PINK BOOK 2

Caprylyl Glycol

CIR EXPERT PANEL MEETING

AUGUST 30-31, 2010

Cosmetic Ingredient Review
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Memorandum

July 30, 2010

To: CIR Expert Panel

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Subject: Caprylyl Glycol and Other 1,2-Glycols

A copy of the tentative safety assessment (draft) on these ingredients is included along with the following: CIR report history, minutes from the June 28-29, 2010 Expert Panel meeting, literature search strategy, comments from the Personal Care Products Council, and safety test data received from the Personal Care Products Council (described below). Studies from a BIBRA toxicity profile on 1,2-Butanediol, received after the last Panel meeting, are identified by a vertical line in the right margin of the report text. Data on Propylene Glycol from the CIR final safety assessment and amended final safety assessment on this ingredient are included (in italics) for use in the safety assessment of other 1,2-glycols, i.e., in the absence of safety test data. A draft discussion relating to the skin penetration enhancement property of 1,2-glycols is also included for the Panel's review.

At the June 28-29 CIR Expert Panel meeting, 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 use concentration data received are included in Table 3. Skin sensitization and other safety test data on decylene glycol, 1,2-hexanediol, caprylyl glycol, and a 50:50 (w/w) mixture of 1,2-hexanediol and caprylyl glycol were received from the Personal Care Products Council after the draft safety assessment was finalized for the Panel's review, and, thus, are not included in this report, but are included in full in the Data section of this panel book. Data on longer chain glycols, e.g., C15-18 glycol were not received.

After reviewing the tentative safety assessment (draft), the Expert Panel needs to determine whether the available data (including propylene glycol) are sufficient for arriving at a conclusion on the safety of 1,2-glycols in personal care products.

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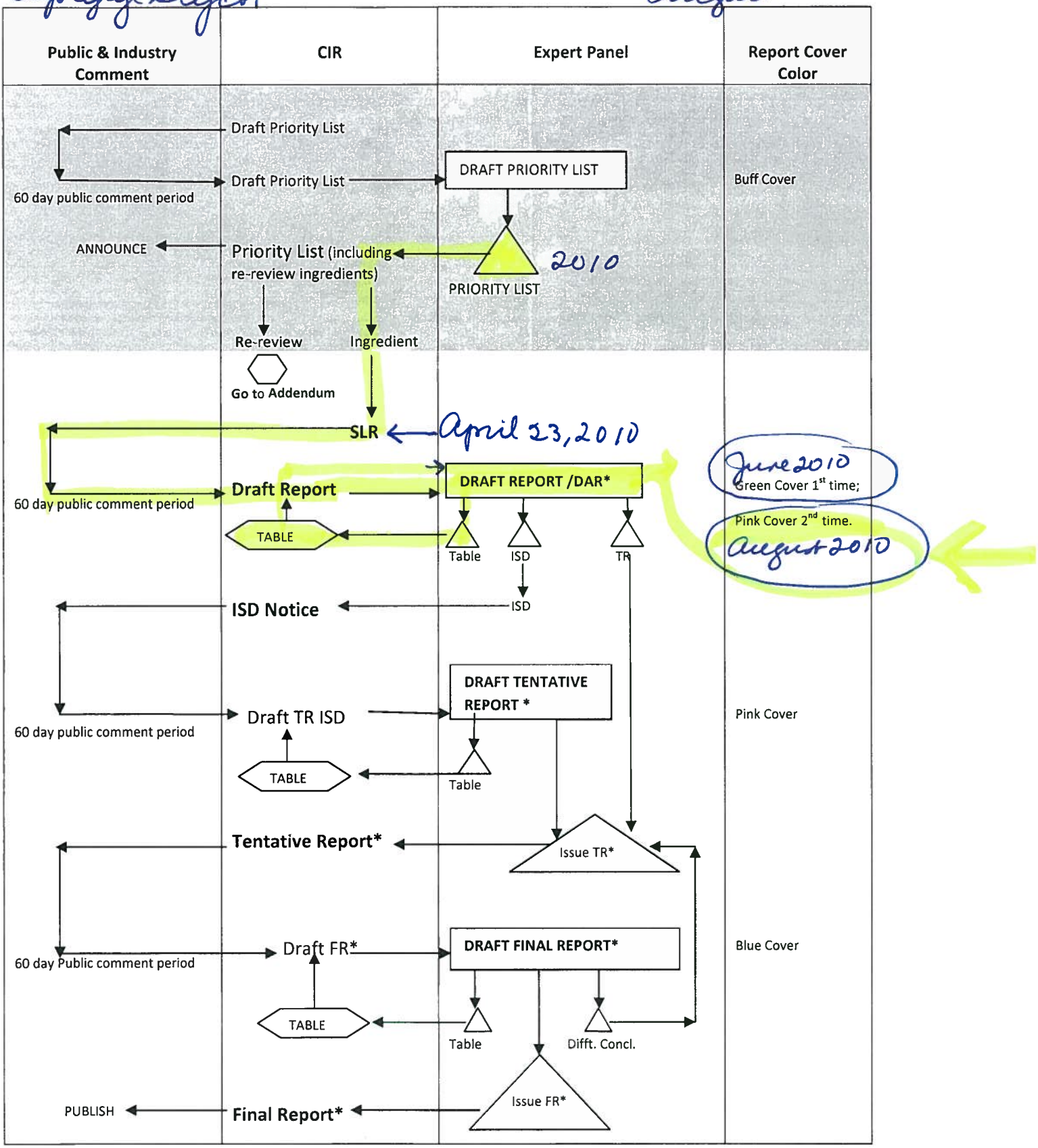
SAFETY ASSESSMENT FLOW CHART

Caprylyl Glycol

August 2010



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

△ Expert Panel Decision

▭ Document for Panel 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: June 28-29, 2010

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

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

Ingredients

1,2-glycols

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

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

(HG) Hexacosyl Glycol OR Hexacosil glicol

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

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

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

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

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

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

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

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

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

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

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

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

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

Branched 1,3-glycols

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

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

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

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

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

Terminal glycols

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

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

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

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

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

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

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

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Transcripts/ Minutes

DR. MARKS: Okay. Next is Caprylyl glycol, Green 2.

DR. HILL: I think that's potayto, potahto, by the way.

DR. MARKS: So this is the first time

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the Panel's seen this. A scientific literature review was issued in April. And we have things like -- issues like read-across data okay. Obviously, what data needs are there?

And I'll open it up to Rons and Tom.

DR. SHANK: I had no data needs.

DR. SLAGA: I also (inaudible) the data in evaluating the safety of, you know, 1, 2-glycols (inaudible).

DR. MARKS: Okay. So, no data in each, Ron. And then on page 21, and 22, are formulas for the 1,2-glycols. Those all -- nothing should be deleted out of that. Do you --

DR. SHANK: Actually, I recommend -- I think propylene glycol, because it's a reference. Throughout the report, we refer to propylene glycol, even though it's not a 1, 2-glycol.

Just put that in as a -- because it's a reference compound.

DR. HILL: Propylene glycol is a 1,2-glycol, is it not? I think so.

DR. MARKS: So, Ron, are you suggesting

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-- and that's one of the questions I have -- we combine with propylene glycol? So that would be -- would that mean you open propylene glycol, which we had a "safe" with "non- irritating" conclusion?

DR. SHANK: No, I was just suggesting that the structure --

DR. MARKS: The structure --

DR. SHANK: -- be given somewhere in the report, since we refer to it frequently in the report.

DR. HILL: So, in terms of long-chain glycols here, we have only cytoxicity for cetyl glycol. We have only cytotoxicity and ocular irritation for lauryl glycol, and cetyl C16 -- right? So, we're being asked to extrapolate to -- it looks like C28 and C20, C20 to 30 mixtures, C18 to 30 mixtures. And I'm bothered by that because there's a shift in cellular processing once you get to longer chains.

And, in fact, if you look at where the data clusters, most of it's pentylene, the C4 and

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the C6 -- very little data outside of that, based on what's in this report, at least.

DR. MARKS: We have irritation and sensitization on the --

DR. HILL: In caprylyl, which is lead --
DR. MARKS: -- hexanediol.
DR. HILL: -- caprylyl, which is the lead ingredient.
DR. MARKS: Right -- which were okay.
DR. HILL: That's C8, right? So we really, we have data that, to me, gives a comfort level with read-across, really up to C8. Not much else I read.
And specifically, with respect to that question on page 2, which is Panel book page 4, you have some branched 1,3s that are listed in here, and they're not included, right? I mean, it's only place I see anything about that in the whole report.
MR. JOHNSON: What page are you on, please?
DR. HILL: Panel book, 4. It looks like

report page 2. Or no, I'm sorry. It's Panel book page 4. It's the literature search. This is just getting literature search, right?
MR. JOHNSON: Yes. Okay. I see where you are.
DR. HILL: But there's nothing -- I'm not sure that the branched 1,3s relate to anything else in the report, do they? Nor do the terminal glycols relate to anything else that's in the report, I think.

Those are very different compounds, in terms of biology.

MR. JOHNSON: Yes -- what happened is that initially, all of those were included in one group --

DR. HILL: Mm-hmm.

MR. JOHNSON: -- but the safety assessment was only on the one key glycol.

DR. HILL: Okay. So maybe -- I guess this is not part of the report anyway.

MR. JOHNSON: No, (inaudible).

DR. HILL: So in a lot places, we can

look at these categories, really data on one or two compounds -- I mean, they're all very small. So, again, we're looking at trying to extrapolate to much longer molecules. And I know that probably the rationale is, well, they don't penetrate the skin as efficiently would be maybe the best way to state that, but --

MS. EISENMANN: Well, primary uses of just (inaudible) compounds, there seems to be a little use of --

DR. HILL: Mm-hmm. I agree.

MS. EISENMANN: -- insofar, in concentration of use information is still out. It's only those three that I'm getting "uses" for.

DR. HILL: Right.

DR. MARKS: So what was the

concentration of use? I had a question on that.

MS. EISENMANN: I don't have it in yet.

DR. MARKS: Okay.

MS. EISENMANN: It's not complete. So I can bring it. But I can say, generally, I think it's less -- it's 1 percent and less.

DR. MARKS: Okay.

MS. EISENMANN: But it's those three compounds that are (inaudible).

DR. MARKS: (inaudible), do you remember what you were going to say?

This brings the general question, Alan, which is -- when a grouping is established, then there will be a certain frequency of use. I guess it comes out of the BCRP, right? Related to that.

So if we're using a threshold, so many uses and then this triggers to be on the priority list, or at least looked at for the priority list. And then we subsequently reduce the size of the groupings substantially, that doesn't change anything, right? I mean, in terms of it's now on the priority list, and lets say we go from 400 to 200 in terms of frequency of use by virtue of cutting down on ingredients, does that matter? Once we've started down the road, we can go down the road?

MR. ANDERSEN: Were we to, for some reason, decide that the lead ingredient, caprylyl

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

DR. MARKS: Sure.

MR. ANDERSEN: But --

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

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

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

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

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

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

DR. HILL: Right, because in that case

you'll be looking at emulsions and (inaudible) type (inaudible).

MR. ANDERSEN: Yes.

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

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

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

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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,

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there's an implicit green light.

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

DR. HILL: Already.

MR. STEINBERG: Yes.

DR. HILL: Yes.

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

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

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

MR. STEINBERG: Right.

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

DR. MARKS: Plus, there would have been

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

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

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

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

DR. MARKS: Right. Above --

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

I made myself a little table --

DR. MARKS: Okay.

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

DR. MARKS: Right. So, with that caveat from Ron -- again, Ron Shank, Tom, do you feel

comfortable including -- and we've certainly done it before -- these other ingredients which are not being used at this point, based on the safety data we have now, so that we could move forward with the ingredients as listed and, say, moving toward

a "safe," issue a tentative report "safe?"

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

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

DR. SLAGA: You two have a --

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

DR. HILL: It is.

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

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

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

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

DR. MARKS: Yeah.

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

DR. MARKS: Yeah. Rachel.

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

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

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

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

MR. BAILEY: I don't see anything -- I

mean, the whole idea of (inaudible) and read-across, regardless of frequency of use, is to be able to extrapolate and use information that's available along the, you know -- it's sort of the fundamental nature of the compound.

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

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

DR. HILL: As a medicinal chemist,

lesson number one is, you can have something that's perfectly inactive, and you add two carbons, and you can have suddenly something that's very active.

We shouldn't really ever extrapolate, unless we have comfort level that, okay, it's

molecular weight 5,000, log P of 20, won't get in the skin.

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

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

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

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

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

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

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

DR. HILL: I'm not worried about

anything happening systemically here. I'm thinking of things strictly that might happen within the skin.

DR. SLAGA: Well, I'm saying that if there is a receptor-type mechanism of a natural

compound, then you can get things --

DR. HILL: I think we used --

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

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

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

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

DR. SLAGA: No.

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

MR. ANDERSEN: Yes, it is.

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

So I just have this -- my gut is

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

So -- I don't know.

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

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

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

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

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

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

about.

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

(Laughter)

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

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

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

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

in the introduction, or in the --

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

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

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

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

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

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

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

DR. MARKS: Alan.

MR. ANDERSEN: I think, there are data

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

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

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

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

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

DR. MARKS: Mm-hmm.

MR. ANDERSEN: Traditionally, with log

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

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

MR. ANDERSEN: Small.

DR. HILL: If it's -- yes. And in this case, it is small.

MR. ANDERSEN: Hence, the empirical data --

DR. HILL: Right.

MR. ANDERSEN: -- that would take any doubt out of it. So actually sensitization and irritation would be a perfectly reasonable thing to request.

It's the first time we've looked at it.

Carol made the point earlier that there may not have been a lot of time to gather data. So if we're (inaudible).

MR. BAILEY: Well, I would object to calling it "insufficient data." If the Panel feels like there's more data needed and we haven't had time to produce it, then I don't think "insufficient data" tool is necessarily the way to go. You might want to table it with a request.

But I think it really -- I mean, in my mind, the first criteria is do you really expect this to be an outcome? In other words, you know, that there would be a sensitization potential for this, number one. Number two, I mean, we bring a lot of expertise and experience to the (inaudible) that I have.

But I think if you really expect it,

then I would say -- in your professional opinions -- to ask for it. If you don't expect it, then I think it's a little questionable to invoke an "insufficient data," and then ask for something that you think that you may not need anyway.

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I mean, I would rather use the resources and efforts of the Science and Support Committee and this Panel to focus on those areas where you really think there's going to be an issue.

So, I mean, just for a kind of a reality check here, in the process.

I mean, we're more than happy to respond to "insufficient data." But I think it really sends a very different message than what's really (inaudible).

DR. MARKS: Well, do we expect to find any data other than for the C15-18 glycol?

MR. BAILEY: Well, you know, I don't know.

DR. MARKS: I mean, that's the only higher weight ingredient being used. So then I think we're still back to, to my mind, to the C15-18. If we have it, fine. If we don't have it, then what do you do with 28? What do you do with 20? What do you do with 14?

MR. BAILEY: Well, I think the chances, in this situation -- and there may be other

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

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

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

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

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

DR. SLAGA: Well, can we, as it was

stated, to see if there is data out there? Request if there is any higher, just for --

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

DR. HILL: The company's using it. So, I mean, I agree with you. It's -- suppose there's

just one company that's using it. They may just decide it is in their best interest to provide data that they have sitting behind the firewall.

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

Do you still like the "insufficient data?"

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

This procedure is in place to keep these things moving forward. And the option to table, in my mind, has to be very specific against an

expectation that you know it's there and you just need to some time to look at it.

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

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

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

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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

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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 23rd. So the 60-day time period was June 23rd. So it did get sent to you before the 60-day time period was over.

DR. MARKS: One could argue both ways, Tom. It's probably good we didn't have the concentration of use, because it gives us a way of handling the issue of higher molecular weight and sensitization. So I'm going to suggest tomorrow, move for our team, that although I'm not the one presenting it, that we table for concentration of use data, and that we would also like to say irritation and sensitization data on the higher --

DR. SLAGA: If it were possible.

DR. MARKS: Yes -- higher weight which,

in this case, is really going to be C15-18, probably, since that's the only one being used.

And then the other thing, Ron -- I want to go back -- Ron Shank, and just be sure we're clear on this.

In the introduction it says, "Propylene glycol is a very short chain 1,2-gliol [sic]." And you, if I heard you correctly, right in the beginning, you said is propylene glycol really a 1,2-gliol [sic]?

Did I hear you right?

MR. JOHNSON: Glycol.

DR. MARKS: So we need to be sure that that statement --

DR. SHANK: I was on California time. I'm sorry.

DR. MARKS: Okay. So propylene glycol is a 1,2. Thank you, Wilbur.

Okay. Any other comments? Well, that was a robust discussion.

SPEAKER: (inaudible)

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

DR. ANSELL: We --

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

DR. ANSELL: Right, and that's basically what the situation was. When we started reviewing the timeline and updating the procedures, we were

really thinking about the old way where you'd identify an ingredient and then we could go out.

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

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

DR. ANSELL: Well, I think the concern

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

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

August -- hopefully -- what the anticipated family will be.

But I mean, this is -- I guess this is -- it's just a little bit exasperating because I guess the other issue is, you know, we're looking at propylene glycol at this meeting and I think a lot of the information -- this report is quite thin. But a lot of the information from propylene glycol could be incorporated in here as a read across. And while we're on it, if we just knew what the concentrations of use of these 1,2 diglycols were, I'd be fine with going safe as used and then moving ahead. But unfortunately we can't, and when it comes time to the next meeting when we look at it, I'm not going to remember all the propylene glycol stuff anymore. It's going to

be wasting a lot of my time.

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

summaries of the propylene glycol data brought in here.

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

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

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

DR. BELSITO: No.

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

And you guys got it actually before the

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

DR. BERGFELD: How much time do you need?

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

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

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

DR. BERGFELD: This one you had two months.

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

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

DR. ANSELL: Yeah, I think she needs two

to three months to pull this together.

DR. KLAASSEN: I guess I was thinking is that until this data is available for these documents, maybe the entire document shouldn't be sent to the committee. Are we kind of wasting our

time a little bit of reading this and then forgetting most of it and having to read it again in August, for example? Maybe the committee shouldn't receive the document until that information is there. I don't -- just a suggestion.

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

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

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

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

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

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

DR. BERGFELD: And you'll table this?

DR. BELSITO: Yeah, it's tabled.

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

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

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

DR. BERGFELD: Is there a second?

DR. MARKS: Second.

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

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

the C15 to 18 glycols.

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

Report

Tentative Report

Caprylyl Glycol and Other 1,2-Glycols

August 30, 2010

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

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INTRODUCTION

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

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

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

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

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

CHEMISTRY

Definition and Structure

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

Chemical and Physical Properties

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

Methods of Production

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

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

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

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

Impurities

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

Analytical Methods

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

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

Based on the chemical formulas included in Figure 1, there is no reason to suspect that any meaningful UV absorption would be associated with these 1,2-glycols.

Reactivity

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

USE

Purpose In Cosmetics

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

Scope And Extent Of Use In Cosmetics

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

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

Noncosmetic Use

Cetyl Glycol

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

Stearyl Glycol

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

Caprylyl Glycol

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

1,2-Butanediol

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

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

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

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

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

1,2-Butanediol

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

Propylene Glycol

The original 1994 CIR final safety assessment reported that, in mammals, the pathway of PG metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases.[1] *When PG was administered i.v. to human subjects (patients), elimination from the body occurred in a dose-dependent manner.*

Percutaneous Absorption

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

Propylene Glycol

The dermal penetration of [^{14}C]PG through excised female hairless mouse skin from the ternary cosolvent containing 10 mol% oleic acid and 6 mol% dimethyl isosorbide in 84% PG was determined. [20] *Over a 24-h period, the cumulative penetration of PG was 57.1% of the applied amount.*

The dermal absorption of PG was determined in the outermost layers of skin using TED-FTIR spectroscopy.[21] *PG was applied to the fingertip of one human subject for 30 min using PG-soaked cotton wool. The site was wiped and allowed to dry for 1 min. The thickness of the surface layer of stratum corneum probed was 0.71 µm. Measurements were performed every 25 min over a 3 h period, with one measurement taking 15 min. The concentration of PG remaining at the surface of the stratum corneum decreased over time. At 12 and 32 min, the maximum concentration of PG was found at a depth of <1 µm, while at 107 and 157 min, the maximum concentration of PG was found at a depth of 3-4 µm. At a depth of 6 µm, the greatest concentration of PG, 0.2%, was seen at 32 min. The authors suggested that PG molecules diffuse into stratum corneum only to a depth of 6-7 µm, approximately. The researchers also suggested that PG molecules do not reach the dermis.*

Skin Penetration Enhancement

The skin penetration enhancement effect of caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol has been demonstrated in vitro. Skin penetration of the following was enhanced: ^{3}H-corticosterone, ^{3}H-triethanolamine, and dihydrovenanthramide D. PG can act as a penetration enhancer for some chemicals and under some conditions. Often, it works synergistically with other enhancers. The mechanism by which PG enhances penetration has not been definitively identified.

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

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

Pentylene Glycol and 1,2-Butanediol

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

Propylene Glycol

PG has been described as a penetration enhancer, and penetration enhancers act by various mechanisms to perturb diffusional pathways through the skin. Proposed mechanisms of penetration enhancement by PG include alteration of barrier function by its effects on a keratin structure or a PG-induced increase in the solution capacity within the stratum corneum.[20]

ANIMAL TOXICOLOGY

Acute Inhalation Toxicity

1,2-Butanediol

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

Acute Oral Toxicity

Oral toxicity data on Caprylyl glycol 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. Overt toxic effects were not observed in ethanol-dependent rats dosed orally with 2.74 g/kg 1,2-butanediol. In the 1994 CIR final safety assessment[1], relatively high LD50s in rats resulted from oral dosing with PG.

Stearyl Glycol

An LD50 of > 5,000 mg/kg was reported for rats dosed orally with stearyl glycol.[23]

Caprylyl Glycol

The acute oral toxicity of caprylyl glycol was evaluated using male and female rats (number and strain not stated).[24] 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.

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).[23] Efforts to obtain the primary references for these studies are underway.

1,2-Butanediol

An acute oral LD50 of 4,192 mg/kg was been reported for 1,2-butanediol in a study involving female Swiss albino mice/ICR.[25] 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.[26] Also, high (unspecified) doses caused narcosis in rats (often leading to death in a few hours), dilation of the blood vessels, and kidney damage.

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

C15-18 Glycol

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

Propylene Glycol

The 24 h oral LD50 for PG was 22.8 g/kg body weight in a study involving 5 female Fischer rats. The lowest recorded 24 h oral lethal dose in this study was 20.9 g/kg body weight. Oral LD50 values (rats) of up to 27 g/kg body weight have been reported in other studies.[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.[19] Details relating to the test procedure were not provided; however, it was presumed that neat material was tested.

Propylene Glycol

The dermal LD50 for PG was > 11.2 g/kg in mice and was 13 g/kg in rats.[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-propanediol), and 1,2-butanediol were compared, caprylyl glycol had the lowest ED_3 value (1.5 mmole/kg), suggesting that its intoxication potency (i.e., ability to induce ataxia) was greatest. Mortalities were observed in mice at the highest i.p. dose of PG (10,400 mg/kg).

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

In a report by Shoemaker,[27] 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-propanediol), 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).[27]

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).[28]

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

Pentylene Glycol (1,2-Pentanediol)

An i.p. TDLo of 3,510 mg/kg has been reported for pentylene glycol in rats.[23] Efforts to obtain the primary reference for this study are underway.

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.[1]

An acute study was performed in which female ICR mice were dosed i.p. with 2600, 5200, or 10400 mg/kg PG.[29] *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.*

Acute Intravenous Toxicity

Propylene Glycol

Acute i.v. LD50's of 6.2 ml/kg (rats) and 6.4 ml/kg (mice) have been reported for PG.[1]

Acute Parenteral Toxicity – Other Studies

Propylene Glycol

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.[1]

Short-term Oral Toxicity

Short-term oral administration of 1,2-butanediol to rats yielded an NOAEL of 200 mg/kg/day. Signs of poisoning were noted at the highest dose of 22 g/kg/day in rats receiving 1,2-butanediol in the diet for up to 8 weeks; abnormalities were not observed in tissues from major organs. 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.

1,2-Butanediol

In an 8-week oral study, groups of rats were fed 1,2-butanediol at concentrations ranging from 5 to 40% in the diet (one dose level per group).[19] 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 poisoning 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.[30] Groups of Crj-CD(SD) rats (10 males, 10 females) were dosed orally, by gavage, with aqueous 1,2-butanediol at doses of 40, 200, or 1,000 mg/kg/day. Males were dosed daily for 42 days, and females were dosed from day 14 before mating to day 3 of lactation. Control rats (10 males, 10 females) were dosed with distilled water.

None of the animals died, and there were no differences in histopathological findings or the following parameters between test and control animals: body weight, food 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. [30] The estimated dose of low concern (EDLC) for this study was calculated as 0.2 mg/kg/day.[7]

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.[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.[31] *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.*

Short-Term Intravenous Toxicity

Propylene Glycol

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.[1]

Repeated Oral Dose Toxicity

1,2-Butanediol

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

Repeated Dermal Dose 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.[19] Details relating to the test procedure were not provided; however, it is presumed that neat material was tested.

Subchronic Inhalation Toxicity

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

Propylene Glycol

Male and female Sprague-Dawley rats (number per group not given) were exposed to 0.16, 1.0, or 2.2 mg PG/l air for 6 h/day, 5 days/wk, for 13 wks in a nose-only inhalation study.[32] 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.

Subchronic 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 (50,000 ppm in diet) PG given in the feed for 15 wks did not produce any lesions.

Pentylene Glycol

Pentylene glycol was administered orally to rats, intermittently over a 28-week period. A TDLo of 2,450mg/kg was reported.[23] Efforts to obtain the primary reference for this study are underway.

Propylene Glycol

No toxic effects were seen in a subchronic oral toxicity studies in which rats were fed 50,000 ppm PG in the diet for 15 weeks, and dogs received 5% PG in drinking water for 9 months and 10% PG in drinking water for 6 months.

Chronic Oral Toxicity

Propylene Glycol

No toxic effects were reported when rats or dogs were given feed containing PG in chronic studies. Rats received up to 50,000 ppm PG in the diet for 104 weeks, and, in another study, dogs received 2 g/kg PG in the diet for 104 weeks.[1]

Cytotoxicity

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

Cetyl Glycol

In an antitumor activity test, 1,2-hexadecanediol (cetyl glycol) was injected intraperitoneally (i.p.) into 8 inbred C57BL/6 mice in which Ehrlich ascites carcinoma (EAC) cells had been implanted. Doses of 80/mg/kg/day were injected for 10 consecutive days. The survival of mice was monitored over a 2-month period. Compared to control mice, dosing with cetyl glycol prolonged the lifespan of animals more than 2.7-fold. Antitumor effects were described as marked, in that 4 of 8 mice injected were alive, with scarce tumor proliferation, at 60 days. Cetyl glycol (130 μg/ml) was found to have a cytocidal effect (irreversible cell degeneration) on cultured EAC cells.[33]

Lauryl Glycol

Osorio e Castro et al.[34] studied hemolysis rates (at 37ºC) of human erythrocytes induced by C_2 and C_8-C_{14} straight chain 1-alkanols, 1,2-alkanediols, and the corresponding benzilidene derivatives (benzaldehyde acetals). The most active compound was 1-dodecanol (50% hemolysis at 15 μM), followed by 1,2-dodecanedol (lauryl glycol, 50% hemolysis at 99 μM) and the C_{10} benzylidene acetal (50% hemolysis at 151 μM).

Pentylene Glycol

Anselmi et al.[35] conducted an *in vitro* DNA fragmentation assay (human promyelocytic leukemia cell line [HL60]) to investigate the apoptosis- and necrosis-inducing potential of brief, 10 min applications of the preservative, pentylene glycol (between 0.01 and 5% [usual concentration as a preservative]). Cells treated with phosphate buffered saline served as controls. The percentage of apoptotic cells was quantified by analysis of DNA content. Pentylene glycol induced apoptosis only at a concentration of 5%. Externalization of phosphatidyl serine, a hallmark of apoptosis, was concomitant with the subdiploid DNA peak in HL60 cells treated with pentylene glycol.

Propylene Glycol

The cytotoxicity of PG was determined in assays that measured inhibition of human foreskin fibroblasts and keratinocytes, inhibition of collagen contraction by fibroblasts, and changes in cell morphology of fibroblasts and keratinocytes.[36] 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.[36] 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.

Ocular Irritation

Based on Draize test results, lauryl glycol has been classified as a severe ocular irritant. Reportedly, undiluted 1,2-butanediol , but not 10% aqueous, induced ocular irritaton in rabbits. In studies reported in the 1994 CIR *final safety assessment[1] and the amended final safety assessment,[2] undiluted PG was, at most, a slight ocular irritant.*

Lauryl Glycol

According to Worth and Cronin,[37] 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 nonirritants by using *in vitro* endpoints of the hen's egg test on the chorioallantoic membrane (the HETCAM test) and the neutral red uptake (NRU) test.

According to one of the prediction models for eye irritation potential, a chemical is more likely to be an eye irritant if its log (TH10) value is low (i.e., if a 10% solution of the chemical produces rapid hemorrhaging of the chorioallantoic membrane) and if its log (IC 50) value is low (i.e., if the chemical is cytotoxic to 3T3 cells). TH10 is defined as the mean detection time for hemorrhage in the vascularized chorioallantoic membrane of embryonated chicken eggs. The IC50 is defined as the concentration of test chemical (mg/ml) resulting in 50% inhibition of neutral red uptake in 3T3 cells. The TH10 and IC50 values for lauryl glycol were 171.0 and 0.02, respectively. [37] Using a logarithm calculator, log 0.02 = -1.70 and log 171.0 = 2.23.

1,2-Butanediol

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

Propylene Glycol

PG (0.1 ml, pH 8.8) was a slight ocular irritant in rabbits in one study, but PG (0.1 ml, pH unknown) did not induce ocular irritation in another study involving rabbits.[1]

The ocular irritation potential of PG was determined using groups of 6 male and female New Zealand white albino rabbits.[38] *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*.

Skin Irritation and Sensitization

Reportedly, repeated applications of 1,2-butylene glycol to the skin of rabbits did not result in skin irritation. 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.

1,2-Butanediol

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

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.[1]

The dermal irritation potential of 100% PG was evaluated with male hairless SKH1 hr/hr mice.[39] *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).*

Immunological Cross Reactivity

There was no evidence of cross reactivity between antipanaxytriol antibody and decylene glycol.

Decylene Glycol

Saita et al.[40] studied the cross reactivities of antipanaxytriol antibody with panaxytriol analogues using the enzyme-linked immunosorbent assay (ELISA). Panaxytriol is an antitumor polyacetylenic alcohol that has been isolated from the roots of *Panax ginseng* C. A. Meyer. The antibody had a high affinity for 1,16-heptadecadiene-4,6-diyne-3,9,10-triol, which is structurally different from panaxytriol only in the C-16,17 positions. The antibody had very limited reactivity with the other panaxytriol analogues, which are different only in the D9,10 positions. No reactivity was found between the antibody and a 1,2-decanediol (decylene glycol). The authors noted that these results indicate that the antibody recognition sites are both the glycol and moiety and the diacetylene moiety of the panaxytriol molecule.

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 studies reviewed in the 1994 CIR final safety assessment[1] and in the amended final safety assessment,[2] 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.

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.[30] The estimated dose of low concern (EDCL) for this study was calculated as 10 mg/kg/day.[7]

Propylene Glycol

The reproductive and developmental effects of PG were evaluated using mice, rats, rabbits, and hamsters.[41] 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.

PG was used as a vehicle in a reproductive and behavioral development study.[42] It was administered to 15 gravid Sprague-Dawley rats orally by gavage on days 7-18 of gestation at a volume of 2 ml/kg. PG did not have any effects on reproductive or behavioral development parameters.

Embryotoxicity

In the 1994 safety assessment, embryonic development was reduced or inhibited completely in cultures of mouse zygotes exposed to 3.0 or 6.0 M PG, respectively.[1] A 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.

Propylene Glycol

Female ICR mice were used to determine whether PG induced cytogenetic aberrations in mouse metaphase II (MII) oocytes that predispose zygotes to aneuploidy.[29] Groups of mice were first given an i.p. injection of 7.5 IU eCG to augment follicular maturation followed 48 h later with 5 IU hCG to induce ovulation. After 3 h, mice were dosed i.p. with 1300, 2600, or 5200 mg/kg PG in distilled water. A control group was given distilled water only. For the MII portion of the study, ovulated oocytes were collected from 20 test animals/group and 30 control animals and processed for cytogenetic analysis 16 h after administration of PG. The number of oocytes collected from test animals was non-statistically significantly increased compared to controls. A statistically significant change in hyperploidy, hypoploidy, or single chromatids was not observed. An increase in the frequency of PCS at each dose was statistically significant, and the incidence of premature anaphase was statistically significantly greater in the 5200 mg/kg dose group as compared to controls. Neither metaphase I nor diploid oocytes were found.

For the zygote portion of the study, the female mice were paired with 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.[29]

GENOTOXICITY

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*.

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.[43]

Propylene Glycol

In the 1994 CIR final safety assessment, ≤10,000 µg/plate PG was not mutagenic in Ames tests with or without metabolic activation.[1] 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).

CARCINOGENICITY

Propylene Glycol

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

CLINICAL ASSESSMENT OF SAFETY

Synergistic Penetration

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.[44] 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.[45] TEWL was determined using 10 subjects (number of males and females not specified) with application of occlusive chambers containing nothing, 300 µl PG, or 300 µl 0.16 M oleic acid in PG, for 3 or 24 h. The fourth site was not treated and not occluded. TEWL measurements were started 3 h after chamber removal to reduce volatile solvents on the skin surface in order to avoid interference with the Evaporimeter™. The site treated with oleic acid/PG increased water loss for a longer period in comparison to the PG only or empty sites. The 3 and 24-h applications of PG resulted in an enhanced water loss ratio of 1.1. With oleic acid/PG, these values were 2.0 and 2.1, respectively.

For the ATR-FTIR portion, an occlusion system containing PG or oleic acid/PG was applied to the forearm of each subject; a third site was untreated. The chambers were removed after 3 h, and ATR-FTIR spectra were recorded. Upon removal at the site where oleic acid/PG was applied, the absorbance at the wavelength measuring free acid indicated the presence of extra free acid, while the absorbance at the wavelength characteristic of esterified ester lipids was similar to untreated and PG-treated sites. The absorbance ratio for these 2 wavelengths leveled off to that of the untreated site 3 h after removal of the chambers, indicating migration of oleic acid into lower cell layers or lateral spreading within the stratum corneum. The researchers also examined ATR-FTIR when the oleic acid/PG site was tape-stripped 5 times, removing 50% of the thickness of the stratum corneum, 2 h after removal of the application chambers. The results indicated oleic acid accumulates in a deeper layer after the tape stripping.[45]

Skin Irritation and Sensitization

A 1,2-hexanediol/caprylyl glycol mixture (in preservative system) did not induce sensitization at a concentration of 0.5% or 15% in human subjects. In studies reported in the 1994 CIR final safety assessment, PG induced skin irritation in normal subjects and patients, and both positive and negative reactions in skin sensitization tests involving normal subjects. Deodorants containing PG did not have skin irritation or sensitization potential in use studies .

Caprylyl Glycol and 1,2-Hexanediol

Levy et al.[46] 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.[46]

Propylene Glycol

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

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.[47] It has also been stated that subjective or sensory irritation sometimes occurs in volunteers after application of various concentrations of PG. Some researchers have proposed classifying skin reactions to PG into 4 groups: (1) irritant contact dermatitis; (2) allergic contact dermatitis; (3) non-immunologic contact urticaria; and (4) subjective or sensory irritation.

Predictive Testing – Irritation/Sensitization

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.

Propylene Glycol

A 24-h single insult occlusive patch test (SIOPT) was performed on an undiluted deodorant formulation containing 69.15% PG using 20 subjects (gender not specified).[48] A clear stick deodorant was used as a reference control. The test sites were scored on a scale of 0-4. With the test formulation, 4 subjects had a score of ± (minimal faint uniform or spotty erythema) and 3 subjects had a score of 1 (pink-red erythema visibly uniform in the entire contact area.) The primary irritation index (PII) for the deodorant containing 69.15% PG was 0.25. This product was significantly less irritating than the reference control, which had a PII of 0.93 and 17/20 subjects with scores between ± and 3.

In another SIOPT, a deodorant formulation containing 68.06% PG was tested undiluted using 20 subjects (gender not specified).[49] A deodorant currently in use was used as a reference control. Three subjects had a score of ± and 1 had a score of 1 to the test formulation. The PII for the test formulation was 0.13, which was not significantly different than the PII of 0.15 for the reference control.

The irritation index for PG and 0.16 M oleic acid/PG was determined using 12 subjects (number per gender not specified) by applying occlusive chambers containing these 2 test substance to the volar forearm for 3 or 24 h.[50] An empty chamber was applied to a third site, and the fourth site was an untreated control. Laser Doppler velocimetry (LDV) was used to measure blood flow upon removal. After 3 and 24 h, the irritation index for PG was 1.1 (6 subjects) and 1.2 (10 subjects),

respectively, indicating a 1-fold increase in blood flow to the test site. The irritation index for oleic acid/PG was 2.1 (6 subjects) and 3.9 (10 subjects) after 3 and 24 h, respectively. Visually, the 24-h application of PG produced only slight erythema, while the 24-h application of oleic acid/PG produced clearly visible irritation.

Thirty-day use studies were completed with 26 male, 40 female, and 24 male subjects to evaluate the potential for deodorant sticks containing 35,[51] 65.2,[52] and 73%,[53] 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.[54]

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

An RIPT was completed with 101 subjects, 30 male and 71 female, to determine the sensitization potential of a stick deodorant formulation containing 73% PG.[56] During the induction phase, semi-occlusive patches containing 0.2 g of the test material were applied to the upper back of each subject for 24 h, 3 times per wk, for a total of 9 applications. The first patch was scored (scale of 0-4) immediately after removal, while all others were scored prior to application of the next patch 24-48 h later. During the induction phase, a score of 2 (moderate reaction) resulted in moving the patch to an adjacent site while a second score of 2 or scores of 3-4 (marked-severe) resulted in discontinuation of dosing. The challenge was performed approximately 2 wks after the final induction patch using the same procedure but at an adjacent previously untested site. Challenge sites were scored 24 and 72 h after application. Scores of + (barely perceptible or spotty erythema) to 2, with some dryness, were observed throughout the study. Four subjects discontinued dosing during the induction phase because of a second moderate reaction. While the authors stated that a stick deodorant formulation containing 73% PG "did not indicate a clinically significant potential for dermal irritation or allergic contact sensitization," the Expert Panel questioned that conclusion since repeated reactions were observed.

Another RIPT was completed with 99 subjects to determine the sensitization potential of a stick antiperspirant formulation containing 86% PG.[57] (Initially, 113 subjects were enrolled in the study; withdrawal was not due to adverse effects.) Occlusive patches containing 0.2 g of the test formulation were applied to the infrascapular region of the back 9 times during induction and once during challenge. One "+" reaction was observed during the entire study. There was no evidence of sensitization with an antiperspirant containing 86% PG.

Provocative Testing-Sensitization

Patients with chronic venous insufficiency (CVI) had sensitization reactions to PG, whereas contact dermatitis patients did not.

Propylene Glycol

Thirty-six patients with CVI were patch tested with 5% PG in petrolatum by application to the back for 2 days.[58] Twelve patients were male; 2, 5, and 5, had 1st, 2nd, and 3rd degree CVI, respetively. Twenty-four patients were female; 5 and 19 had 2nd and 3rd degree CVI, respectively. (Procedural details not provided.) The results were read after 2 and 3 days; doubtful reactions were read after 4 days. The sensitization rate as a percentage of all patients was 8.3%. The sensitization rate of

patients with 2nd and 3rd degree CVI tested with PG was 10 and 8.3%, respectively. Significant differences were found between males and females; 12.5% of females were sensitized while 0% of males were sensitized.

During the period 2000-2004, 308 patients, 111 males and 197 females, with contact dermatitis were patch-tested using the European standard series and some additional chemicals, including PG.[59] Patches were applied to the upper back using Finn chambers that were held in place with Scanpor tape. The patches were removed after 2 days, and the sites were evaluated after 30 min and 4 days. PG, 5% in petrolatum, did not cause any positive reactions.

Photoallergenicity

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

Propylene Glycol

Over a 2-yr period, 30 males and 52 females with photoallergic contact dermatitis were photopatch tested with a standard series of sunscreens as well as some additional chemicals, including PG (dose not given).[60] The allergens were applied in duplicate on the back and covered with opaque tape. After 24 h, the tape was removed, the test sites evaluated, and one set of test sites was irradiated with a UVA dose of 5 J/cm^2 (using a Daavlin UVA cabinet), giving an irradiance of 10.4 mW/cm^2; this provided a 320-400 nm spectrum. The test sites, which were not covered after irradiation, were evaluated 24 and 72 h later. While some positive reactions were observed to other test agents, PG did not produce a photoallergenic or contact allergy response.

Enhancement of Irritation Effects

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

Propylene Glycol

The effect of the addition of PG to an isopropanol vehicle on the irritant reaction of benzoic acid was determined in a non-occlusive test using 15 subjects, 7 males and 8 females.[61] Benzoic acid in isopropanol was tested at concentrations of 31, 62, 125, and 250 mM without PG as well as with the addition of 1, 2, 5, 10, and 25% PG. The vehicles were also tested. Visual appearance, laser Doppler flowmetry, and skin color (using a Minolta chromameter) were measured at 20, 40, and 60 min after application. PG enhanced the strength of the reactions to 125 and 250 mM benzoic acid, but not to 31 or 62 mM benzoic acid. (This was observed using all 3 measurement methods.) Enhancement was observed with the addition of 1% PG, and maximal enhancement was attained with 5%. No reaction to application of the vehicles was observed.

Retrospective Analysis

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

Propylene Glycol

The NACDG performed a number of retrospective analyses on various dermatological conditions. These studies are summarized in Table 4.

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.[62]

Propylene Glycol

A few case reports have been described concerning PG and hand dermatitis or atopic dermatitis. Patch test results generally had a positive reaction to PG in these case studies. Improvement was seen with the avoidance of PG-containing products.[63, 64]

Summary of Propylene Glycol Data

In mammals, the major pathway of PG metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases. When PG was administered i.v. to human subjects (patients), elimination from the body occurred in a dose-dependent manner.

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

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

In both the 1994 safety assessment and currently, few toxic effects were seen in dosing with PG. The oral LD_{50} of PG was >21 g/ kg for rats. The dermal LD_{50} of PG was >11.2 g/kg for mice and was 13 g/kg for rats. All mice survived in a short-term study in which mice were given 10% PG in drinking water for 14 days, and all rats and mongrel dogs survived oral dosing with up to 3.0 ml 100% PG, 3 times per day, for 3 days. In a subchronic study, a dose of ≤50,000 ppm PG given in the feed for 15 wks did not produce any lesions. Subchronic inhalation data reported some effects in rats due to PG exposure of 2.2 mg/l air for 6 h/day, 5 days/wk, for 13 wks, but these effects were inconsistent and without dose-response trends. In the 1994 safety assessment, no toxic effects were reported in chronic studies when rats or dogs were given feed containing 50 g/kg or 5 g/kg, respectively, PG.

Undiluted PG was, at most, a slight ocular irritant. Dermal irritation studies were reported in the 1994 CIR final safety assessment and in the amended final safety assessment. In one study using nude mice, 50% PG may have caused skin irritation, while in another study, 100% PG was minimally irritating to hairless mice. Undiluted PG was at most a mild dermal irritant in a Draize test using rabbits with intact and abraded skin. No reactions to undiluted PG were observed with guinea pigs, rabbits, or Gottingen swine. Using nude mice, hypertrophy, dermal inflammation, and proliferation were observed with 50% PG. These effects were not seen in hairless mice with undiluted PG. PG (concentrations not given) was negative in a number of sensitization/allergenicity 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 basepair 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.

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 are also function as preservatives. The following four 1,2-glycols were reported to FDA as being used: caprylyl glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol. The results of a Personal Care Products industry survey indicate that ingredient use concentrations have ranged from (lowest to highest) 0.00003% (caprylyl glycol) to 10% (1,2-hexanediol); the survey did not include use concentration data on C15-18 glycol.

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

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

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

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

The skin penetration enhancement effect of caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol has been demonstrated *in vitro*.

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-propanediol), 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. Prolonged application or repeated applications of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects.

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

Based on Draize test results, lauryl glycol has been classified as a severe ocular irritant. Reportedly, undiluted 1,2-butanediol was irritating to the eyes of rabbits, but was a non-irritant when tested as a 10% aqueous solution. Also, reportedly, 1,2-butanediol was not irritating to the skin of rabbits. There was no evidence of cross reactivity between antipanaxytriol antibody and decylene glycol.

An NOAEL of 1,000 mg/kg for reproductive/developmental toxicity has been reported for 1,2-butanediol in rats dosed orally. 1,2-Butatnediol was not genotoxic in assays involving bacterial or mammalian cells, and cetyl glycol (130 µg/ml) had a cytocidal effect on cultured Ehrlich ascites carcinoma cells. Marked antitumor effects of cetyl glycol were observed in mice *in vivo* following i.p. doses of 80 mg/kg/day.

A 1,2-hexanediol/caprylyl glycol mixture (in preservative system) did not induce sensitization at a concentration of 0.5% or 15% in human subjects. In a case report, positive reactions were observed in a patient patch tested with 0.5% and 5% 1,2-pentylene glycol, but not in the control group.

DISCUSSION

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

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

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

Table 2. Chemical and Physical Properties

Property	Values	Reference
Arachidyl Glycol		
Molecular weight	314.55	ACD/Labs[65]
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[65]
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[66]
Boiling point	356.1 ± 10.0°C (760 Torr)	ACD/Labs[65]
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[65]
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[67]
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[65]

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[65]
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[65]
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[65]
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[68]
Boiling point	377.2 ± 10.0°C (760 Torr)	ACD/Labs[65]
Flash point	157.6 ± 13.6°C	″
Enthalpy of vaporization	72.30 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	3.09E-07 Torr (25°C)	″
pKA	14.19 ± 0.20 (25°C)	″
logP	6.629 ± 0.216 (25°C)	″
Caprylyl Glycol		
Molecular weight	146.23	ACD/Labs[65]
Molar volume	155.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.937 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	4.2 g/l (25°C)	″
Mass solubility	4.4 g/l (pH 7, 25°C)	″

Table 2. Chemical and Physical Properties

Property	Values	Reference
Molar intrinsic solubility	0.029 mol/l (25°C)	″
Molar solubility	0.030 mol/l (pH 7, 25°C)	″
Melting point	36 to 37°C (not calculated)	Fringuelli[69]
Boiling point	137 to 139°C (not calculated); 243.0 ± 8.0°C (760 Torr)	Mugdan[70]
Flash point	109.1 ± 13.0°C	ACD/Labs[65]
Enthalpy of vaporization	55.78 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	5.59E-03 Torr	″
pKA	14.31 ± 0.10 (25°C)	″
logP	1.316 ± 0.215 (25°C)	″
Decylene Glycol		
Molecular weight	174.28	STN[9]
Molar volume	188.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.922 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.40 g/l (25°C)	″
Mass solubility	0.40 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.0023 mol/l (25°C)	″
Molar solubility	0.0023 mol/l (pH 7, 25°C)	″
Melting point	48-49°C	Swern[67]
Boiling point	93 to 96°C (0.5 Torr) - not calculated; 255.0 ± 0.0°C (760 Torr)	Orito[71]
Flash point	122.4 ± 13.0°C	ACD/Labs[65]
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[65]
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[72]
Refractive index	1.4400 (20°C, λ = 589.3 nm) – not calculated	Emmons[73]
Mass intrinsic solubility	95 g/l (25°C)	ACD/Labs[65]
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[72]; Emmons[73]
Flash point	104.4 ± 0.0°C	ACD/Labs[65]
Enthalpy of vaporization	51.45 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	5.75E-02 Torr (25°C)	″
pKA	14.22 ± 0.20 (25°C)	″
logP	-0.278 ± 0.215 (25°C)	″
1,2-Butanediol		
Molecular weight	90.12	ACD/Labs[65]
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[74]; Tishchenko[75]
Refractive index	1.4380 (20°C, λ = 589.3 nm)	ACD/Labs[65]

Table 2. Chemical and Physical Properties

Property	Values	Reference
Mass intrinsic solubility	230 g/l (25°C)	″
Solubility	Very soluble in water	NIOSH[11]
Mass solubility	230 g/l (pH 7, 25°C)	ACD/Labs[65]
Molar intrinsic solubility	2.55 mol/l (25°C)	″
Molar solubility	2.55 mol/l (pH 7, 25°C)	″
Melting point	-50°C and -114°C (not calculated)	STN[9]
Boiling point	132 to 133°C (760 Torr) – not calculated; 190.3 ± 8.0°C (760 Torr)	Clendenning[72]; Hill[76]
Flash point	93.3 ± 0.0°C	ACD/Labs[65]
Enthalpy of vaporization	49.64 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.48E-01 Torr 10 (20ºC)	″ NIOSH[11]
pKA	14.27 ± 0.20 (25°C)	STN[9]
logP	-0.810 ± 0.215 (25°C)	″
Stability	Stable in neutral, acidic, or alkaline solutions	OECD[7]
Half life	≥ 1 year (25ºC; pH: 4, 7, and 9)	″
1,2-Hexanediol		
Molecular weight	118.17	ACD/Labs[65]
Molar volume	122.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.961 ± 0.06 g/cm^3 (20°C)	″
Refractive index	1.4518 (25°C, λ = 589.3 nm) – not calculated	Zelinski[77]
Mass intrinsic solubility	37 g/l (25°C)	ACD/Labs[65]
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[78]
Flash point	95.8 ± 13.0°C	″
Enthalpy of vaporization	53.48 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.94E-02 Torr	″
pKA	14.22 ± 0.20 (25°C)	″
logP	0.253 ± 0.215 (25°C)	″

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

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

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

Product category	2010 uses (total number of products in category)	2010 concentrations (%)
Shaving cream	7 (128)	0.001 to 0.4
Other	6 (126)	0.4
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	91 (1528)	0.0003 to 1
Depilatories	-	0.5
Face and neck lotions	157 (1652)	0.2 to 1
Body and hand lotions	151 (1875)	0.02 to 1
Body and hand sprays	-	0.0003 to 0.8
Foot powders and sprays	2 (46)	-
Moisturizers	269 (2750)	0.2 to 1
Moisturizing sprays	-	0.3
Night creams and lotions	53 (386)	0.5 to 1
Paste masks (mud packs)	34 (462)	0.3
Skin fresheners	8 (267)	0.00003 to 0.4
Other	77 (1446)	0.2 to 0.6
Suntan products		
Gels, creams, and liquids	3 (106)	0.6 to 1
Indoor tanning preparations	16 (247)	0.5 to 0.7
Other	4 (61)	0.3
Total uses/ranges for caprylyl glycol	1761	0.00003 to 5
Pentylene glycol		
Bath products		
Other	1 (227)	-
Soaps and detergents	19 (1781)	1 to 3
Eye makeup		
Eyeliner	10 (834)	1 to 2
Eye shadow	17 (1343)	-
Eye lotion	35 (260)	0.005 to 4
Eye makeup remover	5 (133)	1
Mascara	11 (528)	2 to 3
Other	18 (412)	-
Fragrance products		
Cologne and toilet waters	1 (1426)	-
Other	2 (641)	1
Noncoloring hair care products		
Conditioners	1 (1313)	0.001
Shampoos	2 (1487)	0.001
Tonics, dressings, etc.	8 (1321)	-
Other	1 (838)	-
Makeup		
Blushers	1 (471)	-
Face powders	13 (724)	2
Foundations	24 (624)	1 to 4
Leg and body paints	1 (29)	
Lipstick	6 (2045)	-
Makeup bases	2 (126)	-
Rouges	1 (107)	
Makeup fixatives	3 (49)	-
Other	4 (536)	0.5
Nail care products		
Cuticle softeners	-	4
Other	-	5
Personal hygiene products		
Deodorants (underarm)	3 (623)	0.2
Other	6 (925)	0.001 to 5

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

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

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

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

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

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

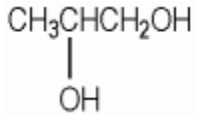
[α]Mean ± SD (n = 3)

Table 5. Retrospective analyses with propylene glycol

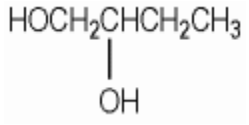
No. of patients	Years studied	% PG	Methods	Findings
not given	1984-1996	10 aq.	data were collected from NACDG-reported studies; the SPIN for each allergen was calculated as the proportion of the population allergic by the weighted clinician-assessed likelihood of relevance of the reaction	the SPIN rank for PG has changed over time: 23 in 1984-1985; 40 in 1992-1994; 41 in 1994-1996[79]
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[80]
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[81]
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[82]
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[83]

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

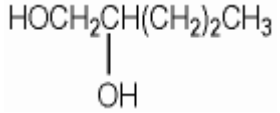
Figure 1. Formulas of 1,2-glycols



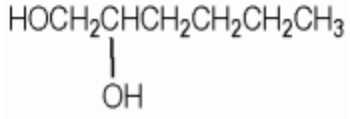
Propylene Glycol



1,2-Butanediol



Pentylene Glycol



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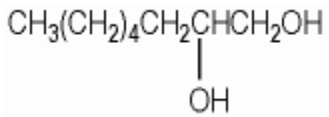
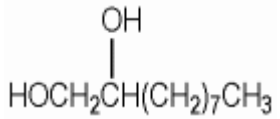
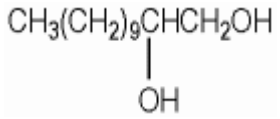


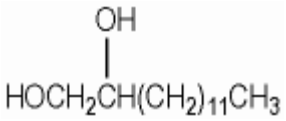
Caprylyl Glycol



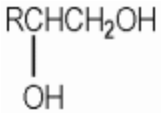
Decylene Glycol



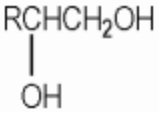
Lauryl Glycol



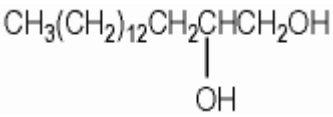
Myristyl Glycol



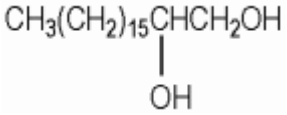
C14-18 Glycol
(wherein R is C12-C16)



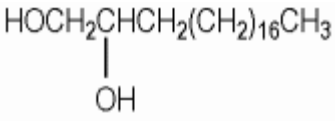
C15-18 Glycol
(wherein R is C13-C16)



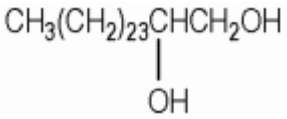
Cetyl Glycol



Stearyl Glycol

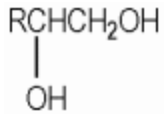


Arachidyl Glycol

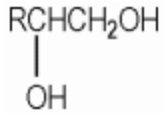


Hexacosyl Glycol

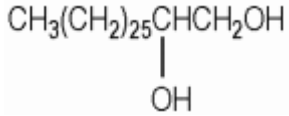
Figure 1. Formulas of 1,2-glycols



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

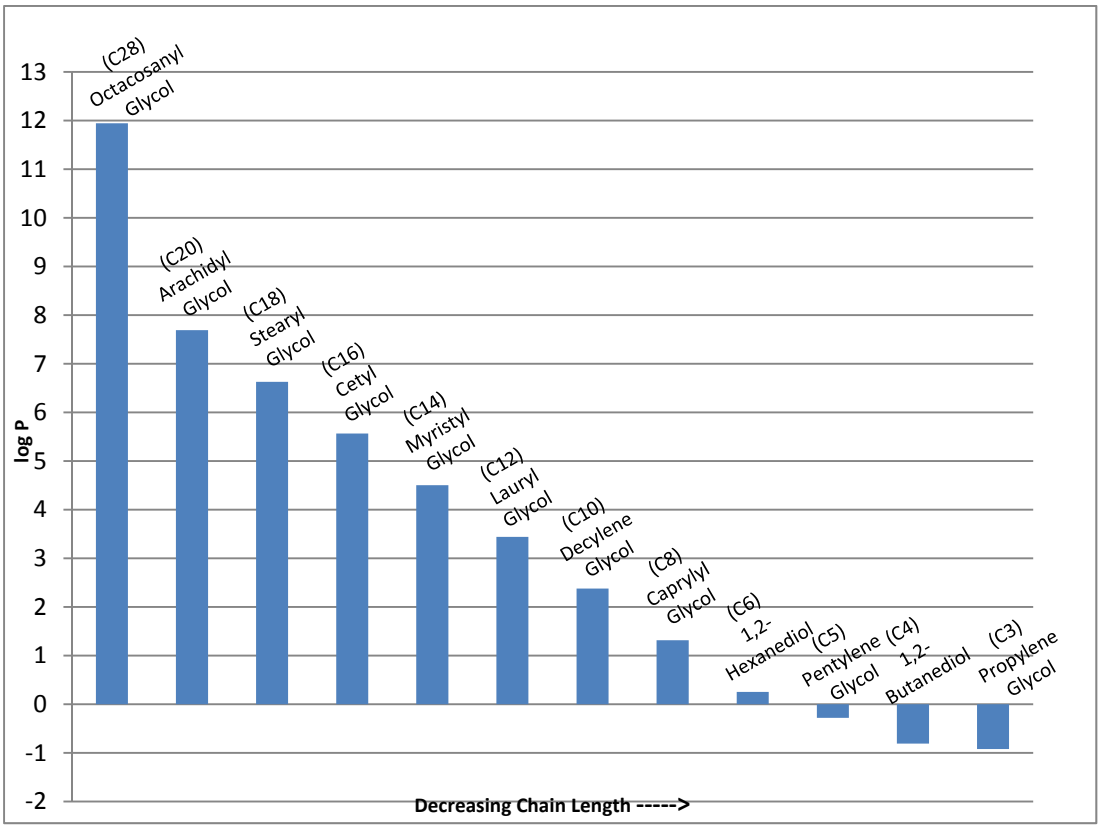


C20-30 Glycol
(wherein R is C18-C28)



Octacosanyl Glycol

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



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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: July 27, 2010

SUBJECT: Summary of Unpublished Data on Decylene Glycol

Symrise. 2010. Tox Data Summary Sheet SymClariol® (Decylene Glycol)

symrise
always inspiring more...

Tox Data Summary Sheet

SymClariol® = Decylene Glycol

CAS-No. 1119-86-4

Test	Result	Date / Source
Human Safety:		
Acute oral toxicity (rat) (OECD 423)	LD50 > 2500 mg/kg	2001, Symrise
Acute dermal toxicity (rat) (OECD 402) (limit test)	LD50 > 2000 mg/kg	2001, Symrise
Primary skin irritation (rabbit) (OECD 404)	moderate skin irritation at 100% PII = 3.2	2002, Symrise
Primary skin irritation (human) (48h semi-occluded patch test)	no skin irritation (0/52) tested at 20% in petrolatum	2005, Symrise
Eye irritation (*in vitro*) (HET-CAM)	no eye irritation at 1% in neutral oil	2007, Symrise
Primary eye irritation (rabbit) (OECD 405)	eye corrosion at 100%	2001, Symrise
Sensitisation test (OECD 406) (guinea pig maximization test)	no skin sensitisation (0/19) intradermal induction: 1% in arachis oil topical induction: 5% in arachis oil challenge: 5 and 2% in arachis oil	2002, Symrise
Sensitisation test (OECD 429) (Local Lymph Node Assay, mouse)	no skin sensitisation tested at 5%, 10%, 25% and 50% in acetone/olive oil (4 :1)	2004, Symrise
Sensitisation test (human repeated insult patch test)	no skin sensitisation (0/55) at 20% in petrolatum	2005, Symrise
Repeated dose toxicity (28d, oral, rat) (OECD 407)	NO(A)EL = 100 mg/kg b.w. dose levels: 100, 300, 1000 mg/kg by gavage	2003, Symrise
Ames-Test (OECD 471) (Salmonella typhimurium: TA1535, TA1537, TA102, TA98 and TA100)	not mutagenic	2003, Symrise

symrise
always inspiring more...

Tox Data Summary Sheet

SymClariol®

CAS-No. 1119-86-4

Test	Result	Date / Source
Facial Stinging Propensitiy (human)	very slight stinging potential (0/10) tested 1% and 2% in neutral oil	2007+2008 Symrise
Ski-irritating on scarified skin (human)	low irritation potential (0/10) tested at 1% in neutral oil	2007, Symrise

Created by Ilse Wingrat
Created on 19/05/2010

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: July 27, 2010

SUBJECT: Summaries of Unpublished Data on 1,2-Hexanediol, Caprylyl Glycol and a 50:50 (w/w) mixture of 1,2-Hexanediol and Caprylyl Glycol

Symrise. 2010. Tox Data Summary Sheet 1,2-Hexanediol.

Symrise. 2010. Tox Data Summary Sheet Caprylyl Glycol.

Symrise. 2010. Tox Data Summary Sheet Symdiol®68 (50:50 (w/w) mixture of 1,2-Hexanediol and Caprylyl Glycol)

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Tox Data Summary Sheet

1,2-Hexanediol

CAS-No. 6920-22-5

Test	Result	Date/Source
Human Safety:		
Sensitisation test (OECD 429) (Local Lymph Node Assay, mouse)	no skin sensitisation tested at 10%, 50% and 100% in acetone/olive oil (3 :1)	2003, Symrise
Prenatal Development Toxicity study (oral, rat) (OECD 414)	NOEL = 300 mg/kg b.w. dose levels: 30, 100, 300 mg/kg by gavage	2006, Symrise

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Tox Data Summary Sheet

Caprylyl Glycol

CAS-No. 1117-86-8

Test	Result	Date/Source
Human Safety:		
Eye irritation (*in vitro*) (HET-CAM)	no eye irritation at 1% and 3% in neutral oil	2008, Symrise
Sensitisation test (OECD 406) (guinea pig maximization test)	no skin sensitisation (0/20) intradermal induction: 5% in peanut oil topical induction: 50% in petrolatum challenge: 50% in petrolatum	1995, Symrise

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Tox Data Summary Sheet

Symdiol® 68 = 50:50 (w/w) mixture of 1,2-Hexanediol and Caprylyl Glycol

CAS-No. n.a. mixture

Test	Result	Date/Source
Human Safety:		
Eye irritation (*in vitro*) (HET-CAM)	severe eye irritation at 1% in aqueous solution	2007, Symrise
Sensitisation test (human repeated insult patch test)	no skin sensitisation (0/56) at 20% in gel	2003, Symrise

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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: June 21, 2010

SUBJECT: Comments on the Draft Report on Caprylyl Glycol and Related Ingredients for the June 28-29, 2010 CIR Expert Panel Meeting

Memo - In the future, it would be helpful if memos were dated with the date they were written.

This report was sent to the CIR Expert Panel before the SLR 60 day comment period was complete. It would have been helpful to delay the first review of this report to the August meeting. By the August meeting, the concentration of use information should be complete, and there would have been some time to request information from companies reporting use of these ingredients (which cannot be done until the use survey is complete). There would also have been more time to receive information that has been requested from NTIS and EPA.

p.2 - It would be helpful if CIR staff could add a sentence as to whether or not the structures of these compounds suggest that they could absorb light in the UV range.

p.2 - In the sentence describing the FDA VCRP, please delete "in 2009". Industry did not provide the use information to FDA in 2009. The information collected over many years was summarized in 2009.

p.4 - In the summary of the Skin Penetration Enhancement section, please provide the compounds for which the penetration was enhanced. Penetration enhancement of one compound should not be used to imply that the penetration of all other compounds will be enhanced.

p.4 - In the sentence under Stearyl Glycol, please delete "median" as LD50 means median lethal dose.

p.7 - In the summary of the Cytotoxicity section, which compound resulted in "marked antitumor effects"?

p.8 - What concentration of Lauryl Glycol was classified as a severe ocular irritant? The title of reference 29 (Prediction models for eye irritation potential based on endpoints of the HETCAM and neutral red uptake tests) suggest that Lauryl Glycol may have been tested in *in vitro* studies for eye irritation. If this is correct, the results of the *in vitro* studies should be presented in this report.

p.9 - It appears that "EDCL" should be "EDLC" - estimated dose of low concern

p.11 - Please provide the compounds for which the penetration was enhanced. Penetration enhancement of one compound should not be used to imply that the penetration of all other compounds will be enhanced.

p.13-16, Table 13 - It is not clear why scientific notation is used for some values, e.g., Vapor pressure 2.11E-09 Torr, but not other values, e.g., Molar solubility 0.00000000020 mol/L (pH 7, 25°C).

p.24-25, References - Reference 5 now ends with REF. A number of references have "%" signs by the date. Websites should include the date they were accessed. The website listed for reference 17 (http://iaspub.epa.gov) is to the EPA server. It was not clear how information on 1,2-Butanediol could be obtained from this site.