguments are valid and we go insufficient with those greater than C-12, that will give industry 90 days, particularly the one manufacturer reportedly using C-15, 18 to give its absorption data.

DR. BERGFELD: Dan?

DR. LIEBLER: I would like to just get some clarification on why the issue of penetration is problematic here because we have the shorter chain glycols that are in the range that the -- that nobody seems to be arguing about, they penetrate very well. And then we have longer chain glycols that also may penetrate. So, why is there a problem with the longer chain glycols that also penetrate?

DR. BERGFELD: Ron Hill?

DR. HILL: So, I think the general nature of my concerns is that we're also into the chain length ranges where these molecules would potentially be heavily associated with membrane lipids, in particular if they are, in fact, metabolized to fatty acids, alphahydroxy acids, that there's a very reasonable chance that they will be incorporated into lipids in the cells, in, for example, in the stratum corneum. And I spent yesterday afternoon reading a pretty large body of literature about lipid trafficking in the stratum corneum and I think there's a lot of things that we aren't considering on that basis, that that really is -- reflects the biological nature of my concern with these longer chain molecules.

Now, I'm not sure if they stay as glycols, there's a problem, but I think we have no data whatsoever about what happens to these in terms of possible association with cell membranes and what that might do in the cells in the upper layers of the skin. And so I didn't have much of a concern when we kept the molecular -- the chain links below 12 because I don't think that's likely to be problematic.

DR. BERGFELD: Dan?

DR. LIEBLER: So, it's possible that these are metabolized alphahydroxy fatty acids, which by itself is not a red flag --

DR. HILL: No.

DR. LIEBLER: -- but I don't see the distinction. I'm not sure I understand why a C -- was it C-10 -- should not be a problem and a C-12 or a C-14 should be a problem in that respect. I think this is really just speculative and I don't see -- in the absence of data about these, I actually think that the lack of data indicating there are problems caused by the compounds in the C-4 to C-12 range, I think that the idea that something at C-14 or C-15 is going to be causing problems is really just highly speculative and I can't support that.

DR. HILL: Paul?

DR. SNYDER: So, I think the difference is, is at the shorter chain we do have repeat dose toxicity studies that show that there is no systemic toxicity. That's the difference. I think that Ron would probably agree that at longer lengths, if you're concerned about absorption, we don't have any repeat dose systemic toxicity studies to support the fact that these are not a problem.

DR. BERGFELD: Jim?

DR. MARKS: But Dan and Paul and Curt, I'd like you to answer, so what I interpret, you don't -- you're not concerned about the toxicology of the longer carbon compounds and the data we have for the shorter compounds you would read across and say it would be unlikely there is any significant toxicologic effect. Assuming they penetrate you're not concerned about that?

DR. LIEBLER: Correct.

DR. BERGFELD: That whole team is shaking their heads yes. How about the team over here? Ron and Ron Hill? You're giving up, Dr. Hill?

DR. HILL: I'm just not certain either way.

DR. BERGFELD: Okay. How about you, Ron or Tom?

DR. SLAGA: I agree with the last statement.

DR. BERGFELD: You agree with him. Okay. You agree? Okay. So, Don?

DR. BELSITO: We, in our team, had a very protracted talk because I remember when we were doing the glycerol diesters there was a concern about deposition in the epidermis and even though they wouldn't get absorbed, whether there would be a difference in dermal toxicity. And it was felt that by my glycol experts on my team that this really would not be an epidermal issue.

So, we actually felt they all could be safe as used. However, if the other team wants to go with insufficient for the large ones, at this point, since it's a pink report, I wouldn't object. We always can hack it out when it gets to the blue.

DR. BERGFELD: Jim, you want to conclude?

DR. MARKS: I didn't see the way Ron Shank -- whether he shook his head --

DR. BERGFELD: He shook -- yes.

DR. MARKS: Yes, so what I would do, although this may -- Ron Hill may be a dissenter -- is I would withdraw my motion and make a move that a tentative report issued for all these that they're safe as used.

DR. BERGFELD: Is there a --

DR. BELSITO: Second.

DR. BERGFELD: Do we have any other discussion? Seeing none, call the question, all those in favor, please indicate by raising your hands.

Abstaining? One abstaining. Thank you. All right, thank you very much. Then moving on to Dr. Belsito's, the Alkyl Benzoate Group.

Report

Final Report

1,2-Glycols as Used in Cosmetics

June 27, 2011

The 2011 Cosmetic Ingredient Review Expert Panel members are: Chair, 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, Scientific Analyst/Writer.

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ABSTRACT: Caprylyl glycol and related 1,2-glycols are used mostly as skin and hair conditioning agents and viscosity agents in cosmetic products, and caprylyl glycol and pentylene glycol also function as cosmetic preservatives. The Expert Panel noted that these ingredients are dermally absorbed and that modeling data predict decreased skin penetration of longer-chain 1,2-glycols. The Panel concluded that negative oral toxicity data on shorter-chain 1,2-glycols and genotoxicity data support the safety of all of the 1,2-glycols reviewed in this safety assessment. Thus, it was concluded that these ingredients are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This report assesses the safety of 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, 4 are being used in personal care products: caprylyl glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol. The remaining 12 ingredients are not in current use.

A CIR final safety assessment on propylene glycol (PG), short-chain 1,2-glycol, and polypropylene glycols was published in 1994.[1,1] 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. The fundamental carbon backbone contains a hydroxyl group at the 1 and 2 positions, and the length of the carbon backbone varies from one structure to another. 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. The solubility of these ingredients in water ranges from highly soluble (1,2-butanediol, octanol/water partition coefficient of -0.8) to not very soluble (octacosanyl glycol, octanol/water partition coefficient of approximately 11.9).

No information on the chemical and physical properties of C14-18, C15-18, C18-30, and C20-30 glycols were found, but 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]

Composition/Impurities

The heavy metals specification for > 98% caprylyl glycol (Dermosoft® Octiol) is 5 ppm max (as Pb).[8] Decylene glycol (as SymClariol®) contains 98% to 100% decylene glycol.[9] 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.[10,11] Decylene glycol has been analyzed via gas chromatography, and has been identified using mass, IR, and NMR spectroscopy**.** [11, 12] 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. [11]

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.[13] 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, decylene glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol.[14] 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%).[15] 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

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]

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.[18]

Stearyl Glycol

Stearyl Glycol has been used as a surfactant (in octanol/water microemulsion) in a transdermal delivery system for the drug, 8-methoxypsoralen.[19]

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. Based on metabolism modeling data on caprylyl glycol (1,2-octanediol), 1,2-hexanediol, decylene glycol(1,2-decanediol), and lauryl glycol (1,2-dodecanediol), it is likely that C-oxidation, C-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. C-hydroxylation and beta-oxidation are more likely to be favored metabolic pathways for the longer alkyl chain compounds, 1,2-decanediol and 1,2-dodecanediol, than for the shorter alkyl chain length compounds, 1,2-hexanediol and 1,2-octanediol.

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

A metabolism assessment for the following 1,2-glycols (C6 – C12) was provided by the Personal Care Products Council: caprylyl glycol (1,2-octanediol, C8), 1,2-hexanediol (C6), decylene glycol (1,2-decanediol, C10), and lauryl glycol (1,2-dodecanediol, C12).[20] Because metabolism database searches did not yield information on these four compounds, the possible metabolic fates of each were determined based on structural features, a substructure search, and a Meteor™ (9.0) metabolism prediction. The results of this assessment indicated that it is likely that *C*-oxidation, *C*-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. Furthermore, *C*-hydroxylation and beta-oxidation are more likely to be favored metabolic pathways for the longer alkyl chain compounds, 1,2-decanediol and 1,2-dodecanediol, than for the shorter alkyl chain length compounds, 1,2-hexanediol and 1,2-octanediol.

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.[21] 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. After PG was applied dermally to the fingertip of a human subject, the concentration of PG remaining at the surface of the stratum corneum decreased over time. Following topical application of 5% caprylyl glycol in 70% ethanol/30% propylene glycol (5% Dermosoft Octiol in alcoholic solution) to female pig skin in vitro, approximately 97% of the test solution was dermally absorbed within 24 h post-application. Based on dermal penetration modeling data on caprylyl glycol (1,2-octanediol), 1,2-hexanediol, decylene glycol (1,2-decanediol), and lauryl glycol (1,2-dodecanediol), the default values for % dose absorbed per 24 h were 80% for 1,2-hexanediol and 1,2-octanediol and 40% for 1,2-decanediol and 1,2-dodecanediol. Also, because of the limited percutaneous absorption data on 1,2-glycols, 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).

Caprylyl Glycol

The dermal absorption and skin penetration of 5% Dermosoft Octiol in alcoholic solution (5% caprylyl glycol in 70% ethanol/30% propylene glycol) *in vitro* was evaluated using skin from the backs of female pigs (~ 130 days old) in Franz diffusion cells. The partition coefficient of caprylyl glycol was estimated using an appropriate computer program (ACD logD-Suite) to be log $P_{ow} \approx 1$ (pH 3 to 7.4). The solution was applied topically to excised pig skin for 24 h. The investigators used an analytical method that only measured the parent compound, caprylyl glycol, and the total recovery was only 55%.

Approximately 97% of the recovered material was found in the skin within 24 h post-application, and the following distribution (as % of dermal absorbed caprylyl glycol) was reported: ~10% in stratum corneum, ~9% in epidermis, and ~81% in dermis. Caprylyl glycol was not detected in the receptor fluid, and this was likely a result of metabolism in the skin. The authors noted that, normally, the metabolism of caprylyl glycol takes place mainly in the epidermis/dermis. Therefore, undetectable amounts of the unchanged substances (below the detection limit) may penetrate into the receptor fluid. Because size of the sample (N = 2; taken from same pig) was very small and considered non-representative, it was not possible to perform an inductive statistical analysis. Therefore, according to the authors, the descriptive results achieved in this study have to be considered as a trend and interpreted as such.[22]

In addition to the dermal penetration study, a study in which caprylyl glycol was incubated with and without cut up pig skin for 24 h was completed. [22] Compared to the sample without pig skin, 50% of the caprylyl glycol was lost in the presence of skin during the 24 h incubation. The investigators attributed this loss to chemical or metabolic degradation, and suggested that the poor recovery in the dermal penetration study was likely a result of the metabolism.

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

Dermal penetration modeling information on the following 1,2-glycols (C6 – C12) was provided by the Personal Care Products Council: caprylyl glycol (1,2-octanediol, C8), 1,2-hexanediol (C6), decylene glycol (1,2-decanediol, C10), and lauryl glycol (1,2-dodecanediol, C12).[23] Dermal penetration predictions were made on the basis of Jmax (maximal flux) values calculated from Kp estimations and calculated water solubility. Based on the calculated Jmax values, assignment of default % absorption values was done, as described by Kroes et al.[24] Utilizing this approach, the default values for % dose absorbed per 24 h were 80% for 1,2-hexanediol and 1,2-octanediol and 40% for 1,2-decanediol and 1,2-dodecanediol.

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. 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.[25] 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, 1,2-Hexanediol, and Decylene Glycol

Warner et al.[12] 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.

1,2-Butanediol and Pentylene Glycol

In a study by Heuschkel et al.,[26] 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.

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.[21] Further details relating to this study were not available.

Acute Oral Toxicity

Acute 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).[27] 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.[28,28]

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.[29] 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.[30] 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.[21]

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).[31]

Stearyl Glycol

An LD50 of > 5,000 mg/kg was reported for rats dosed orally with stearyl glycol.[31]

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

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.[21] Details relating to the test procedure were not provided; however, it was presumed that neat material was tested.

Decylene Glycol

In an acute dermal toxicity study involving rats, the LD50 for decylene glycol (SymClariol®) was > 2,000 mg/kg.[28]

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, 1,2-Butanediol, and Pentylene Glycol

In a report by Shoemaker,[32] 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).[32]

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).[33]

Muscle incoordination was observed in rats at an i.p. dose of ~ 2.94 g/kg 1,2-butanediol.[21] An i.p. TDLo of 3,510 mg/kg has been reported for pentylene glycol in rats.[31]

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.[34] 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]

Short-Term Oral and Parenteral Toxicity

A no-observed effect level (NOEL) of 50 mg/kg/day and a no-observed adverse-effect-level (NOAEL) of 300 mg/kg/day for systemic toxicity in rats were reported in a 28-day oral toxicity study on > 98% caprylyl glycol (Dermosoft® Octiol). The NOAEL was based on findings of irritation on the pars non-glandularis and limiting ridge of the stomach; analogous structures do not exist in man. An NOAEL of 100 mg/kg/day was reported for rats in a 28-day oral toxicity study on 98% to 100% decylene glycol (SymClariol®); squamous epithelial hyperplasia of the forestomach was observed at higher doses. 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. 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. Intravenous dosing with PG over a 2-week period resulted in little toxicity in rats.

Caprylyl Glycol

In a 28-day oral toxicity study, > 98% caprylyl glycol (Dermosoft® Octiol) was administered to groups of Wistar rats at doses of 50, 300, and 1000 mg/kg/day, respectively, according to OECD guidelines.[35] The number of animals per group was not stated and the control group was not identified. The authors reported no test substance-related mortalities or toxicologically relevant clinical signs during weeks 1 through 3 or week 4 (functional observational battery). Additionally, there were no differences in food consumption, body weight, hematological/clinical biochemistry parameters, or macroscopic findings that were considered toxicologically relevant. Test substance-related findings (males and females) included slightly reduced locomotor activity and increased mean absolute and relative kidney weights at the highest dose. Whether or not microscopic changes were observed in the kidneys was not stated.

Systemic effects were not observed at doses up to 300 mg/kg/day. Test substance-related microscopic changes were observed in the stomachs of rats in 300 and 1000 mg/kg/day dose groups. These findings were considered indicative of an irritative potential of the test substance on the pars non-glandularis and limiting ridge of the stomach. The authors noted that analogous structures do not exist in man. Study results indicated a no-observed effect level (NOEL) of 50 mg/kg/day, and a no-observed adverse-effect-level (NOAEL) of 300 mg/kg/day for systemic toxicity. The NOAEL was based on findings (irritation) in the stomach likely due to local irritative effects.[35]

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 basic diet (one dose level per group).[21] A control group only received basic diet. There 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.[36] 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 weights, 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. [36]

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.[21]

Decylene Glycol

In a 28-day oral toxicity study, 98% to 100% decylene glycol (SymClariol®) was administered to groups of SPF-bred Wistar rats (5 males, 5 females/group) at doses of 100, 300, and 1000 mg/kg/day, respectively, according to OECD guidelines.[37] The vehicle control group received 2.5% ethanol in distilled water. Rats in each group were killed after day 28. Two additional groups (same composition) were untreated and dosed with 1000 mg/kg/day, respectively, for 28 days. The animals in these groups were killed after a 14-day non-treatment period. In all groups, a functional observational battery was performed (week 4) before animals were killed. All of the animals survived the 28-day dosing period, and there were no toxicologically-relevant clinical signs during the study. Mean locomotor activity was significantly reduced in males and females in the 1000 mg/kg/day dose group, and this finding was deemed test substance-related. Reduced feed consumption was also noted in females at this dose level. Mean body weights of males and females were similar to those of negative control animals.

There were no test-substance-related differences in hematological or clinical biochemical parameters that were of toxicological relevance. The presence of ketone in the urine of males and females of the 1000 mg/kg/day dose group was considered likely representative of metabolic adaptation to the test substance. Both absolute and relative organ weights of dosed animals were comparable to those of negative control rats. Toxicologically-relevant macroscopic findings were not observed. Squamous epithelial hyperplasia, ulceration, and inflammation of the forestomach were observed at doses of 1000 mg/kg/day, and squamous epithelial hyperplasia of the forestomach was less severe and occurred at a lower incidence in the of 300 mg/kg/day dose group. After a 14-day recovery period, squamous epithelial hyperplasia remained in the animals previously dosed with 1000 mg/kg/day, but the severity and incidence of this finding after the treatment period was largely reversible. Both the NOEL and the NOAEL in this study was 100 mg/kg body weight/day.[37]

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. 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 2.2 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. 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. In a 92- to 97-day oral toxicity study involving mice, rats, dogs, and monkeys dosed with a formulation containing 1000 mg/kg propylene glycol, there were no adverse effects on body weight, food consumption, clinical pathology, histopathology, or adverse clinical observations.

Pentylene Glycol

Pentylene glycol was administered orally to rats, intermittently over a 28-week period. A TDLo of 2,450mg/kg was reported.[31]

Propylene Glycol

A 92- to 97-day study was conducted to assess the safety and tolerability of propylene glycol as an alternative formulation vehicle in general toxicology studies in the mouse, rat, dog, and monkey.[38] In Sprague-Dawley (Crl:CD[SD]VAF/Plus) rats (10/sex; 6 ± 1 weeks old) and CD1 (Crl:CD1[Icr]VAF/Plus) mice (10/sex; 6 ± 1 weeks old), the vehicle was administered orally via gavage at dose volumes of 5 ml/kg (rats) and 10 ml/kg (mice) for 92 to 93 days. In beagle dogs (4/sex; 7 to17 months old) and cynomolgus monkeys (*Macaca fascicularis*, 4/sex; juvenile to young adult), the vehicle was administered orally by gavage (dose = 1,000 mg/kg; dose volume of 5 ml/kg) for 95–97 days. Effects on clinical observations, body weight and food consumption parameters, clinical pathology, and histopathology were evaluated across all species. The suitability of formulations containing up to 1000 mg/kg propylene glycol for use in preclinical safety studies was confirmed by a lack of effects on all parameters examined.[38]

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

Repeated Dose Dermal Toxicity

1,2-Butanediol

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.[21] Details relating to the test procedure were not provided; however, it is presumed that neat material was tested.

Cytotoxicity

The cytotoxicity of cetyl glycol, lauryl glycol, and pentylene glycol has been demonstrated in vitro. 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. Propylene glycol was moderately cytotoxic to human fibroblasts and keratinocytes in vitro.

Pentylene Glycol

Anselmi et al.[39] 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.

Lauryl Glycol

Osorio e Castro et al.[40] 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).

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.[41]

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. 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. 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 decylene glycol induced corrosion when instilled into the eyes of rabbits. In an in vitro ocular irritation assay (HET-CAM), 1% decylene glycol 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 (NRR) 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.[42]

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%).[43]

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. [21]

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 (NRR) assay using rabbit cornea fibroblasts, HET-CAM, and the reconstituted human epithelial culture (REC) assay.[44] 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.[44]

Decylene Glycol

In an ocular irritation study (OECD 405 protocol) involving rabbits, decylene glycol (SymClariol®) 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.[28]

Lauryl Glycol

According to Worth and Cronin,[45] 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 (units not stated) 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.[45] Using a logarithm calculator, log 0.02 = -1.70 and log 171.0 = 2.23.

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. 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 guinea pig maximization test, results were negative for caprylyl glycol at a challenge concentration of 50% in petrolatum. Undiluted decylene glycol (SymClariol®) 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-butanediol 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.[42]

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.[21] 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.[46]

Decylene Glycol

In a skin irritation study (OECD 404 protocol) involving rabbits, 100% decylene glycol (SymClariol®) 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.[28]

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.[28]

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. 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 developmental 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.[36] The estimated dose of low concern (EDCL) for this study was calculated as 10 mg/kg/day, using an NOAEL of 1,000 mg/kg/day and a reproductive toxicity uncertainty factor of 100.[7]

1,2-Hexanediol

The developmental toxicity of Hydrolite-6 (99% 1,2-hexanediol) was evaluated using groups of 24 mated Sprague-Dawley rats of the Crl:CD strain.[47] Three groups received oral doses (gavage) of 30, 100, and 300 mg/kg/day, respectively, between days 5 and 19 of gestation. The negative control group received vehicle (not stated) only. Pregnant females were killed on day 20 of gestation and subjected to macroscopic necropsy. Doses up to 300 mg/kg/day were well-tolerated, and did not induce any effects on clinical condition, body weight, body weight change, food intake, or necropsy observations. There were also no effects on embryo-fetal survival, growth, or development at doses up to 300 mg/kg/day. It was concluded that Hydrolite-6 at doses up to 300 mg/kg/day was not associated with any adverse effect on the pregnant rat or the developing conceptus. The Hydrolite-6 (1,2-hexanediol) NOEL for the pregnant female and for embryo-fetal survival, growth, and development was considered to be 300 mg/kg/day.

Propylene Glycol

A continuous breeding reproduction study was conducted using COBS Crl:CD-1 (ICR)BR outbred Swiss albino mice (6 weeks old). 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.

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.[48] 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.

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. 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. 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.

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

GENOTOXICITY

Caprylyl glycol, > 98% (Dermosoft® Octiol) did not induce gene mutations in Chinese hamster V79 cells (test concentrations up to 1489 µg/ml) and >98% caprylyl glycol (ADEKA NOL OG) did not induce chromosomal aberrations in Chinese hamster lung cells in vitro with or without metabolic activation at concentrations up to700 µg/ml. Decylene glycol (SymClariol®) 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.

Caprylyl Glycol

The genotoxicity of > 98% caprylyl glycol (Dermosoft® Octiol) was evaluated in a gene mutation assay involving Chinese hamster V79 cells *in vitro* according to OECD and European Commission guidelines.[49] Test concentrations up to 1480 µg/ml were evaluated. The first experiment (with and without metabolic activation) involved a 4-h treatment period, whereas, the second experiment involved 4-h and 24-h treatment periods (without activation). A substantial or reproducible dose-dependent increase in the mutation frequency was not observed in either of the 2 experiments. Appropriate reference mutagens (positive controls, unnamed) induced a distinct increase in mutant colonies. Negative control cultures were not described. Caprylyl glycol, > 98% (Dermosoft® Octiol) did not induce gene mutations under the experimental conditions reported, and therefore, was considered non-mutagenic.

The genotoxicity of > 98% caprylyl glycol (ADEKA NOL OG) was evaluated in the chromosome aberrations assay using Chinese hamster lung (CHL/IU) cells *in vitro* according to Ministry of Health and Welfare (Japan) genotoxicity test guidelines.[50] Short-term treatment of cultures (with and without metabolic activation) involved concentrations up to 700 µg/ml and continuous treatment involved concentrations up to 180 µg/ml, both with and without metabolic activation. Negative and positive control cultures were not identified. In all test cultures, the number of structural and numerical chromosomal aberrations was not increased when compared to negative control cultures. The positive control was genotoxic. The test substance did not induce chromosomal aberrations with or without metabolic activation.

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.[51]

Decylene Glycol

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

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. 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. 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.

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.[43]

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]

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]

Decylene Glycol

The skin irritation potential of decylene glycol (SymClariol®) was evaluated using 52 subjects in a 48 h 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. [28]

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.[28]

Propylene Glycol

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. 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. 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). 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). 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. 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, 65.2, and 73% PG, 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.

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. 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. 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. (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. 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. 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). 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.[57]

Propylene Glycol

> A few case reports have been described concerning PG and hand dermatitis or atopic dermatitis. The cases generally had positive patch test reactions to PG. Improvement was seen with the avoidance of PG-containing products.
>
> 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 five 1,2-glycols were reported to FDA as being used: caprylyl glycol, decylene glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol. The results of a Personal Care Products Council industry survey indicate that ingredient use concentrations have ranged from (lowest to highest) 0.00003% (caprylyl glycol) to 10% (1,2-hexanediol). Use concentrations of pentylene glycol (up to 5%) were also included in this survey. C15-18 glycol was included in this survey, but no uses or use concentrations were reported.

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.

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 isolated from the urine of rabbits fed 1,2-butanediol in the diet. Based on metabolism modeling information on caprylyl glycol, 1,2-hexanediol, decylene glycol, and lauryl glycol, it is likely that *C*-oxidation, *C*-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. *C*-hydroxylation and beta-oxidation are more likely to be favored metabolic pathways for the longer alkyl chain compounds, 1,2-decanediol and 1,2-dodecanediol, than for the shorter alkyl chain length compounds, 1,2-hexanediol and 1,2-octanediol.

Following topical application of 5% caprylyl glycol in 70% ethanol/30% propylene glycol (5% Dermosoft Octiol in alcoholic solution) to female pig skin *in vitro*, approximately 97% of the test solution was dermally absorbed within 24 h post-application. Based on dermal penetration modeling information on caprylyl glycol, 1,2-hexanediol, decylene glycol, and

lauryl glycol, the default values for % dose absorbed per 24 h were 80% for 1,2-hexanediol and 1,2-octanediol and 40% for 1,2-decanediol and 1,2-dodecanediol.

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.

A no-observed effect level (NOEL) of 50 mg/kg/day and a no-observed adverse-effect-level (NOAEL) of 300 mg/kg/day for systemic toxicity in rats were reported in a 28-day oral toxicity study on > 98% caprylyl glycol (Dermosoft® Octiol). The NOAEL was based on findings of irritation on the pars non-glandularis and limiting ridge of the stomach; analogous structures do not exist in man. An NOAEL of 100 mg/kg/day was reported for rats in a 28-day oral toxicity study on decylene glycol (SymClariol®). 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 toxicity 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. In a 92- to 97-day oral toxicity study involving mice, rats, dogs, and monkeys dosed with a formulation containing propylene glycol (dose = 1000 mg/kg), there were no adverse effects on body weight, food consumption, clinical pathology, histopathology, or adverse clinical observations.

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 promyelocytic 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 decylene glycol (SymClariol®) 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 (NRR) 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 guinea pig maximization test, results were negative for caprylyl glycol at a challenge concentration of 50% in petrolatum. Undiluted decylene glycol (SymClariol®) 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 developmental toxicity study involving rats, an NOEL of 300 mg/kg was reported for 1,2-hexanediol.

Caprylyl glycol, > 98% (Dermosoft® Octiol) did not induce gene mutations in Chinese hamster V79 cells (concentrations up to 1480 µg/ml) and >98% caprylyl glycol (ADEKA NOL OG) did not induce chromosomal aberrations in Chinese hamster lung cells (concentrations up to 700 µg/ml) *in vitro*. Decylene glycol (SymClariol®) was non-genotoxic in the Ames test, and 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%). Decylene glycol (SymClariol®) 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.

Propylene Glycol

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 in human subjects. Often, it works synergistically with other enhancers. The mechanism by which PG enhances penetration has not been definitively identified.

Based on the 1994 safety assessment and more recent information, 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. Hypertrophy, dermal inflammation, and proliferation were also observed with 50% PG in nude mice. These effects were not seen in hairless mice with undiluted PG. 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. 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 available safety test data for 1,2-glycols indicate that they are not acute toxicants, are not genotoxic in almost all assays, are not carcinogenic, and are not significant dermal irritants, sensitizers or photosensitizers. Data on the following 1,2-glycols were reviewed: caprylyl glycol, lauryl glycol, stearyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, 1,2-hexanediol, C15-18 glycol, and propylene glycol. The CIR Expert Panel recognizes that many of the studies included in this safety assessment are on propylene glycol. However, because increasing the chain length of the carbon backbone likely will not increase the potential for toxicity of longer-chain 1,2-glycols, data on propylene glycol may be used to support the safety of all 1,2-glycols reviewed in this safety assessment.

Results from an *in vitro* skin penetration study on 5% caprylyl glycol in 70% ethanol/30% propylene glycol (5% Dermosoft Octiol) using female pig skin indicated significant percutaneous absorption of caprylyl glycol. Dermal penetration modeling data on caprylyl glycol (C8), 1,2-hexanediol (C6), decylene glycol (C10), and lauryl glycol (C12) predicted that skin penetration would decrease with increasing chain length. Acknowledging the dermal absorption of these compounds, the Expert Panel determined that evaluation of reproductive/developmental toxicity data would be key to determining a safe level. The results of oral reproductive/developmental toxicity studies on propylene glycol (C3), 1,2-butanediol (C4), and 1,2-hexanediol (C6) were negative, and there was no evidence of systemic toxicity in other oral repeated dose toxicity studies involving caprylyl glycol (C8), propylene glycol (C3), 1,2-butanediol (C4), pentylene glycol (C5), and decylene glycol (C10). The available repeated dose toxicity data include some 28-day oral toxicity studies, but not 28-day dermal toxicity data, and dermal reproductive/developmental toxicity data also were not available. However, the Expert Panel agreed that

these oral toxicity data can be used to evaluate the safety of 1,2-glycols in products applied to the skin in the absence of dermal studies, because 1,2-glycol blood levels following oral exposure would be higher when compared to dermal exposure and systemic toxicity was absent in the oral studies.

The Expert Panel acknowledged that while dermal absorption modeling data predicted that skin penetration decreases with increasing chain length, significant dermal penetration of the longer chain 1,2 glycols may occur. Metabolism modeling data on caprylyl glycol, 1,2-hexandiol, decylene glycol and lauryl glycol predicted that *C*-oxidation, *C*-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. The Expert Panel agreed that the negative oral reproductive/developmental toxicity (up to C6) and other negative oral repeated dose toxicity data (up to C10) may be extrapolated to longer –chain 1,2-glycols. The negative results of bacterial/mammalian genotoxicity assays on caprylyl glycol, 1,2-butanediol, and decylene glycol were also considered, and the Expert Panel agreed that these data can also be extrapolated to longer-chain 1,2-glycols as well. Thus, the modeling data predictions of decreased skin penetration of longer-chain 1,2-glycols and those relating to their metabolic fate, together with the negative oral toxicity data on shorter-chain 1,2-glycols and genotoxicity data, support the safety of all of the 1,2-glycols reviewed in this safety assessment in products applied to the skin.

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 industry is advised to consider the impact of the penetration enhancing activity of these ingredients on the safety of other ingredients in formulation.

CONCLUSION

The CIR Expert Panel concluded that the following cosmetic ingredients are safe in the present practices of use and concentration described in this safety assessment:

- 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*

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

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[58]
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[58]
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[59]
Boiling point	356.1 ± 10.0°C (760 Torr)	ACD/Labs[58]
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[58]
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[60]
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[58]

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[58]
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[58]
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[58]
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[61]
Boiling point	377.2 ± 10.0°C (760 Torr)	ACD/Labs[58]
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		
Form	Specification: Colorless liquid with mild odor (as > 98% caprylyl glycol [Dermosoft® Octiol])	Straetmans[8]
Molecular weight	146.23	ACD/Labs[58]
Molar volume	155.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″

Table 2. Chemical and Physical Properties

Property	Values	Reference
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)	″
Molar intrinsic solubility	0.029 mol/l (25°C)	″
Molar solubility	0.030 mol/l (pH 7, 25°C)	″
Glycol value	Specification: 740 to 770 (as Dermosoft® Octiol)	Straetmans[8]
Melting point	36 to 37°C (not calculated)	Fringuelli[62]
Boiling point	137 to 139°C (not calculated); 243.0 ± 8.0°C (760 Torr)	Mugdan[63]
Flash point	109.1 ± 13.0°C	ACD/Labs[58]
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		
Form	Whitish to white waxy mass (as 98% to 100% decylene glycol [SymClariol®])	Symrise[9]
Molecular weight	174.28	STN[11]
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[60]
Melting point	42 to 52°C	Symrise[9]
Boiling point	93 to 96°C (0.5 Torr) - not calculated; 255.0 ± 0.0°C (760 Torr)	Orito[64]
Flash point	122.4 ± 13.0°C	ACD/Labs[58]
Flash point	>100ºC (as SymClariol®)	Symrise[9]
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[58]
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[65]
Refractive index	1.4400 (20°C, λ = 589.3 nm) – not calculated	Emmons[66]
Mass intrinsic solubility	95 g/l (25°C)	ACD/Labs[58]
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[65]; Emmons[66]
Flash point	104.4 ± 0.0°C	ACD/Labs[58]
Enthalpy of vaporization	51.45 ± 6.0 kJ/mol (760 Torr)	″

Table 2. Chemical and Physical Properties

Property	Values	Reference
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[58]
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[67]; Tishchenko[68]
Refractive index	1.4380 (20°C, λ = 589.3 nm)	ACD/Labs[58]
Mass intrinsic solubility	230 g/l (25°C)	″
Solubility	Very soluble in water	NIOSH[13]
Mass solubility	230 g/l (pH 7, 25°C)	ACD/Labs[58]
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[11]
Boiling point	132 to 133°C (760 Torr) – not calculated; 190.3 ± 8.0°C (760 Torr)	Clendenning[65]; Hill[69]
Flash point	93.3 ± 0.0°C	ACD/Labs[58]
Enthalpy of vaporization	49.64 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.48E-01 Torr 10 (20ºC)	″ NIOSH[13]
pKA	14.27 ± 0.20 (25°C)	STN[11]
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		
Form	Colorless to light yellow liquid with a characteristic odor (as Hydrolite-6, 99% 1,2-hexanediol)	Symrise[70]
Molecular weight	118.17	ACD/Labs[58]
Molar volume	122.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.961 ± 0.06 g/cm^3 (20°C)	″
Relative density (D20/4)	0.9490 to 0.9540 (as Hydrolite-6)	Symrise[70]
Refractive index	1.4518 (25°C, λ = 589.3 nm) – not calculated	Zelinski[71]
Refractive index (n20/D)	1.4400 (as Hydrolite-6)	Symrise[70]
Solubility	Readily soluble in water and oil	
Mass intrinsic solubility	37 g/l (25°C)	ACD/Labs[58]
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[72]
Flash point	95.8 ± 13.0°C	″
Flash point	>100ºC (as Hydrolite-6)	Symrise[70]
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 Frequency and Concentration of Use According to Duration and Type of Exposure[14,15]

	Caprylyl Glycol		Decylene Glycol		Pentylene Glycol	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	269	0.3 to 5	NR	NR	114	0.005 to 4
Possible Ingestion	NR	NR	NR	NR	6	NR
Inhalation	27	0.2 to 0.5	NR	NR	6	1
Dermal Contact	1843	0.0003 to 5	1	NR	775	0.001 to 5
Deodorant (underarm)	36	0.03 to 2	NR	NR	3	0.2
Hair - Non-Coloring	101	0.0002 to 2	NR	NR	8	0.001
Hair-Coloring	1	0.002 to 5	NR	NR	NR	NR
Nail	8	0.0004 to 0.5	NR	NR	1	4 to 5
Mucous Membrane	NR	NR	NR	NR	6	0.001 to 5
Bath Products	63	0.0004 to 1	NR	NR	1	NR
Baby Products	11	0.6	NR	NR	NR	NR
Duration of Use						
Leave-On	1721	0.00003 to 5	1	NR	713	0.005 to 5
Rinse off	416	0.0004 to 2	NR	NR	105	0.001 to 5
Totals/Conc. Range	2137	0.00003 to 5	1	NR	818	0.001 to 5
	1,2-Hexanediol		**C15-18 Glycol**			
	# of Uses	Conc. (%)	# of Uses	Conc. (%)		
Exposure Type						
Eye Area	35	0.3 to 0.7	NR	NR		
Possible Ingestion	39	0.3	NR	NR		
Inhalation	2	10	NR	NR		
Dermal Contact	215	0.00005 to 10	1	NR		
Deodorant (underarm)	3	NR	NR	NR		
Hair - Non-Coloring	4	0.0003 to 0.3	NR	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	1	0.4	NR	NR		
Mucous Membrane	14	0.3	NR	NR		
Bath products	2	0.2	NR	NR		
Baby Products	3	NR	NR	NR		
Duration of Use						
Leave-On	182	0.2 to 10	1	NR		
Rinse off	51	0.00005 to 0.8	NR	NR		
Totals/Conc. Range	233	0.00005 to 10	1	NR		

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 4. Corticosterone and TEA Permeability Coefficients in the Presence of Permeation Enhancers[12]

Enhancer	Enhancer Concentration (M)	Permeability Coefficient of CS$^{\alpha}$ (cm/s x 10^7)	Permeability Coefficient of TEA$^{\alpha}$ (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

$^{\alpha}$Mean ± SD (n = 3)

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

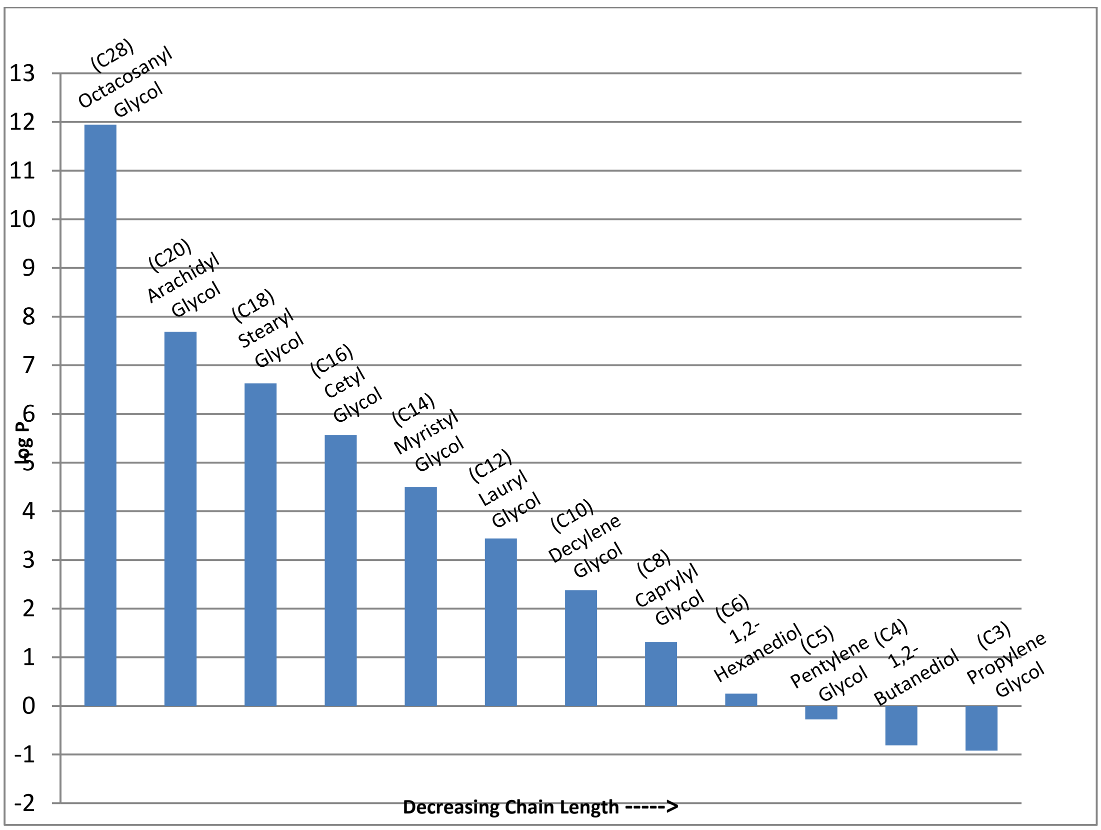
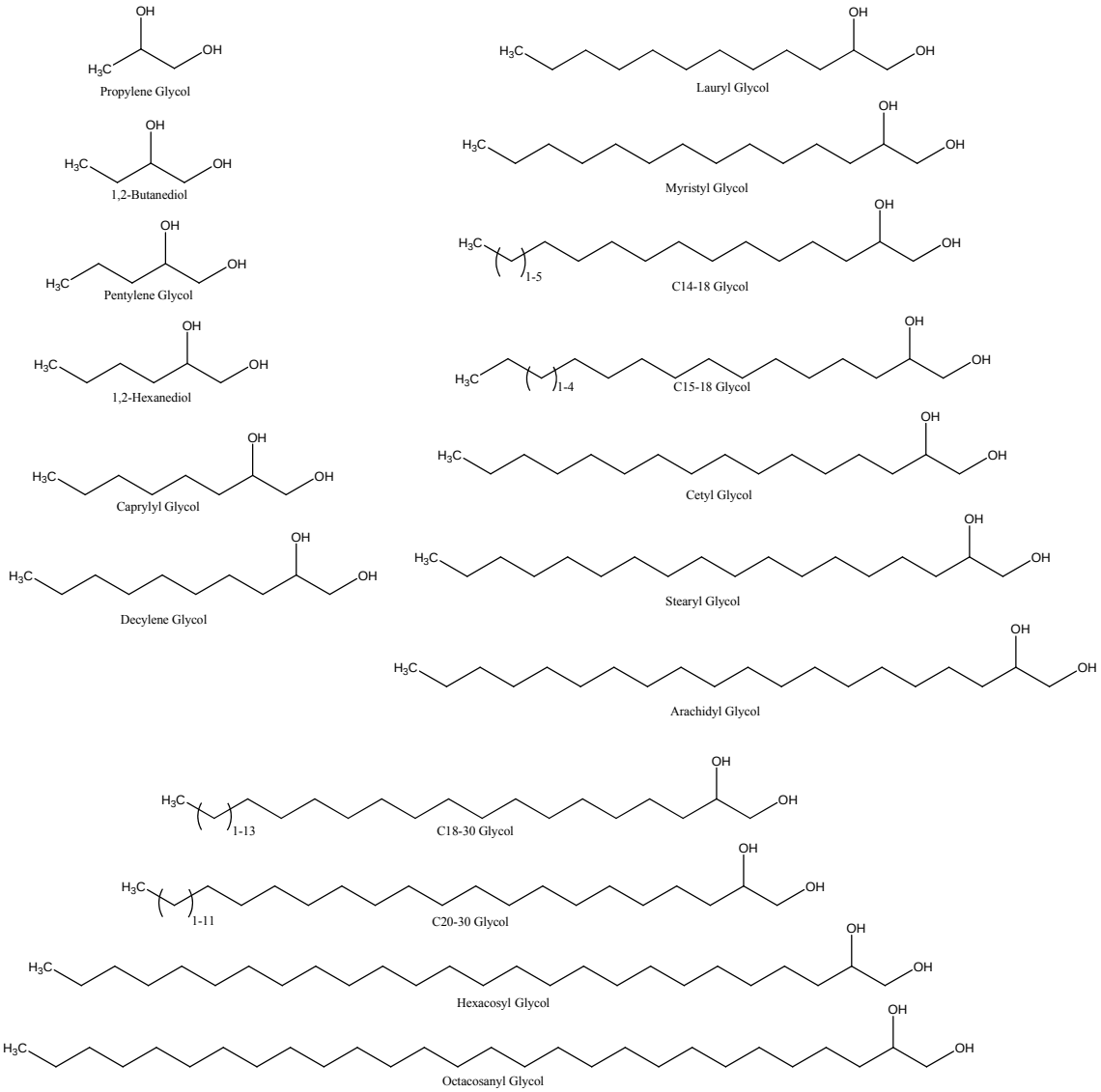


Table 5. Retrospective analyses with propylene glycol

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[73]
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[74]
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[75]
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[76]
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[77]

IVDK – Information Network of Departments of Dermatology
NACDG – North America Contact Dermatitis Group
SGD – scattered generalized distribution
SPIN – significance-prevalence index number, a parameter that assesses the relative importance of different allergens

Figure 1. Formulas of 1,2-Glycols



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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: March 25, 2011

SUBJECT: Comments on the Tentative Report on 1,2-Glycols as Used in Cosmetics

p.1 - As this is the Tentative Report, the Abstract should be included in the report so it can be reviewed by the public.

p.3 - In is not clear how the following is related to the Noncosmetic Use of Caprylyl Glycol. "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." Is there something missing that would relate this sentence to Caprylyl Glycol?

p.3, 23 - The information on esterified butylene glycol is not relevant to this report.

p.5 - The summary of the Percutanous Absorption section should summarize the information on Propylene Glycol percutaneous absorption. The following sentence should be deleted from this summary. "Propylene Glycol is metabolized to lactate in mammals."

p.5, Percutaneous Absorption Summary and Description of Caprylyl Glycol Dermal Penetration Study, p.23 - Only a total of 55% of the Caprylyl Glycol applied to the pig skin was recovered. Therefore, it does not make sense to state that "approximately 97% of the test solution was dermally absorbed within 24 hours." Please look at the Figure in Section 3.4 of the study. Approximately 97% of the recovered material (rather than 97% of the applied material) was found in the skin. It also does not make sense to state "Caprylyl Glycol was not detected in the receptor fluid, and, thus was not percutaneously absorbed." What is the difference between "dermally absorbed" and "percutaneously absorbed"? It is correct to state that Caprylyl Glycol was not detected in the receptor fluid, likely a result of metabolism in the skin rather than it not being absorbed into the skin. If the investigators would have used radiolabeled Caprylyl Glycol, they probably would have found radioactivity in the receptor fluid. But they were only measuring the parent compound, which they showed partially disappeared when it was incubated with pig skin.

p.5 - In the Propylene Glycol penetration study (first paragraph), did the investigators really study cumulative penetration of Propylene Glycol, or were they measuring radioactivity.

p.8 - In the summary of the Acute Intraperitoneal Exposure section the substance that resulted in muscle incoordination in rats at an ip dose of about 2.94 g/kg is not clear.

p.9 - If the heading Repeated Dose Oral Exposure is going to be used, all of the repeated dose oral exposure studies should be in this section. If the duration subsection (Subchronic and Chronic Oral Exposure) is left in this report, the Repeated Dose Oral Exposure subsection needs to be called Short-term Oral Exposure. As only oral studies are described in this section "and Parenteral" needs to be deleted from this heading.

p.9 - The following sentences need to be deleted from the Repeated Dose Oral (or Short-term Oral) Exposure summary as these studies are not described in this section. "Repeated applications of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects." "Intravenous dosing with PG over a 2-week period resulted in little toxicity in rats." The 2-week intravenous study of Propylene Glycol in rats does not currently appear to be presented anywhere in this report.

p.10 - In the summary of the Subchronic Inhalation Exposure section, "22 mg/liter" needs to be changed to 2.2 mg/liter (or there should be a study in the section that includes a 22 mg/liter exposure concentration). The summary should also state what happened to the rats exposed to Propylene Glycol at 2.2 mg/liter for 13 weeks.

p.11 - Please included the concentrations (or doses) that resulted in effects in the summary of the Cytotoxicity section.

p.12 - In the summary of the Ocular irritation section, please use the INCI name rather than the trade name.

p.13 - What are the units of TH10, minutes, seconds?

p.14 - The sentence about Propylene Glycol in the summary of the Skin Irritation and Sensitization section does not adequately reflect the information presented later in the report. Propylene Glycol was negative for dermal sensitization in several guinea pig studies, but 0.5 ml resulted in weak sensitization in one study. If available, the concentrations/doses that were not sensitizing should be included in the section.

p.15 - Rats were only exposed to 1,2-Hexanediol during gestation. Therefore, in the summary of the Reproductive and Developmental Toxicity section, it would be more appropriate to call this study a developmental toxicity study (as in the body of the section), rather than a "prenatal reproductive toxicity" study.

p.16 - Please provide the duration of exposure used in the *in vitro* study of Propylene Glycol in mouse zygotes.

p.17, 24 - In the summary of the Genotoxicity section, please use the test concentrations rather than the purity of the Caprylyl Glycol tested. Units of mg/ml are concentrations, rather than dose.

p.20 - In the last paragraph, please include the name of the ingredient the deodorant sticks contained at 35%, 65.2% and 73%.

p.22 - Please revise the following sentence, "Patch test results generally had a positive reaction to PG in these case studies." Perhaps you mean that the cases had positive patch test reactions to Propylene Glycol.

p.22 - In the Summary, please include the use concentrations of Pentylene Glycol that were reported and list the ingredients for which no concentration of use information is available.

p.23 - The following sentence can be deleted because the previous sentence describes modeling (using partition coefficients) used to predict dermal penetration. "Also, because of the limited percutaneous absorption data, the available octanol/water partition coefficients were used to

predict skin penetration in the absence of *in vitro* percutaneous absorption data on other 1,2-glycols." If this sentence is left in, what are the predictions?

p.24 - Move the Propylene Glycol study in the first paragraph on this page with the rest of the Propylene Glycol studies. Did the formulation really contain 1000 mg/kg Propylene Glycol? Or were the rats dosed with 1000 mg/kg bw of the formulation?

p.24 - In the Summary please provide the species used in the negative maximization test of Caprylyl Glycol.

p.25 - Please do not use "currently" as the information will not be "current" by the time the report is published. Use of the actual date information or "more recent" would be more appropriate.

p.25, fifth paragraph - The studies in nude mice are described twice in this paragraph.

p.25 - In what media was the 5% concentration (reproductive and developmental toxicity study in mice)?

p.25 - What concentrations of Propylene Glycol were used in the SCE assay using human cultured fibroblasts and Chinese hamster cells?

p.25 - What species was used in the study in which Propylene Glycol and oleic acid synergistically enhanced the penetration of both compounds?

p.26 - The first paragraph of the Discussion appears to apply that there were only studies of Propylene Glycol used to support the safety of these ingredients. In the first paragraph, it would also be helpful to note that there were also studies concerning 1,2-Butanediol, Caprylyl Glycol and Decylene Glycol.