PINK

Safety Assessment of Tromethamine as Used in Cosmetics

CIR EXPERT PANEL MEETING

JUNE 10-11, 2013

Cosmetic Ingredient Review

Commitment & Credibility since 1976

May 10, 2013

MEMORANDOM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Subject: Tentative Safety Assessment For Tromethamine, Aminomethyl Propanediol, And Aminoethyl Propanediol As Used In Cosmetics

At the March, 2013 meeting, the Panel tabled the safety assessment for tromethamine to include aminomethyl propanediol (AMPD) and aminoethyl propanediol (AEPD) and to allow time for the submission of irritation/sensitization data at the reported use concentration (4%) and impurity data. A search was conducted for new data on these ingredients and appropriate data added to the document.

Updated use data have been received from FDA. The Council also provided updated concentration of use data for tromethamine. There were no significant changes in the types of use of tromethamine. However, the updated concentration of use data show the highest concentration of use to be 3.7%. The Council is conducting a survey of concentrations of use for AMPD and AEPD. This report contains the concentration of use data from the 2009 report which is presented in the Use section and table.

Note that the new irritation/sensitization data that were submitted by the Council includes products containing tromethamine up to 2%, which is below the 3.7% reported use.

The Panel is to affirm that the data is sufficient to make a decision of safety for tromethamine and the two added ingredients. The Discussion section should also be reviewed and amended to reflect the Panel's thinking.

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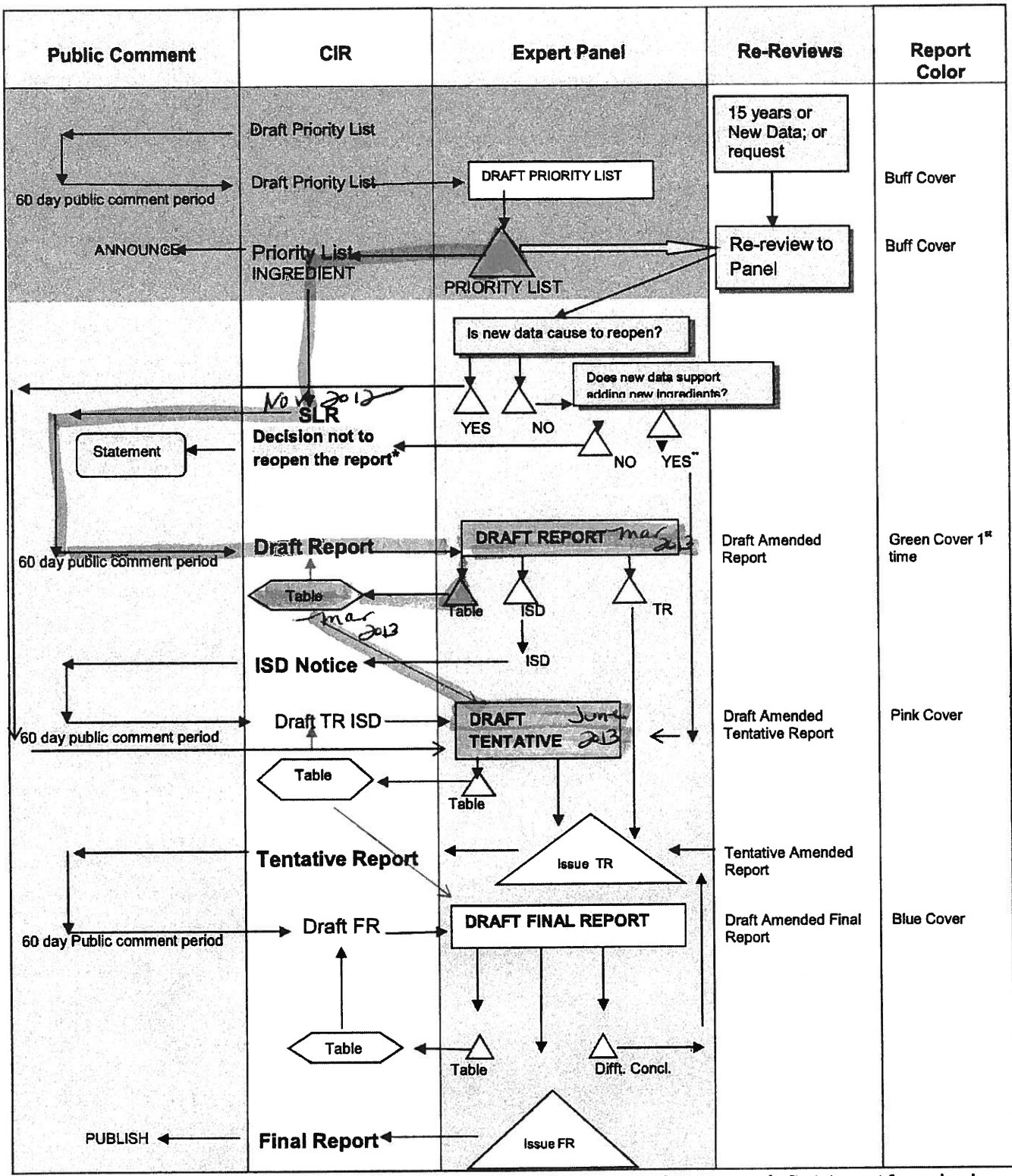
Tromethamine

June 2013

SAFETY ASSESSMENT FLOW CHART



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

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

△ Expert Panel Decision

History of Tromethamine

November, 2012 – SLR was posted for public comment.

March, 2013 – Panel added AEPD and AMPD to the report. The report was table to allow the incorporation of the new ingredients and to allow time for submission of data on sensitization/irritation of tromethamine and impurity data.

June, 2013 – The Panel examines the three ingredients together in the report.

Tromethamine Data Profile for June, 2013. Writer - Lillian Becker																		
	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Tromethamine	X		X	X	X		X	X		X	X	X		X	X	X	X	
AMPD									O	O	O	O	OX			OX		
AEPD													X	X				

X – Data in current report.

O – Data from old reports.

Search Strategy for Tromethamine

Scifinder – “tromethamine” and CAS no.

Google - “tromethamine” and CAS no.

EPA HPV Database – CAS no.

Scifinder – CAS nos. of AEPD and AMPD.

TRANSCRIPTS FOR TROMETHAMINE
FROM MARCH, 2013

DAY 1
DR. MARKS

DR. MARKS: Let's go ahead and resume for another about an hour. The next ingredient is tromethamine.

[discussion about file formats]

DR. MARKS: At least at this point what we've like the panel members on the Marks and Wilma team would like to see is the memo in both documents whether it's Word or it's PDF at this point and we'll go forward and see how things evolve. Now we have a draft report from Lillian on tromethamine as used in cosmetics. This is the first time that the panel has seen this report. You can see under the memo the Science and Support Committee has suggested that not using the aminomethyl propanol as an analog approach, but to use the AEPD, the aminomethyl propanediol. It's just this one ingredient. Correct? A single ingredient. Rons and Tom, how do you feel about using these analogs to come to the conclusion that this ingredient is safe? You'll recall that the AMPD already from a 2009 CIR that we concluded that that ingredient was safe.

DR. SLAGA: I feel we can use them and I think it's safe as used.

DR. HILL: I totally disagree. I don't think there's any reason to use those. There is no justification for using them. There is no reason to think the biohandling would be similar. And I don't see why we need that data to conclude safe.

DR. MARKS: You feel that you could conclude safe without using it?

DR. HILL: Absolutely.

DR. MARKS: Ron Shank?

DR. SHANK: I also agree safe as used whether you use the other data or not.

DR. BERGFELD: I do too.

DR. SHANK: I really don't know whether it's useless or not.

MS. WEINTRAUB: I raise the concern also. I think it's not at all well explained or rationalized why an analog would be used for this ingredient. I think so much of the work we do on this panel is looking at data sources and making decisions based on what we have and asking for data and I think there is a lack of explanation about why an analog would be used in this situation versus so many others that we find ourselves in. It seems to me that there's a lack of evidence provided us as to why an analog would be acceptable.

DR. ANSELL: We'll have a technical response, but I believe that fundamentally we need to continue to advance the concepts of QSAR, that asking for a study is very 15 minutes ago. What we want to do is identify questions and come up with the best data to respond to those questions and often today that may not be a study. It may not be an animal study. It could be a computational method. It could be an in vitro method. It could be a variety of methods. I think we're going to be seeing more and more of that as we go forward.

MS. WEINTRAUB: May I respond to that? It seems to me, and this has been one of my underlying principles, that if an ingredient is being used in a specific product then it's up to the manufacturer and others in the supply chain to prove through data the use of the ingredient that it doesn't pose various types of impacts and that using the types of more modern scientific technologies that are available, I don't know that that necessarily means that data is not provided specifically about that ingredient. I understand it's making comparisons and assumptions, but it seems that there needs to be a very good rationale for why there can be a complete analog used for a specific ingredient.

DR. ANSELL: We agree absolutely. That is my point exactly, that this is not making

decisions in the absence of data. This is looking at a much richer data package. My concern was simply that if we look at the carcinogenicity and say there is no carcinogenicity study, that's not really what we want to talk about; is there a concern and how do we conclude that there is no concern and I think we've seen through this morning that we can do that in a variety of ways even if there is no specific animal study. So I think we're in agreement.

DR. HILL: I teach QSAR and the like at the graduate level. I'm a medicinal chemist. There are situations where the complete data packet is more valuable than the information on that particular one alone. This is not one of those situations. That's my point. Moreover, we have an agent that's administered intravenously on a routine basis for various and sundry purposes and I think there is plenty of other toxicology data out there to support the fact that this isn't going to be problematic and that we just need to drag that data in. That was my feeling on this.

DR. HUGHES: Let me explain where this came across. My name is Brian Hughes. I'm with the Dow Chemical Company. Probably where we did use surrogates to be able to explain this was cause of lack of reproductive developmental data in the HPD program. That's where I think we used the surrogate. Unfortunately we used the surrogate AMP which has some problems with it versus AEPD which is the propanediol. If you take a look at the reproductive developmental studies you'll find out that we did that after we submitted the AEPD document and found out that the tris amino even at the limit dose doesn't have the problems AMP does and is more related to AEPD. That's where that read- across approach came in. The idea that the panel agrees if I can say that that tris amino can stand on the merits itself, we would agree to that.

DR. MARKS: I was looking at skin sensitization and I didn't see any animal nor human sensitization to trimethylamine and looking at AMPD and AEPD was reassured with that. It would have been nice to see an HRIPT on the trimethylamine but I didn't see any. That's what I liked and thought was reassuring. Ron Hill, I heard initially where you don't like this in this case at all and all of you felt that it could be safe on its own, that even with the skin you didn't have a problem.

DR. SHANK: Why do you feel that two analogs, AMPD and AEPD, are so unlike the ingredient?

DR. HILL: That extra hydroxyl group gives us a completely different character. The only other commonality there is that primary amino group. I suppose if you have reason to believe that there will be some sensitization -- I don't have a problem with keeping the data in, but I want to make sure that it's viewed in the proper context in the way it's discussed.

DR. SHANK: All three compounds are 1, 3 propanediols. All three compounds are two amino substitution. I think there's quite a bit of structural similarity.

DR. HILL: I know Dan doesn't like when I use the word biohandling, but I know exactly what I mean by that and there is no reason to necessarily believe that the biohandling other than the primary amino group would be in common. Again I have no problem with leaving the data in, but I'd make sure that it's not overused because I don't think we need to. Overextrapolated I guess is the word I should have used.

DR. MARKS: Is there a way you could suggest in your editing how you would like to -- was there anything (inaudible) specifically? Obviously this is going out as a tentative so it seems to me that there wasn't an issue in terms of moving it on as a tentative report with a safe conclusion. Is that correct? Then we could handle that issue of the read-across. Of course we're doing that all the time, reading across, but if you want to, Ron Hill, make some specific editorial comments it might be helpful for the next edition. Are there any other comments? Rachel, do you feel comfortable now hearing the discussion that as Ron Shank mentioned, the structural similarity and Ron Hill is concerned about the biologic handling of that so there's some difference there. Tom Slaga feels fine with the read- across. Then the actual compound or ingredient that we're reviewing feels safety in that as is without the read- across.

MS. WEINTRAUB: At a minimum I think that type of analysis needs to be in the report.

Whether or not I agree with it or not, I think the panel needs to justify why it's doing it and explain it thoroughly.

DR. MARKS: Lillian, you're going to capture that obviously.

DR. SLAGA: We do that in all the reports, read- across.

DR. MARKS: Yes. Absolutely.

DR. HILL: I think Rachel's point, and I can't disagree, is why don't we have the sensitization data on this ingredient given the volume of use. I'm always for more science.

DR. MARKS: Ron, I was willing to go with safe, but I can't imagine there isn't an HRIPT on one of these. Was it 400 or something? I'll have to look. What was the use? How many ingredients or how many products was this used in?

DR. GILL: 480 leave-on and 69 rinse-off.

DR. MARKS: It's over 500. It's hard to believe that there is not one HRIPT on any of those.

DR. HILL: On the other hand, because there's pharmaceutical use here and intravenous use, I couldn't dream up anything that would happen dermally that didn't show up in all of that so that's a lot of my comfort level.

DR. MARKS: Wilma?

DR. BERGFELD: I'd like to make a comment.

DR. MARKS: Was there one there that I missed?

DR. ANSELL: We simply note Lillian's comment to the panel where a patch test at 3.1 percent was provided.

DR. MARKS: A patch test? What page are you on?

DR. ANSELL: I have no idea. I'm referencing Lillian's report to you guys of February 22. This is in the report where it mentions a patch test on Panel Book page 13 with reference to 56.

DR. MARKS: What panel book?

DR. ANSELL: Panel Book page 13 is where I'm seeing it. I'm searching for the word "patch" in the report. Here's a patch test of dermatitis patients.

DR. MARKS: That's not an HRIPT. I want a perspective. At any rate, I don't think it would inhibit us from moving forward, but that was my comment that I would have liked to see at least one HRIPT. I don't think it would cause me to say insufficient by any means, but it would be more robust. Lillian, your comment?

DR. BERGFELD: I made a comment earlier about the document and the headings. I'd like to draw your attention to this one in particular to the table of contents. I understand there's been a movement from animal to human as a topic heading to nonhuman and human. I understand that. But what I don't understand under "Irritation and Sensitization," you have irritation and then right in the middle of that you have dermal human and those are all animal and others where I think you need to isolate the human away from the nonhuman. It shouldn't be in the middle of two nonhuman studies or to follow it or have a separate heading as nonhuman and human. That's at your table of contents under "Irritation and Sensitization."

MS. BURNETT: You'd want the dermal nonhuman and the intradermal nonhuman together and then the human?

DR. BERGFELD: I think you should cluster your nonhuman together and your human together. You shouldn't be interspersing them.

MS. BURNETT: Our template had been whatever our test is, human/nonhuman, next test our data point, end point, human/nonhuman. We can change that.

DR. BERGFELD: I'd like to hear comments from other people because it happened in multiple documents. It wasn't just this one. I like the heading under irritation to put in the nonhuman and human. I like that. But the fact that you intermix them was a little bit problematic.

DR. MARKS: Are there any other comments? Rachel?

MS. WEINTRAUB: I had another comment and that's about footnote 52. It seemed like there was very little detail on the study. It just said Syrian hamsters. It didn't say how many. It seemed like it was a much less-detailed study than we normally have and I wanted to get the panel's interpretation about whether that was sufficient. It's on page 5 of the report, page 14 PDF.

DR. HILL: This is reference 52?

MS. WEINTRAUB: Yes, footnote 52.

DR. HILL: It's because the focus of the study was not on trimethylamine but, rather, benzo[a]pyrene.

MS. WEINTRAUB: Yes, I noticed that.

DR. HILL: That isn't informative to the lack of carcinogenicity of this compound that I think we probably have. Did we capture the wrong piece of data here?

DR. MARKS: What do you want to do with that, Ron? Do you want to leave that study out? Do you think it should stay in?

DR. HILL: What does Ron Shank think? Tom, what do you think?

DR. SHANK: This was in the control. Right? Tromethamine. So it's valid. Then we have some genotoxicity data at least in a bacterial assay not (inaudible) and the APD was not (inaudible). I have no concern over the carcinogenicity.

DR. SLAGA: I don't have any concern either.

DR. MARKS: Does that answer your question, Rachael?

DR. ANDERSEN: I think in fairness, the fact that that's a vehicle control arm could be added to the sentence to clarify just what it is we're dealing with here and that would make a lot more sense.

DR. MARKS: Thank you, Alan. Are there any other comments? Tomorrow I will be moving the tromethamine on to a tentative report with a conclusion of safe. Then a lot of our discussion, Lillian, will be captured in that.

Dr. BELSITO

DR. BELSITO: Okay. So, tromethamine. This is another first for us, and the first thing we're being asked is whether it was appropriate to look at data on amino ethylpropanediol and amino methylpropanediol to support safety.

So I guess I would ask Dan and Paul their comments on this.

DR. LIEBLER: Yes. So, in short, yes, I agree with the substitution of these two for the other one.

And particularly, the other one was particularly bad because there was not an alkyl group at the carbon that has the amine, and so the amine can undergo chemistry that gives rise to a whole bunch of other products that wouldn't happen with tromethamine.

So I think the other compound -- I don't remember the name of it, but the structure -- the carbon that had the amine just had a hydrogen on it. So that was a problem for me in terms of a valid analog.

So AMPD and AEPD strike me as very reasonable. And this is the report that had the funky floating labeling.

MS. BURNETT: Font.

DR. LIEBLER: Well, funky font. I think George Clinton cut that in 1975 -- funky font. (Laughter)

DR. BELSITO: So just looking at this report and even allowing for the use of data on other chemicals to support safety, I was a little concerned about the lack of sensitization data that we have for use of this up to 4 percent.

And I know that amino ethylpropanediol was negative at 10 percent, but tromethamine has two hydroxyl groups on it. So I think it's potentially more reactive, and I'm not sure that you can

predict -- Dan, correct me if I'm wrong -- predict the sensitization based upon the others where you have only one hydroxyl and then you have methyl groups that could be interfering with the stochiometric cooking-up of this molecule with a protein carrier.

So I just thought it's the first time we're looking at it. You know, can't we get some data at 4 percent?

That was my only comment. Dan, what do you think of that? Total dumbness?

DR. LIEBLER: No, not total dumbness, but I don't -- I mean, I think that if you're concerned -- I don't think there's a chemical reason to be concerned, really. But if we've got nothing on tromethamine, it would be great to have something on it.

I mean, having the data on these other two compounds is great in a supporting role, but if you had some sense -- you're looking for sensitization or irritation at that highest concentration of use.

DR. BELSITO: Sensitization, yes.

DR. SNYDER: So we have up to 4 percent on tromethane, but we have no data on tromethamine.

DR. BELSITO: Right.

DR. SNYDER: Okay.

DR. LIEBLER: Right. Yes. Okay, and that's not a valid substitute.

DR. BELSITO: And all we have is really irritation data. We have no sensitization data.

DR. BRESLAWEC: Irritation data.

DR. BELSITO: What?

DR. BRESLAWEC: Never mind.

DR. BELSITO: And, again, it's the first time we're looking at it. I think it would be nice.

My other comments really were since I won't be here tomorrow, if you guys do decide to go safe as used, we need the same type of language that they have on page 10 of the report about the regulation under Europe Annex 3 with nitrosamine content.

And then everything else was just -- it looks like really just things like, do you mean cellulites or cellulitis? Acidemia, not academia?

(Laughter)

DR. LIEBLER: I thought that was an impurity. It gave me a good laugh.

I do have a more serious point about this that I think throughout the report is important. Under impurities, you indicate that when tromethamine is heated at decomposition it emits toxic fumes. Totally irrelevant, I mean. So I don't think that needs to be there.

But there must be specifications for the material that's used to correct acidosis when administered to people.

And then there's, of course, enormous use of this material as a buffer in biochemistry and chemistry as TRIS.

So the question I would have is, what are the differences between the specs for the cosmetic ingredient and reagent grade TRIS, for example, that you'd buy from like Sigma or the material that's infused to correct acidosis?

So that information must be available from industry.

And then, when you describe the studies, particularly the in vitro studies but even some of the in vivo studies, where tromethamine is present in the cells, for example, the effects could be quite different depending on whether the free base is used or whether a salt was used, like a hydrochloride or so forth. It isn't clear from the descriptions that you paraphrase from the cited work whether or not that's even known or whether it was described in the paper.

If you add the free base, you're going to, you know, make the -- unless the system that was studied is well buffered, you're going to raise the pH and the effects could be just due to pH changes. And if you add the salt, it's less likely that that's going to happen.

And then the in vivo study mostly referred to controlling the pH of the blood when the

material was added.

It's very important that all of the citations are as specific as possible about the chemical form of tromethamine that was used.

DR. BELSITO: Okay. Have you made notes about these?

DR. LIEBLER: Yes, I flagged them all. I flagged them several places.

DR. BELSITO: Okay. Any other comments?

DR. SNYDER: So we're going to go insufficient for sensitization data.

DR. BELSITO: At concentration of use. See what they say -- the other team.

DR. SNYDER: What specific ingredient?

DR. BELSITO: It's only one ingredient -- tromethamine.

DR. SNYDER: Tromethamine, okay.

DR. EISENMANN: Concentration --

DR. BRESLAWEC: Concentration of use. I think you mean impurity data.

DR. BELSITO: No, sensitization at 4 percent.

DR. BRESLAWEC: Oh, at concentration of use.

DR. BELSITO: At concentration of use, yes.

DR. EISENMANN: Well, you know, you've already reviewed AMPD.

DR. BELSITO: Yes, I know.

DR. EISENMANN: AEPD is in the dictionary. I mean, I don't have -- it doesn't have any uses as far as I'm aware, but it is in the dictionary.

DR. SNYDER: Okay.

DR. EISENMANN: What I'm saying is --

DR. LIEBLER: So an analog is in the dictionary.

DR. EISENMANN: Yes. If you're putting the data in this report, if you want to put the ingredient in the report, that's the question.

DR. BELSITO: Sure.

DR. LIEBLER: Oh, I see.

DR. BELSITO: If the ingredient is in the dictionary, even if it has no uses, if we have data on it, put it in the report.

DR. EISENMANN: Right, and if you're reviewing it in this group.

DR. BELSITO: Yes. Fine.

DR. LIEBLER: So we're adding?

DR. SNYDER: We agreed. We already agreed to add those two -- AMPD and AEPD.

DR. BELSITO: No, we agreed to use the data --

DR. SNYDER: Data.

DR. BELSITO: -- to say safe.

DR. LIEBLER: So now we're adding which?

MS. BECKER: AMPD has been reviewed. So are you're talking about AEPD too?

DR. EISENMANN: It's in the dictionary.

DR. BELSITO: If it's in dictionary, add it.

MS. BECKER: You want to add it here, or should we add it with AMPD, or do you want all three together?

DR. EISENMANN: Well, if you're reviewing the data on all three, probably all three should be in there.

DR. BELSITO: Yes. Fine. You're looking -- what is it called, Halyna?

MS. BECKER: No.

DR. BELSITO: Okay.

MS. BECKER: It's processing.

DR. BELSITO: Okay. Any other comments? Carol?

DR. LIEBLER: And insufficient for impurities right now, or get the impurities?

DR. BELSITO: Insufficient for impurities and sensitization in concentration of use.

DAY 2

Dr. Marks presenting on tromethamine.

DR. MARKS: This is the first time the panel has reviewed this ingredient. It's a single ingredient, tromethamine, and there was the use of analogs in coming to the safety assessment, AEPD and AMPD aminomethyl propanediol, which the CIR had issued a safe conclusion back in 2009. Our team felt we could move forward and issue a tentative draft report with a conclusion of safe and I make that motion safe.

DR. BERGFELD: Paul?

DR. SNYDER: Yes, again, Don really was concerned about sensitization. We don't have sensitization on nitromethane methylamine. There was sensitization data for the AEPD analog, which was only up to I believe 1 percent, but we have concentration of use up to 4 percent for these and we also don't have impurities, and, so, we were proposing to go insufficient for sensitization data at concentration of use and impurities.

We also discussed it was raised about bringing the two analogs actually into this report. The AMPD has been reviewed and a report is published on that. AEPD is in the dictionary, but it has not been reviewed. And, so, we wanted to pursue or put on the table the potential to maybe bring all of the ingredients together into one report and then address the data needs and then I would take care of another ingredient that's out there that's in the dictionary that hasn't been reviewed.

SPEAKER: I like that.

DR. HILL: Well, our initial discussion yesterday was to wipe those other two ingredients out of the report as being not relevant, but actually in the part of the country where I now reside, we would call this crawfishing. Because I made those strong statements yesterday, I would at least like to say that in my mind if we consider sensitization mechanisms as most likely involving the amino group if they were to occur that it at least adds to the weight of evidence.

But I did make the statement that given the large number of uses with this, why don't we have it, and I think my comfort level is the fact that this molecule is used systemically and it has been used systemically for a long time, in fact parenteral dosage forms at relatively high levels. I'm not 100 percent sure that includes any possibility of dermal sensitization, but we don't have any literature that suggests that would be a problem, nor are there really any case report. But I still feel like maybe we ought to have it.

In terms of mechanisms, because there is that systemic use and a lot of data for that that we don't have for the other two, the only drawback I see for bringing these other two in is I'm not sure that any data on tromethamine helps to support the safety of these other two in my mind because in terms of sensitivity mechanisms, I mean, I just looked with a group of students the other afternoon about the difference between certain people with certain genotypes and actually the molecular mechanism of action which has kind of now been revealed, why those people react to a back genotypes react to abacavir versus other people that don't at the very detailed molecular level.

And, so, it's very subtle difference based on that genetic difference and coming up with mechanisms for sensitization that could apply in this particular case. So, I'm not sure a read-across would be appropriate, although there's no evidence that suggests that any of the three are sensitizers. So, I mean, combining them, don't combine them, I don't care, but I think we need data honestly.

DR. BERGFELD: Dan?

DR. LIEBLER: So, I thought these three compounds, actually, they belong together in a report. I think they're actually good analogs of each other and I'm not sure what specifics you're referring to with abacavir, but that's another molecule entirely, so --

DR. HILL: Well, but the point was --

DR. LIEBLER: I mean, the --

DR. HILL: Is what fits in the pocket of the complement presenting functionality, and there was just a very small variation in the pocket based on the amino acid difference. And, so, the point is to get sensitization, you need haptic information, and I felt like in tromethamine, we actually have stearic shielding, is not the right -- but occlusion of the amino group that isn't there in the other two. So, on the one hand, ABD and AEPD are a little more lipophilic and you'd predict a little better dermal penetration, I guess.

But I don't have a problem with lumping them; I'm just saying they need to be individually considered and I don't consider that read-across would be appropriate for sensitization on those three if you put them together and that was why I was arguing strongly at the beginning yesterday to take that data out as being irrelevant. But then what I thought about it some more, I thought well, if it's coming, the amino group would be involved; then it at least would add to the weight of evidence.

DR. LIEBLER: Well, I think the inclusion of the three together makes sense and if we have further discussion of the potential for read-across or reinforcing use of data for these compounds, we'll enjoy that discussion next time.

DR. MARKS: I withdraw my motion, and, Paul, would you go ahead and restate your motion?

DR. BERGFELD: Before you --

DR. MARKS: I guess the question is: Do we reopen? If we're going to combine them, obviously, we're reopening AMPD since that was already concluded to be safe. And I think our team supports moving forward as you did or proposed.

DR. SNYDER: So, I think rather than going insufficient, I propose Alan gives us his blessing that we would table this, we would reopen the one that's been reviewed, we would bring in the one that hasn't been reviewed but is in the dictionary, and then we would indicate to industry that we would like to have sensitization data at concentration of us and impurities.

DR. BERGFELD: And, so, you've made a motion to table. There's no discussion, but is there a second?

SPEAKER: Second.

DR. BERGFELD: Then all those in favor of tabling?

(Hands raised)

DR. BERGFELD: Okay, unanimous. Now we'll have discussion. Rachael is up and then Halyna.

MS. WEINTRAUB: I just wanted to mention that I raised the concern about the fact that an analog essentially was used for this ingredient and I thought there was insufficient rationale for that and I think when we use an analog, it's significant because so much of our work is based on providing data and evidence to support the safety of ingredients. So, I think we need to use analogs wisely and only with sufficient rationale where it truly makes sense and I think that this tabling and looking back in the way that we are, I think is actually a good course to go because it will give us other opportunities to find more data to support these.

DR. BERGFELD: Thank you. Halyna?

DR. BRESLAWEC: (off mic)

DR. BERGFELD: Okay. All right. So, we'll move forward then with those comments.

Safety Assessment of Tromethamine, Aminomethyl Propanediol, and Aminoethyl Propanediol as Used in Cosmetics

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ABSTRACT

Tromethamine, aminomethyl propanediol, and aminoethyl propanediol are aliphatic or substituted aliphatic compounds. These ingredients function as a fragrance ingredient and a pH adjuster in cosmetics. The CIR Expert Panel reviewed relevant animal and human data related to these ingredients. The similar structure, properties, functions and uses of these ingredients enabled grouping them and using the available toxicological data to assess the safety of the entire group. *The Panel concluded that tromethamine, aminomethyl propanediol, and aminoethyl proanediol are safe as used as cosmetic ingredients in the practices of use and concentration of this safety assessment.* [*This conclusion to be verified by the Panel at the June, 2013 meeting*]

INTRODUCTION

Tromethamine (also referred to as Tris and THAM) is an aliphatic compound. Aminomethyl propanediol (AMPD; 2-amino-2-methyl-1,3-propanediol) and aminoethyl propanediol (AEPD; 2-amino-2-ethyl-1,3-propanediol) are substituted aliphatic compounds. These ingredients function as fragrance ingredients and pH adjusters in cosmetics.

The similar chemical structures, physicochemical properties, and functions and concentrations in cosmetics enable grouping these ingredients and reading across the available toxicological data to support the safety assessment of the entire group.

CIR issued a safety assessment of AMPD in 1990, concluding that AMPD is safe in the present practices of use up to 1%.[1] This conclusion was amended in 2009 with a safe as used conclusion.[2] The summaries of these safety assessments are provided below. New data received are incorporated in this report. Also included in the text is nay information provided on the pH or form (i.e., free base, salt) of these ingredients.

CHEMISTRY

Definition and Structure

Tromethamine conforms to the structure in Figure 1. AMPD and AEPD are shown in Figure 2. Definitions and functions are provided in Table 1.

Physical and Chemical Properties

Physical and chemical properties are presented in Table 2.

Tromethamine is reported to be stable when exposed to light and air but is unstable with freezing.[3,4]

Method of Manufacture

Tromethamine is prepared by the reduction of tris(hydroxymethyl)nitromethane.[5,6] Tromethamine may also be manufactured by additively reacting nitromethane with formaldehyde to yield tris(hydroxymethyl) nitromethane, which is then hydrogenated with the aid of Raney nickel catalyst.[4,7]

Impurities

No published impurity data were discovered and no unpublished data were submitted.

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 3).[8] A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for tromethamine.[9] The Council is currently conducting a survey for the maximum used concentrations of AMPD and AEPD. Concentration of use data for AMPD from 2007 are presented here.

Tromethamine is used in 488 leave-on products and 70 rinse-off products up to 3.7% (in nail cream and lotions). Products include eye makeup (up to 2%), fragrance preparations (up to 0.2%), and skin care preparations (up to 3.1%).

AMPD was reported by the VCRP to be used in 131 leave-on products including 121 in the eye area. It is also reported to be used in 2 rinse-off products (skin cleansing products).

In 2007, it was reported that AMPD was used up to 3% in leave-on products, up to 7% in rinse-off products, and up to 2% in products diluted for bath.[2] These include: 7% in hair dyes and colors before dilution; 0.5% in face and neck sprays; 0.07%-0.5% in face and neck creams, lotions, and powders; 0.1 %-0.5% in body and hand sprays; 0.05%-1% in body and hand creams, lotions, and powders; 0.4% in foot cream; 0.03%-0.5% in foot powders and sprays;0.5% in moisturizing sprays; 0.5% in moisturizing creams, lotions, and powders; 0.5% in night sprays; 0.5% in night creams, lotions, and powders; 0.09% in an antibacterial hand soap; 0.2% in a hand sanitizer; 2% in pore strips; and 2% in a body polish.

There were no reported uses for AEPD by the VCRP.

Tromethamine was reported to be used in fragrance preparations up to 0.2% as well as in face powders and fragrance powders up to 0.05% that may be propellant and pump spray products, and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10, with

propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.[10-13] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[14-19]

Non-Cosmetic

Tromethamine is used in the synthesis of surface-active agents, vulcanization accelerators, and pharmaceuticals. It is also reported to be used as an emulsifying agent for mineral oil and paraffin wax emulsions, leather dressings, textile specialties, polishes, cleaning compounds, and so-called soluble oils. It is used as an absorbent for acidic gases and as a biological buffer.[20] Tromethamine was reported to be used as a commercial emulsifier.[21]

Tromethamine has several medical uses which include:

- Orally administered tromethamine citrate syrup (1.5-9 mmol/kg) is used to treat renal acidosis, adjusted to maintain urinary pH, and for chemolysis of renal calculi.[22]
- Intravenously administered tromethamine (15 mmol/kg or 3.5 L of 0.3 mol/L maximum) is used in the treatment of adult and infant respiratory distress syndromes and in the management of increased intracranial pressure after trauma, over several days.[23-25]
- Intravenously administered tromethamine is used to treat acidosis during pulmonary bypass and cardio surgery that requires hypothermic techniques.[26-29]
- Intravenously administered tromethamine is used to treat acidosis in burn victims.[30]
- Tromethamine (~60% of 0.15 mol/L) administration by peritoneal has been used for the treatment of intoxication with salicylates, barbiturates and methyl alcohol (methanol).[24,31,32]
- Tromethamine, mixed with hydrochloric acid (to a pH of 9.2) or acetate, sodium bicarbonate and disodium phosphate (to a pH of 8.1), is used for peritoneal dialysis to treat acidemia in humans and will cause alkalization of the plasma.[24]

In veterinary medicine, tromethamine is an amine pH buffer prescribed for the prevention and correction of metabolic acidosis, usually as a 0.3 M solution (0.3 mEq/mL) in a 7.5% sodium bicarbonate (q.v.) solution.[33]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Tromethamine is eliminated by the kidneys. Ionized tromethamine (chiefly as the bicarbonate salt or tromethamine citrate) is rapidly and preferentially excreted in urine at a rate associated with the infusion rate. Urinary excretion continues over a period of 3 days; 75% or more appears in the urine after 8 hours. Other studies report 50% - 75% of an i.v. dose was recovered in urine within 24 h. Recovery of tromethamine in urine from healthy adults is reported to be 64% and 77% after 2 and 3 days, respectively.[22,34-36] Excretion of tromethamine is accompanied by osmotic diuresis, since clinical doses of tromethamine considerably adds to osmolarity of glomerular filtrate.[4]

Tromethamine is a buffer that is primarily eliminated from plasma through renal filtration of its protonated form.[24,37] Tromethamine may accumulate in patients with renal insufficiency, and produce an 'osmolar gap' with pseudohyponatremia.

It is not known whether tromethamine is distributed into human milk.[34]

Dermal/Percutaneous

TROMETHAMINE

Dermal absorption was < 1% when radiolabeled tromethamine hydrochloride (0.1% and 10%; 100 μL) was administered to dermatomed, thawed human skin in Franz cells.[38] The receptor fluid was sampled at 2, 4, 6, 8, and 10 h. After washing, the retention of tromethamine hydrochloride in the dermis and epidermis was 0.13%-0.14% and 0.69%-0.22%, respectively. The test material was not retained in the horny layer. The washing waters contained more than 90% of the applied dose. Recovery of the test material by washing was > 90%.

Oral

TROMETHAMINE

Oral administration of tromethamine (20 g) resulted in alkalization of the body fluids.[39]

In human subjects, daily administration of tromethamine citrate syrup (3 and 6 mmol/kg) produced urinary alkalization (pH increasing from a range of 5.6 - 6.8 to 7.2-7.3).[31]

Intravenous

TROMETHAMINE

When administered intravenously (i.v.) in a bolus or over a short-term, tromethamine rapidly distributes into the intracellular spaces and raises the pH of plasma.[23,35-37,40-44] The cells slowly take up the tromethamine; the rate of uptake

increases when the pH is more alkaline. However, one study's conclusion contradicts the findings of previous studies suggesting that tromethamine permeates very slowly into intracellular space. A representative set of studies are presented here as well as the study with the opposite conclusion.

In rats of different ages (5 to 240 days old) the renal excretion of tromethamine was studied.[40] In older rats the renal excretion of tromethamine was slower than in rats of other age groups. Stimulation of diuresis by i.p. injection of mannitol, thiazide, or by oral water load resulted in an increase in tromethamine excretion in 5- and in 240-day-old rats. The renal excretion of tromethamine was also increased by repeated administration of tromethamine in all age groups, except in newborn rats.

When ^{14}C-tromethamine is administered i.v. to nephrectomized Sprague-Dawley rats (n = 21-26; with blood stabilized at pH 7.5, 7.4, 7.2), the following was found: 1) tromethamine diffuses very slowly into the intracellular spaces of various tissues; 2) the intracellular concentration of tromethamine increased faster with the higher pH; 3) the rate of increase of tromethamine was the same in spleen, heart, skeletal muscle, and brain tissue; 4) tromethamine diffusion into liver cells is rapid, which is not so for spleen, heart, skeletal muscle, and brain tissue; and 5) the intracellular steady state was only reached in the liver.[44]

The rats were nephrectomized and catheterized (venous and arterial). After administration of the test material, some of the rats were killed and necropsied at 60, 180, 360, 720, and 1440 min. The experiment was repeated (n = 26) with the blood stabilized at pH 7.4. The authors concluded that the mechanism of tromethamine therapy is its elimination of H^+ ions from the extracellular space and the generation of bicarbonate that then penetrates the intracellular compartments.[44]

When ^{14}C-tromethamine (5 µci) was administered i.p. to nephrectomized Wistar rats (n = 6), the half-life in the plasma was 90 min.[41] The half-times to equilibrium for tromethamine distributed to heart and skeletal muscle were 2.7 and 5 h, respectively. Distribution to the brain and cerebrospinal fluid were very slow and a constant tissue:plasma ratio in the brain was not obtained at 24 h. The rats were killed and samples of blood, cerebrospinal fluid, skeletal muscle and cerebral cortex analyzed at 10, 20, 30, 40, 50, 60, 90, 120, 180, 240, 300, and 360 min after the test material was administered

In a second experiment, when administered i.p. to rats, the largest amount of ^{14}C-tromethamine was collected in skeletal and heart muscle at 12 and 24 h. Accumulation was slower in brain tissue and cerebrospinal fluid.[41]

Rabbit (strain and n not provided) were intravenously injected with tromethamine (5 - 100 ml/kg; 0.3 M at pH 5.5 and 7.4) daily for 1 – 99 days.[43] Urinalysis revealed that the amount of tromethamine excreted in the urine reached a maximum at the end of infusion, and dropped rapidly after infusion stopped. Only a small quantity of chloride was excreted in any group. Rabbits administered tromethamine at pH 5.5 excreted a larger amount of chloride than those administered tromethamine at pH 7.4. At the end of the 7 hours, 44% of the infused tromethamine was found in the urine in the pH 7.4 group, while with tromethamine having pH 5.5, 77% was found in the urine. Blood sampling showed that the glucose concentrations dropped during the infusions, but returned to normal or above normal following the end of the infusions (tromethamine-induced hypoglycemia persisted longer than the tromethamine-neutralized). Both treatments caused transient hypoglycemia. Studies with extracted blood (tromethamine added to blood droplets at varying levels) also determined that there was no deleterious effect on erythrocytes.

Tromethamine (121 mg/kg; 1 mmol/kg; pH 7.4) was mostly eliminated by the kidneys (82% was recovered in the urine at 24 h) when administered i.v. to healthy subjects (n = 6) and subjects with metabolic acidosis (n = 20).[37] Tromethamine did accumulate in the tissues, but equilibrium was slow.

The distribution of ^{14}C labeled tromethamine was determined between intra- and extracellular space of nephrectomized Sprague-Dawley rats (n = 5) as a function of time at constant plasma pH of 7.4.[45] An equilibrium in the distribution of tromethamine between external and internal cellular space was observed at 6-12 h after administration. The authors concluded that tromethamine permeates very slowly into intracellular space, in contrast to previous conclusions that it quickly diffuses into intracellular spaces to restore intracellular acidosis. The authors concluded that tromethamine passed from extracellular space in a multi-exponential fashion, indicating that it passes to different body tissues at variable rates and is in ionized form when transferring across cellular membranes.

Cytotoxicity

TROMETHAMINE

In cytotoxicity assays using multiple cell lines, the IC_{50} for tromethamine ranged from 129.07 - 404.37 µg/ml. In the 2,5-Diphenyl-3,-(4,5-dimethyl-2-thiazolyl) tetrazolium bromide (MTT) assay, after exposure for 24 h, the IC_{50}s were ~330 µg/ml for 3T3 cells, ~160 µg/ml for 3T6 cells, ~340 µg/ml for HaCaT cells, ~180 µg/ml for NCTC 2544 cells, ~340 µg/ml for HeLa cells, and ~405 µg/ml for MCF-7 cells. In the neutral red uptake (NRU) assay, the IC_{50}s were ~295 µg/ml for 3T3 cells, ~130 µg/ml for 3T6 cells, ~160 µg/ml for HaCaT cells, ~ 190 µg/ml for NCTC 2544 cells, ~190 µg/ml for HeLa cells, and ~ 315 µg/ml for MCF-7 cells.[46]

Blood Effects

TROMETHAMINE

Because tromethamine (in the form of R-NH_2) is a proton acceptor with a pK of 7.8, it is an effective buffer that can be used to maintain the pH of body fluids.[24]

Tromethamine administered i.v. caused a decrease in blood glucose levels in rats, rabbits, dogs, and humans.[42,47,48] Tromethamine lowered the blood sugar of dogs after the removal of the pancreas when given a few hours after pancreatectomy, but had little or no effect on the blood sugar of pancreatectomized dogs if insulin was withheld for 18 hours or longer before tromethamine was administered.

Hypoglycemic effect of tromethamine was due to the release of insulin and its activity.[48] Tromethamine-induced hypoglycemia is associated with a transient stimulation of insulin secretion in rats. A bolus injection of neutralized tromethamine (5 mmol/kg; pH 7.4), caused a transient increase of plasma insulin concentration (130 ± 20 μU/mL) but did not change the glucose concentration in male Wistar rats (n = 6). However, a continuous infusion of tromethamine (0.5 mmol/kg/min) for 90 min decreased the plasma glucose concentration (8.7 + 0.42 to 5.1 + 0.33 mmol/L) after 30 min. The plasma insulin concentration was elevated during the first 20 min (max +122 ± 21 μU/mL after l0 min). In streptozotocin-diabetic rats (administered 48 h prior to the experiments), an infusion of tromethamine changed neither glucose nor insulin concentration in plasma.

TOXICOLOGICAL STUDIES

Acute Toxicity

Oral – Non-Human

TROMETHAMINE

The oral LD_{50} for mice was reported to range from 3350 to 5500 mg/kg (Table 4). For rats, the LD_{50} was > 5000 mg/kg. The LC_{50} was between 1000 and 2000 mg/kg.[49-51]

Dermal – Non-Human

TROMETHAMINE

The dermal LD_{50} of tromethamine for rats was reported to be > 5000 mg/kg for rats (Table 4).[52]

Subcutaneous – Non-Human

TROMETHAMINE

The subcutaneous LD_{50} was reported to be > 1000 mg/kg for mice and rats (Table 4).[50]

Intraperitoneal – Non-Human

TROMETHAMINE

The intraperitoneal LD_{50} of tromethamine for mice was reported to be ~3350 mg/kg (Table 4).[53,54]

Intravenous – Non-Human

TROMETHAMINE

The intravenous LD_{50} of tromethamine for mice was reported to be 16.5 mM/kg (Table 3). There were no mortalities reported at < 5000 mg/kg. The LD_{50} for rats was reported to range between 3.28 and 4.04 g/kg and up to ~6000 mg/kg. There were no treatment related mortalities in rabbits administered tromethamine up to 500 mg/kg. In dogs, the LC_{50} was reported to be >125 mg/kg.[43,50,55,56]

Dogs (breed not specified) exhibited profuse diuresis during i.v. treatment with tromethamine.[35] Dogs (n = 5) were anesthetized and rendered apneic using succinylcholine chloride. Apnea was then induced by barbiturates. Under oxygen saturation, tromethamine (0.3 M; 1.1 ml/kg/min) was administered i.v.

Repeated Dose Toxicity

Oral – Non-Human

TROMETHAMINE

The lowest observed adverse effects level (LOAEL) for tromethamine for Sprague-Dawley rats (n not provided) was reported to be 2500 ppm when incorporated into feed (0, 25, 150, 250, 2500 ppm) for 3 months.[57] Specific adverse effects were not provided.

The NOAEL for local toxicity was 100 mg/kg/d and ≥ 1000 mg/kg/d for systemic toxicity for Crl:CD(D) rats (n = 10) orally administered tromethamine (100, 300, 1000 mg/kg/d adjusted to pH 9) by gavage in a reproduction study.[52] Males (n = not provided) were treated for at least 2 weeks before breeding up to 29 days. Females (n = 12) were treated from 2 weeks prior to breeding, through gestation, and through 4 days of lactation for up to 54 days. There were no systemic effects but there was irritation to the forestomach.

When tromethamine (2500 mg/kg) was orally administered to rats (n = 38; strain not provided) for 15 days, there were no mortalities or clinical signs observed.[52]

When tromethamine (250-4000 mg/kg) was orally administered to rats (n = 36; strain not provided) for 31 days, there were no mortalities or clinical signs observed except for moderate diarrhea in the highest dose.[52]

Dogs (n – 12/dose; strain not specified) orally administered tromethamine (250, 1000, 4000 mg/kg) for 30 days had

no mortalities.[52] Dogs in the mid dose group had occasional loose stool and vomiting. Dogs in the high dose group had frequent loose stool and vomiting. Urinalysis showed reduced urinary potassium in the mid and high dose groups. The authors considered the NOAEL to be 4000 mg/kg because none of the effects were considered permanent.

Dermal – Non-Human

TROMETHAMINE

There were no clinical signs to rabbits (strain and n not provided) dermally administered tromethamine (100%) on clipped skin for 4 h for 5 days.[51]

Intravenous – Non-Human

TROMETHAMINE

There were no clinical signs or mortalities observed to mice (strain and n not provided) administered i.v. tromethamine (10, 50 mL/kg; 0.155 M; pH 5.5, 7.4) for 10 days.[43] Histological examination of the organs did not identify any adverse effects from the treatment.

Other than necrotic effects at the injection site (ear) and transient body temperature changes, there were no adverse effects to New Zealand White rabbits (n = 4/sex) administered tromethamine (0.5 g/kg; 0.3 M) for up to 20 days.[56] Two rabbits/sex were necropsied within 24 h of the last dose. The rest had 20-days recovery before necropsy.

There were no effects on feed and water consumption and body temperature. Body weights fluctuated throughout the study in all animals, including control animals, but not in any treatment-related pattern. Of the treated rabbits, 7/8 had inflammatory lesions of the external ear. The lesions varied from swelling and redness to dry gangrene and erosion.

Weekly blood samples were normal for: total serum proteins, albumin/globulin (A/G) ratio, serum bilirubin, cephalin flocculation, serum transaminase, red blood cell count, differential counts, hemoglobin, microhematocrit, and platelet counts. White blood cell counts in excess of 13,000 were seen in 5/8 rabbits receiving tromethamine. In all cases, elevated white blood cell counts coincided with dry gangrene in the external ear. Urinalysis findings were unremarkable.

Of the treated rabbits necropsied after recovery, 2.4 had grossly visible infarcts in the kidneys; there were none in the control group. No gross lesions were observed in any other organ or tissue. In 7/8 test animals with gross lesions of the ear, there were microscopic lesions of chronic cellulitis and necrosis at injection sites in the subcutaneous tissues of the ear. Those with kidney lesions also had chronic interstitial nephritis. Infiltrations of lymphocytes were observed in tissue sections of the liver and kidney of 3 treated rabbits. The infiltrations were observed in animals in the recovery and non-recovery groups. Peracute toxic nephrosis was observed in 1 rabbit, which also had urolithiasis.[56]

Treatment-related mortalities occurred a few days after starting the i.v. administration of tromethamine (100 ml 0.3 M at pH 5.5 and 7.4) to rabbits (strain not provided; n = 2-3).[43] Tromethamine was administered i.v. over 5 h daily for 19 d. Other groups were administered tromethamine (5 and100 ml 0.3 M/kg at pH 5.5 and 7.4) over 5 h daily for 1 – 99 d.

The neutralized tromethamine was less toxic. Observed clinical signs included anorexia, bloody urine, hind leg paralysis, and irregular respiration. Observations at necropsy included abnormally red lungs, necrosis at the point of infusion, bleached liver, darkened spleen, bloated stomach, and lesions on the heart and kidney. Histology examination of the organs was negative.[43]

There were no treatment-related mortality or clinical signs to rabbits (strain not provided; n = 3) administered i.v. tromethamine (50 and 10 ml/kg 0.155 M; over 30 sec) once daily for 10 d.[43] Histological study of the organs was negative.

Rabbits (n = 5) administered tromethamine (1500, 3000 mg/kg; 0.2 mL/kg/min in Ringer's solution; 0.34 M) by catheter for 21 days had two mortalities (days 6 and 12) in the high dose group.[52] Clinical signs included rapid, shallow breathing during infusion.

Catheterized dogs (n = 5) administered i.v. tromethamine (1500, 3000 mg/kg: 0.34 M in Ringer's solution; 0.5 mL/kg/min) for 21 days exhibited sporadic convulsions and vomiting.[52] One dog in the high dose group died during treatment. Three dogs in the low dose group had increased retention of bromosulfophthalein (BSP). Infarcts (multiple abscesses) of the liver were observed in three dogs in the low dose group. Colonies of bacteria, acute inflammatory exudate, and hypertrophy of the Kuppfer cells were observed in the same livers.

The no observed adverse effects level (NOAEL) for Sprague-Dawley rats (n = 6/sex) administered tromethamine i.v. (0.5 and 1.5 g/kg; 0.3 M) for 10 and 20 days was reported to be ~ 500 mg/kg.[56] Rats were allowed 24 h or 7 d for recovery. On day 11, a second high dose group was treated with additional tromethamine using i.p. injection.

There were no mortalities in the 20-d low dose group. There was dry gangrene at injection sites in the 10- and 20-d low dose groups. In the 20-d groups, about half of the rats had mild inflammation of various parts of the visceral peritoneum, or fat necrosis and hemorrhage of the serosa of various parts of the stomach, intestine, and peritoneum. Microscopic examination of tissues 24 h after injection i.p. showed 5/6 rats of the 20-d low dose group had chronic cellulitis at injection sites, and peracute toxic nephrosis of the kidneys, but not in animals allowed the 7-day recovery period. In the 20-d high dose group, all rats necropsied at 24 h and 5/6 rats in the 7-day recovery group had similar findings.[56]

Intraperitoneal – Non-Human

TROMETHAMINE

Tromethamine (30 mL/kg: 0.075 M) administered i.p. to dogs (n = 3) under anesthesia for days caused no clinical signs during treatment.[52] One dog died on day 3; this was attributed to heartworms. There were no histopathological signs attributed to the test substance.

Intratracheal – Non-Human

TROMETHAMINE

Tromethamine (in an unknown mixture with 0.9% saline; 2 mL; vehicle control in an experiment) did not decrease survival or average body weight of male Syrian hamsters (n = 28-29) when administered over the lifetime of the hamsters compared to hamsters in the no treatment group.[58] There were no differences in survival (88 ± 22 vs. 78 ± 25 weeks) and average body weight (116 ± 10 vs. 114 ± 6 g) between the vehicle and the no treatment groups.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

TROMETHAMINE

The NOAEL for reproduction and teratogenicity for tromethamine using rats was ≥ 1000 mg/kg/d. [52] Female Crl:CD(D) rats (n = 10) were orally administered tromethamine (100, 300, 1000 mg/kg/d adjusted to pH 9) by gavage. Males (n = 10) were treated for at least 2 weeks before breeding up to 29 days. Females (n = 12) were treated from 2 weeks prior to breeding, through gestation, and through 4 days of lactation for up to 54 days.

Tromethamine had no effect on mating performance or conception. There were no effects to mating index, fertility index, gestation period, deliver index, and number of live pups. There were no effects observed to the F1 pups at birth.

GENOTOXICITY

In Vitro

TROMETHAMINE

Tromethamine (1 mg/mL; pH 7.4) was toxic but not mutagenic to *Escherichia coli* (CHY832) in an RK assay.[59] The *E. coli* were killed at 42°C but not at 30°C.

AEPD

In an in vitro mammalian chromosome aberration test using Chinese hamster lung (CHL/IU) cells, AEPD (75, 150, 300, 600, 1200 µg/mL in saline) was not genotoxic with and without metabolic activation when exposed for 24 and 48 h.[52]

AEPD (156, 313, 625, 1250, 2500, 5000 µg/plate in water) was not mutagenic to *S. typhimurium* (strains TA98, TA100, TA1535, TA1537) and *E. coli* (strain WP2 uvr A), with or without metabolic activation.[52]

AEPD (12, 38, 119, 337, 1192 µg/mL with metabolic activation; 15, 44, 132, 397, 1192 µg/mL without) was not mutagenic to Chinese hamster ovary (CHO) cells in an in vitro mammalian cell gene mutation test with or without metabolic activation.[52] AEPD was cytotoxic at 1192 µg/mL.

The above study was repeated with the same results.[52]

CARCINOGENICITY

TROMETHAMINE

When administered intratracheally as the vehicle control to male Syrian hamsters weekly for their entire lifespan, tromethamine (2 ml in 0.9% saline) did not induce tumors.[58]

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

TROMETHAMINE

In a Draize test, rabbits (strain and n not provided) were dermally administered tromethamine, both in solution (25%, saturation; pH 10.8) and as a crystalline product, to intact and abraded skin.[60] There was no noticeable irritation produced by any state of the test material on intact skin. There was mild irritation by the crystals at saturated states on abraded skin. All signs of irritation were completely resolved in 48 h. The author concluded that tromethamine was a mild irritant under these conditions.

Tromethamine (40% in distilled water) was not irritating to rabbits (n = 6) in a Draize test.[61]

In a dermal irritation test using New Zealand White rabbits (n = 3 males), tromethamine (0.5 g in enough water to make a paste) was not irritating when administered to shaved skin under semi-occlusion[52] Test sites were observed at 1, 24, 48 and 72 h.

Intradermal – Non-Human

TROMETHAMINE

Intradermally injected tromethamine (0.1 mL) was severely irritating to rabbits (strain and n not provided) at a pH of 10.4 (0.2, 0.3 M) and at pH 7.4 (0.6, 1 M).[43] The causes of local necrosis around the infusion site were investigated using injected Trypan dye. The irritation caused by the solutions was evaluated by observing the amount of extravasated dye. The neutral tromethamine (pH 5.5) had reduced irritation/local necrosis. At pH 7.4, tromethamine was not irritating at lower doses (0.2, 0.3 M). The authors suggested that the pH of the tromethamine is the probable cause of the dermal irritation.

Dermal – Human

TROMETHAMINE

A cosmetic product containing tromethamine (3.1%; neat) was not irritating when administered in a patch test (n = 11) for 48 h.[62]

Ocular

TROMETHAMINE

Tromethamine (0.1 g; finely ground) was not an ocular irritant when administered to New Zealand White rabbits (n = 3.[52] The eyes were observed at 1, 24, 48, and 72 h with a hand slit lamp. Fluorescein was used at 24 h. There was slight/ moderate redness and chemosis at 1 h; the irritation effects cleared by 24 or 72 h. No damage to the iris or cornea was observed.

Tromethamine (100%) was not an ocular irritant when administered to rabbits (strain and n not provided).[52]

Sensitization

Non-Human

AEPD

AEPD (0.05% - 0.5%; 0.5 ml) was not a sensitizer to male Hartley guinea pigs (n = 10) in a Buehler sensitization assay.[52] Some of the guinea pigs showed mild erythema during the initial five applications at 0.5% of the induction period, so the concentration was reduced to 0.05% the last five applications. Challenge was at 0.5% and 1%. No further data on the physical or chemical characteristics of the test material were provided.

In a Draize test, AEPD (0.05% - 1% in saline; 0.5 ml; 85.34% pure) was not a sensitizer to male Hartley guinea pigs (n = 10).[52] Some of the guinea pigs showed mild erythema during the initial five applications at 1% of the induction period, so the concentration was reduced to 0.05% the last five applications. Challenge was at 0.5% and 0.01%. No further data on the physical or chemical characteristics of the test material were provided.

AMPD

In a peptide reactivity assay for screening contact allergens, it was concluded that AMPD (4 nM) is not expected to cause dermal sensitization.[52] The peptide consisted of seven amino acids with an acetylated N-terminus and was incubated for 24 h. The positive control was diethyl maleate; the negative control was the vehicle, acetonitrile. The average depletion values for the test substance, the negative control, and positive control were 4.22 ± 1.84%, 4.83 ± 1.66%, and 96.13 ± 0.21%.

Human

TROMETHAMINE

In a human repeated insult patch test (HRIPT; n = 101) of a mascara containing tromethamine (1.8%; ~0.2 g), there were no signs of irritation or contact sensitization observed.[63]

In an HRIPT (n = 102) of a mascara containing tromethamine (2%), there were no signs of irritation or sensitization observed.[64]

In an HRIPT (n = 102) of a mascara containing tromethamine (2%), there were no signs of irritation or contact sensitization observed.[65]

In an HRIPT (n = 102) of a water-based eyeliner stick containing tromethamine (2%), there were no signs of irritation or sensitization observed. The authors concluded that this product is not contraindicated for usages entailing repeated applications on human skin.[66]

In an HRIPT (n = 85) of a fragranced body lotion containing tromethamine (1.8%), there were no indications of dermal irritation or allergic contact sensitization.[67]

AEPD

In a patch test of 16 components of metalwork fluids (MWF; n = 160; including current metalworkers exposed to MWF, some with occupational dermatitis), only one had a positive reaction to AEPD (1% aq.) on day 3 of observation.[68] This subject was not among the subjects that were exposed to MWF. The authors used industrial grade metalwork chemicals; AEPD was reported to be 85% pure. In a follow up study on just metalworkers (n = 144) exposed to MWF, only one tested positive for AEPD (2% pet.)[69] Analysis of 17 different MWFs revealed that AEPD was present at 0.06% - 0.39% with a

median of 0.09%.[70]

CLINICAL USE

TROMETHAMINE

Tromethamine (20 g in 3.3% glucose) was administered i.v. to male subjects (n = 4) with respiratory acidosis due to emphysema or carcinoma of the lung over 40 min.[39] Blood pH increased, O_2 tension decreased, and CO_2 tension remained unchanged (except for in 1 subject which decreased) over the administration time. Urinary pH increased within 20 min of the start of infusion with the exception of the same subject; the increase happened at 40 min.

Case Studies

TROMETHAMINE

A 30-year-old woman developed severe respiratory acidosis following cardiac surgery.[39] After she was administered tromethamine (120 g in water) by gastric tube over 24 h, the acidosis was resolved but she developed severe diarrhea. She also developed tetany which was controlled with calcium gluconate. Her arterial pH rose from 7.1 to 7.45 and she had no further acidosis. While she died from other complications, there were no adverse effects from the tromethamine treatment observed at autopsy.

A 40-year-old man, who had a 9-rib thoracoplasty, presented with extensive pneumonia.[39] He was unconscious within 12 h with slow, gasping respirations. A tracheotomy and 100% oxygen were not helpful. O_2 saturation was 97%, CO_2 tension was 160 mm Hg, and pH was 6.95. He was administered tromethamine (30 g in water; 10%) over 1 h. Arterial blood was then at 92% saturation and CO_2 tension was 80 mg Hg with a pH of 7.2. Additional tromethamine (10 g) was administered after 5 h. O_2 saturation was 49%, CO_2 tension was 68 mm Hg, and the pH was 7.29. No adverse effects from the tromethamine treatment were reported.

SUMMARY OF DATA FROM THE AMPD SAFETY ASSESSMENTS

2009

AMPD is a substituted aliphatic alcohol used as a cosmetic ingredient.[2]

AMPD occurs in solid and liquid forms. AMPD is soluble in both water and alcohols.

AMPD function as a pH adjuster in cosmetic products. AMPD is also a fragrance ingredient. AMPD is used in concentrations up to 2%.

A hair spray containing 0.50% AMPD was nontoxic to rats.

When both albino rats and Syrian Golden hamsters were exposed in a 13-week subchronic inhalation toxicity study to a hair spray formulation containing 0.1350% AMPD for 4 hours per day, 5 days per week, no significant compound-related adverse effects were observed.

Cosmetic formulations containing 0.40% AMPD were moderate ocular irritants.

AMPD was not mutagenic, with and without metabolic activation, in *S. typhimurium* strains TA 1535, 1537, 98, and 100.

In a primary irritancy test of a cosmetic formulation containing AMPD, scattered incidences of questionable responses were observed in two thirds of the panelists. In addition, 2 of 15 panelists had slight redness at least once during the observation period.

A cosmetic formulation containing 0.073% AMPD was not a primary irritant, and it was neither a fatiguing agent nor a sensitizer. In another study, a cosmetic formulation containing 0.50% AMPD was not a sensitizer.

1990

AMPD is a substituted aliphatic alcohol. It occurs in solid and liquidforms. AMPD is soluble in both water and alcohols. AMPD functions as an emulsifying agent for cosmetic creams and lotions, and as a neutralizing agent in hair sprays. AMPD is used in concentrations up to 5%. All uses at concentrations above 1% involve neutralization of AMPD with fatty acids.

In industry, AMPD is used in the synthesis of surface-active agents, as a vulcanization accelerator, in pharmaceuticals, and as emulsifying agents for a variety of products.

According to the classification of Hodge and Sterner, a hair spray containing AMPD was practically nontoxic to albino rats. Additionally, when both albino rats and Syrian Golden hamsters were exposed in a subchronic inhalation toxicity study to hair spray formulations containing AMPD, no significant compound-related adverse effects were observed.

Cosmetic formulations containing AMPD were also non- to minimally irritating to rabbit skin.

Cosmetic formulations containing AMPD were moderate ocular irritants.

AMPD was not mutagenic, with and without metabolic activation, in S. typhimurium strains TA1535, 1537, 98, and 100.

In a primary irritancy test of a cosmetic formulation containing AMPD, scattered incidences of questionable responses were observed in two-thirds of the panelists. In addition, 2 of 15 panelists had slight redness at least once during the observation period.

A cosmetic formulation containing AMPD was not a primary irritant, and it was neither a fatiguing agent nor a sensitizer. In another study, a cosmetic formulation containing AMPD was not a sensitizer.

SUMMARY

Tromethamine is an aliphatic compound that functions as a fragrance ingredient and a pH adjuster. AMPD and AEPD are substituted aliphatic compounds. AMPD was previously reviewed by the Panel and found to be safe as used.

Tromethamine is used in 480 leave-on cosmetic products and 69 rinse-off products up to 4% in skin care preparations. AMPD was reported in the VCRP data to be used in 131 leave-on products including 121 in the eye area. It is also reported to be used in 2 rinse-off products (skin cleansing products). There were no reported uses in the VCRP for AEPD.

No data about impurities were discovered or submitted.

Tromethamine has several medical uses, including treatment for acidosis under several circumstances.

Tromethamine is eliminated by the kidneys in mammals. There was little dermal absorption in human skin.

Tromethamine was cytotoxic to multiple cell types in the range of 129 – 405 µg/ml.

Tromethamine administered i.v. caused a fall in blood glucose levels in rats, rabbits, dogs, and humans.

The oral LD_{50} for mice was reported to range from 3350 to 5500 mg/kg. For rats, the LD_{50} was > 3000 mg/kg. The LC_{50} was between 1000 and 2000 mg/kg. The dermal LD_{50} of tromethamine for mice and rats was reported to be > 1000 mg/kg and > 2000 mg/kg for rabbits. The intraperitoneal LD_{50} of tromethamine for mice was reported to be ~3350 mg/kg.

The LOAEL for tromethamine for rats was reported to be 2500 ppm when incorporated into feed for 3 months. The local NOAEL for orally administered tromethamine was 300 mg/kg/d for 14 – 37 days. Tromethamine at 1000 mg/kg caused loose stool and vomiting in dogs.

There were no adverse clinical signs in rabbits dermally administered tromethamine at 100% on clipped skin for 4 h for 5 days.

Intravenous toxicity of tromethamine was minimal at neutral pH. However, at a more alkaline pH range, gangrene at the injection sites, tissue necrosis, inflammatory lesions, visible infarcts in the kidneys, bleached liver, darkened spleen, and lesions on the heart were reported. Anorexia, bloody urine, and paralysis were also observed.

Intratracheal tromethamine in an unknown mixture with 0.9% saline did not decrease survival or average body weight of hamsters when administered over their lifetime.

There were no adverse effects on reproduction at 1000 mg/kg/day to rats.

Tromethamine was toxic, but not mutagenic, to *E. coli* in an RK assay. AEPD was not mutagenic in a chromosome aberrations tests up to 5000 µg/plate.

Tromethamine at 2 ml did not induce tumors when administered intratracheally to hamsters weekly for their entire lifespan.

Tromethamine was a mild irritant to rabbits at 25% with a pH of 10.8. At 40%, tromethamine was not irritating.

Intradermal injections of tromethamine were severely irritating to rabbits at pH 10.4 but were only mildly irritating at pH 7.4. Tromethamine was mildly irritating at 25% with a pH of 10.8 and not irritating at 40% in distilled water. Tromethamine in a paste with water was not irritating to the shaved skin of rabbits.

AEPD was not a sensitizer to guinea pigs at 0.05%. It was an irritant at 0.5%.

AMPD was not expected to be a dermal sensitizer in a peptide reactivity assay.

In a patch test of subjects, some with professional contact of metalwork fluids that contain AEPD, only 1/160 had a positive reaction.

A cosmetic product containing 3.1% tromethamine was not irritating a patch test.

Tromethamine was not an ocular irritant to rabbits at 100%.

AEPD was not a sensitizer to guinea pigs up to 1%.

Five products containing tromethamine up to 2% were not irritating in HRIPTs. There was only one positive reaction among 233 subjects with past or present exposure to metalworking fluids to AEPD at 85%.

Tromethamine at 20 g administered i.v. was not toxic to subjects being treated for respiratory acidosis.

DISCUSSION

Although there are data gaps, the similar chemical structures, physicochemical properties, and functions and concentrations in cosmetics allow grouping these ingredients together and interpolating the available toxicological data to support the safety of the entire group.

The Panel discussed the issue of incidental inhalation exposure from tromethamine in fragrance preparations up to 0.2% as well face powders and fragrance powders up to 0.05% that may be propellant and pump spray products. The limited data available from inhalation studies, including acute and chronic exposure data, suggest little potential for respiratory effects at relevant doses. AMPD was not toxic to hamsters and rats in subchronic inhalation studies.

The Expert Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. These ingredients are reportedly used at concentrations up to 2% in cosmetic products that may be aerosolized and up to 0.05% in

other products that may become airborne. The Panel noted that 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, these ingredients are not likely to cause any direct toxic effects in the upper respiratory tract, based on the properties of the tromethamine, AEPD, and AMPD and on data that shows that these ingredients are not irritants. Coupled with small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for these ingredients to cause systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, and genotoxicity. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

The Panel noted that tromethamine has long time use as a pharmaceutical at high pH levels (> 7) to treat acidosis-related ailments and as a biological buffer. Tromethamine did not penetrate skin and toxicity studies, including reproductive/developmental toxicity, showed that these ingredients were not toxic at levels greater than those used in cosmetics. This information along with negative dermal irritation/sensitization assays, including tests of products containing these ingredients, reassured the Panel that there are no safety concerns for these ingredients.

It is expected by the Panel that cosmetic grade tromethamine, AMPD, and AEPD contain impurities at levels below any amount of concern. OR However, the Panel was concerned that no information on impurities was available. [*The Panel will edit and amend this Discussion at the June, 2013 meeting*]

CONCLUSION

The CIR Expert Panel concluded that tromethamine, aminomethyl propanediol, and aminoethyl propanediol are safe in the present practices of use and concentration described in this safety assessment.* [*This conclusion to be verified by the Panel at the June, 2013 meeting*]

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

TABLES AND FIGURES

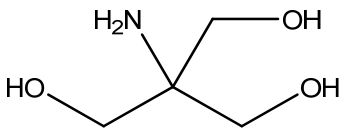
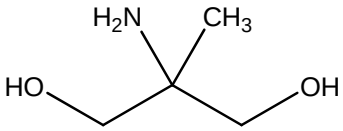
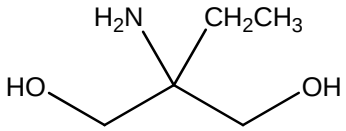


Figure 1. Tromethamine.



2-amino-2-methyl-1,3-propanediol
(AMPD)



2-amino-2-ethyl-1,3-propandiol
(AEPD)

Figure 2. AMPD and AEPD.

Table 1. Definitions and functions of the ingredients in this safety assessment.

Ingredient	Definition	Function
Tromethamine CAS No. 77-86-1	An aliphatic compound that conforms to the structure in Figure 1.	Fragrance ingredient; pH adjuster
Aminomethyl propanediol CAS No. 115-69-5	A substituted aliphatic diol that conforms to the structure in Figure 2.	Fragrance ingredient; pH adjuster
Aminoethyl propanediol CAS No. 115-70-8	A substituted aliphatic diol that conforms to the structure in Figure 2.	pH adjuster

Table 2. Chemical and physical properties of tromethamine.

Property	Value	Reference
Tromethamine		
Physical Form	Crystalline powder	20
Color	White	71
Odor	Slight, characteristic	4
Molecular Weight g/mol	121.14	20
Density/Specific Gravity @ 20°C	~1.3	72
	1.32	72
Vapor pressure mmHg @ 25°C	2.20^{e-05}	71
@ 20 °C	0.000267	72
Melting Point °C	171-172	20
	169	72
Boiling Point °C	219-220	20
	288 (decomposition)	72
Solubility g/L water	550	71
	678-689	72
ethylene glycol	0.0791	20
ethanol (95%)	0.022	20
acetone	0.020	20
Other Solubility g/L		
Diethyl ether	Insoluble	73
Chloroform	Practically insoluble	4
Benzene	Practically insoluble	4
Carbon tetrachloride	Practically insoluble	4
log K_{ow} @ 20 °C	-2.31	
Disassociation constants (pKb) @ body temperature	7.8	4
@ 25 °C	8.22	72
AMPD		
Physical Form	Liquid or chrystals	20
Color	Colorless liquid	73
Odor	Liquid-amine odor; crystals-odorless	73
Molecular Weight g/mol	105.14	20
Melting Point °C	109-111	20
	105.14	72
Boiling Point °C	151-152	20
@ 10 mm Hg	151	72
Water Solubility g/L @ 20°C	.250	20
Other Solubility		
Alcohols	Soluble	20
log K_{ow}	< -0.8	72
Disassociation constants (pKa, pKb) @ 25°C	8.76	72
AEPD		
Physical Form	Crystalline	20
	Liquid	72
Molecular Weight g/mol	119.16	20
Density/Specific Gravity @ 20 °C	1.08	72
Vapor pressure mm Hg @ °C	0.00217[a]	72
Melting Point °C	37.5-38.5	20
	-3	72
Boiling Point °C	152-153	20
	259-260	72
Water Solubility	Miscible	20
	> 950	72
Other Solubility		20
Alcohols	Soluble	
log K_{ow} @ 20 °C	-1.02	72
Disassociation constants (pKa, pKb) @ 25°C	9.03	72

[a] Converted from 0.29 Pa.

Table 3. Frequency of use according to duration and exposure of the ingredients in this safety assessment. The concentration of use data for AMPD is from 2007. The Council is conducting a survey for the concentration of use for AMPD and AEPD.[2,8,9]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	
	Tromethamine		AMPD		AEPD		
Total/range	**558**	**0.00009-3.7**	**133**	**0.0001-7**	**NR**	**NS**	
Duration of use							
Leave-on	488	0.0002-3.7	131	0.0009-3	NR	NS	
Rinse-off	70	0.00009-3.1	2	0.0001-7	NR	NS	
Diluted for (bath) use	NR	NR	NR	2	NR	NS	
Exposure type							
Eye area	75	0.8-2	121	0.3-1	NR	NS	
Incidental ingestion	1	0.002-0.03	NR	NR	NR	NS	
Incidental Inhalation-sprays	10	0.2-2	NR	0.0009-3	NR	NS	
Incidental inhalation-powders	NR	0.0002-0.05	NR	0.3-0.5	NR	NS	
Dermal contact	531	0.00009-3.1	16	0.0009-2	NR	NS	
Deodorant (underarm)	NR	NR	NR	0.0009-0.4	NR	NS	
Hair-noncoloring	11	0.001-0.8	NR	0.0001-3	NR	NS	
Hair-coloring	NR	NR	NR	0.5-7	NR	NS	
Nail	1	3.7	NR	0.0009-0.1	NR	NS	
Mucous Membrane	13	0.00009-0.03	NR	0.03-2	NR	NS	
Baby	NR	NR	NR	NR	NR	NS	

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

Table 4. Acute toxicity data for tromethamine.

Species (n)	Dose(s)	Results	Reference
		Acute oral toxicity	
Mice, strain not provided (10)	2000, 3500, 5000, 7000, 10000 mg/kg by gavage	LD_{50} = 5500 mg/kg	49
Swiss mice (10)	1000, 2000, 3000 mg/kg as 5% and 20% solutions by gavage	LD_{50} >3000 mg/kg. No toxicity noted. Abundant urine output for some mice.	50
Mice, strain not provided (not provided)	2000, 2500, 3530, 5000, 7000 mg/kg by gavage	LD_{50} = ~3350 mg/kg	49
Wistar rat (10)	1000 and 3000 mg/kg by gastric tube as 20% solution	No toxicity noted. Abundant urine output was recorded for some rats.	50
Wistar rat (10)	1000, 2000, 3000 mg/kg by gavage as 5% and 20% solutions by gavage	LD_{50} >3000 mg/kg. No toxicity noted. Abundant urine output for some rats.	50
Wistar rat, female (3)	5000 mg/kg in water by oral gavage; 3 doses with 2-day intervals	LD_{50} > 5000 mg/kg. No deaths or clinical signs.	52
Rabbits, strain not provided (not provided)	Delivered neat by gavage	LC_{50} between 1.00 - 2.00 g/kg. Weakness and collapse. Coma preceded deaths. No CNS signs or convulsions. Toxicity was due to alkalinity; neutralization reduced toxicity.	51
		Acute dermal toxicity	
Wistar rats (3)	5000 mg/kg for 24 h under semiocclusion on shaved skin	No mortalities or clinical signs.	52
		Acute subcutaneous toxicity	
Mice, strain not provided (5)	500 or 1000 mg/kg as 5% solution by subcutaneous injection	500 mg/kg caused irritation at the injection site. 1000 mg/kg caused the formation of lesions. LD_{50} > 1000 mg/kg	50

Table 4. Acute toxicity data for tromethamine.

Species (n)	Dose(s)	Results	Reference
Rat, strain not provided (5)	500 or 1000 mg/kg as 5% solution by subcutaneous injection	500 mg/kg caused irritation at the injection site. 1000 mg/kg caused the formation of lesions. LD_{50} > 1000 mg/kg	[50]
Acute intraperitoneal toxicity			
Mice, strain not provided (10)	2000, 2500, 3250, 3600, 4000, mg/kg by intraperitoneal injection at 0.015 ml/g.	LD_{50} = ~3350 mg/kg.	[53]
Male CD-1 mice (4-11)	100 mg/kg after drug-induced hypothermia/ shock using lipopolysaccharide	Hypothermic response was reduced at 4, 24, and 48 h. No other effects were reported.	[54]
Acute intravenous toxicity			
Mice, strain not provided (10)	0.3 M. i.v. injection (pH 5.5, 10.4) with and without dextrose or sodium chloride and observed for 24 h.	LD_{50} = 16.5 mM/kg. Mice convulsed immediately before dying. Neutralizing the pH and the additives did not change toxicity.	[43]
Mice, strain not provided (10)	100, 200, 400, 500, 1000, 3000, 5000, 6000, 7000 mg/kg as 1% solution	No mortality at doses < 5000 mg/kg. 6000 mg/kg, 40% mortality; 7000 mg/kg, 100%. Muscle weakness accompanied by respiratory difficulty prior to death. LD_{50} = ~ 6100 mg/kg	[50]
Sprague-Dawley rat (3/sex)	2.0, 2.5, 3.0, 3.5 g/kg of 0.6M; 4.0 and 4.5 g/kg of 0.9M in saline injected over 1 min followed by 2-h observations then necropsy.	Most rats died during treatment or within 10 min of treatment. The rest survived the observation period. No gross lesions observed except for in the liver and kidneys. Peracute toxic nephrosis was observed in the kidneys; moderate degree of pyknosis of the nuclei of isolated segments of the renal tubular epithelium in 2 and 2.5 g/kg groups, and was dose dependent. In higher dose levels, the lesions were severe pyknosis of the nuclei of swollen renal tubular epithelial cells of carried segments of the cortex. The cytoplasm of the affected cells was coagulated, distinctly granular, and intensely eosinophilic. Lumens of the affected tubules were distended with eosinophilic, amorphous tissue debris and secretions. Lethargy was observed sporadically in rats at 3-4 g/kg dose groups. All had lesions of acute toxic hepatitis. The lesion was characterized by pyknosis of the nuclei of the hepatocytes and cloudy swelling of the cytoplasm of hepatocytes. However, the lesions did not constitute a consistent characteristic lesion as did the peracute toxic nephrosis. LD_{50} = 3.28 – 4.04 g/kg.	[56]
Rat, strain not provided (10)	100, 200, 400, 500, 1000, 3000, 5000, 6000, 7000 mg/kg as 1% and 2% solutions	No observations of toxicity at < 3000 mg/kg. 5000 mg/kg, 30% mortality; 6000 mg/kg, 60%; and 7000 mg/kg, 70%. LD_{50} = ~6000 mg/kg.	[50]
Male Wistar rats (6)	0.5mmol/kg/min @ pH 10.9 or 7.4	Both pH levels were well tolerated for 50-70 min; then metabolic alkalosis developed, then death. Plasma concentration increased linearly to 53.7 ± 9.09 mmol/L @ 60 min. No effects observed to BP, heart rate, ECG, and Na^+ and K^+ plasma or erythrocyte concentration. The authors stated that depressed ventilation was the cause of death. When infusion was stopped at 20 min, the rats recovered.	[55]
Rabbit, strain not provided (5)	250 and 500 mg/kg as 5% solution	No treatment-related mortality. Changes in respiratory rate and amplitude were observed.	[50]
Dog, breed not provided (5)	125 mg/kg as 5% solution	Alterations in respiratory rate and amplitude. LC_{50} > 125 mg/kg	[50]

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TRANSCRIPTS FOR TROMETHAMINE
FROM MARCH, 2013

DAY 1
DR. MARKS

DR. MARKS: Let's go ahead and resume for another about an hour. The next ingredient is tromethamine.

[discussion about file formats]

DR. MARKS: At least at this point what we've like the panel members on the Marks and Wilma team would like to see is the memo in both documents whether it's Word or it's PDF at this point and we'll go forward and see how things evolve. Now we have a draft report from Lillian on tromethamine as used in cosmetics. This is the first time that the panel has seen this report. You can see under the memo the Science and Support Committee has suggested that not using the aminomethyl propanol as an analog approach, but to use the AEPD, the aminomethyl propanediol. It's just this one ingredient. Correct? A single ingredient. Rons and Tom, how do you feel about using these analogs to come to the conclusion that this ingredient is safe? You'll recall that the AMPD already from a 2009 CIR that we concluded that that ingredient was safe.

DR. SLAGA: I feel we can use them and I think it's safe as used.

DR. HILL: I totally disagree. I don't think there's any reason to use those. There is no justification for using them. There is no reason to think the biohandling would be similar. And I don't see why we need that data to conclude safe.

DR. MARKS: You feel that you could conclude safe without using it?

DR. HILL: Absolutely.

DR. MARKS: Ron Shank?

DR. SHANK: I also agree safe as used whether you use the other data or not.

DR. BERGFELD: I do too.

DR. SHANK: I really don't know whether it's useless or not.

MS. WEINTRAUB: I raise the concern also. I think it's not at all well explained or rationalized why an analog would be used for this ingredient. I think so much of the work we do on this panel is looking at data sources and making decisions based on what we have and asking for data and I think there is a lack of explanation about why an analog would be used in this situation versus so many others that we find ourselves in. It seems to me that there's a lack of evidence provided us as to why an analog would be acceptable.

DR. ANSELL: We'll have a technical response, but I believe that fundamentally we need to continue to advance the concepts of QSAR, that asking for a study is very 15 minutes ago. What we want to do is identify questions and come up with the best data to respond to those questions and often today that may not be a study. It may not be an animal study. It could be a computational method. It could be an in vitro method. It could be a variety of methods. I think we're going to be seeing more and more of that as we go forward.

MS. WEINTRAUB: May I respond to that? It seems to me, and this has been one of my underlying principles, that if an ingredient is being used in a specific product then it's up to the manufacturer and others in the supply chain to prove through data the use of the ingredient that it doesn't pose various types of impacts and that using the types of more modern scientific technologies that are available, I don't know that that necessarily means that data is not provided specifically about that ingredient. I understand it's making comparisons and assumptions, but it seems that there needs to be a very good rationale for why there can be a complete analog used for a specific ingredient.

DR. ANSELL: We agree absolutely. That is my point exactly, that this is not making

decisions in the absence of data. This is looking at a much richer data package. My concern was simply that if we look at the carcinogenicity and say there is no carcinogenicity study, that's not really what we want to talk about; is there a concern and how do we conclude that there is no concern and I think we've seen through this morning that we can do that in a variety of ways even if there is no specific animal study. So I think we're in agreement.

DR. HILL: I teach QSAR and the like at the graduate level. I'm a medicinal chemist. There are situations where the complete data packet is more valuable than the information on that particular one alone. This is not one of those situations. That's my point. Moreover, we have an agent that's administered intravenously on a routine basis for various and sundry purposes and I think there is plenty of other toxicology data out there to support the fact that this isn't going to be problematic and that we just need to drag that data in. That was my feeling on this.

DR. HUGHES: Let me explain where this came across. My name is Brian Hughes. I'm with the Dow Chemical Company. Probably where we did use surrogates to be able to explain this was cause of lack of reproductive developmental data in the HPD program. That's where I think we used the surrogate. Unfortunately we used the surrogate AMP which has some problems with it versus AEPD which is the propanediol. If you take a look at the reproductive developmental studies you'll find out that we did that after we submitted the AEPD document and found out that the tris amino even at the limit dose doesn't have the problems AMP does and is more related to AEPD. That's where that read- across approach came in. The idea that the panel agrees if I can say that that tris amino can stand on the merits itself, we would agree to that.

DR. MARKS: I was looking at skin sensitization and I didn't see any animal nor human sensitization to trimethylamine and looking at AMPD and AEPD was reassured with that. It would have been nice to see an HRIPT on the trimethylamine but I didn't see any. That's what I liked and thought was reassuring. Ron Hill, I heard initially where you don't like this in this case at all and all of you felt that it could be safe on its own, that even with the skin you didn't have a problem.

DR. SHANK: Why do you feel that two analogs, AMPD and AEPD, are so unlike the ingredient?

DR. HILL: That extra hydroxyl group gives us a completely different character. The only other commonality there is that primary amino group. I suppose if you have reason to believe that there will be some sensitization -- I don't have a problem with keeping the data in, but I want to make sure that it's viewed in the proper context in the way it's discussed.

DR. SHANK: All three compounds are 1, 3 propanediols. All three compounds are two amino substitution. I think there's quite a bit of structural similarity.

DR. HILL: I know Dan doesn't like when I use the word biohandling, but I know exactly what I mean by that and there is no reason to necessarily believe that the biohandling other than the primary amino group would be in common. Again I have no problem with leaving the data in, but I'd make sure that it's not overused because I don't think we need to. Overextrapolated I guess is the word I should have used.

DR. MARKS: Is there a way you could suggest in your editing how you would like to -- was there anything (inaudible) specifically? Obviously this is going out as a tentative so it seems to me that there wasn't an issue in terms of moving it on as a tentative report with a safe conclusion. Is that correct? Then we could handle that issue of the read-across. Of course we're doing that all the time, reading across, but if you want to, Ron Hill, make some specific editorial comments it might be helpful for the next edition. Are there any other comments? Rachel, do you feel comfortable now hearing the discussion that as Ron Shank mentioned, the structural similarity and Ron Hill is concerned about the biologic handling of that so there's some difference there. Tom Slaga feels fine with the read- across. Then the actual compound or ingredient that we're reviewing feels safety in that as is without the read- across.

MS. WEINTRAUB: At a minimum I think that type of analysis needs to be in the report.

Whether or not I agree with it or not, I think the panel needs to justify why it's doing it and explain it thoroughly.

DR. MARKS: Lillian, you're going to capture that obviously.

DR. SLAGA: We do that in all the reports, read- across.

DR. MARKS: Yes. Absolutely.

DR. HILL: I think Rachel's point, and I can't disagree, is why don't we have the sensitization data on this ingredient given the volume of use. I'm always for more science.

DR. MARKS: Ron, I was willing to go with safe, but I can't imagine there isn't an HRIPT on one of these. Was it 400 or something? I'll have to look. What was the use? How many ingredients or how many products was this used in?

DR. GILL: 480 leave-on and 69 rinse-off.

DR. MARKS: It's over 500. It's hard to believe that there is not one HRIPT on any of those.

DR. HILL: On the other hand, because there's pharmaceutical use here and intravenous use, I couldn't dream up anything that would happen dermally that didn't show up in all of that so that's a lot of my comfort level.

DR. MARKS: Wilma?

DR. BERGFELD: I'd like to make a comment.

DR. MARKS: Was there one there that I missed?

DR. ANSELL: We simply note Lillian's comment to the panel where a patch test at 3.1 percent was provided.

DR. MARKS: A patch test? What page are you on?

DR. ANSELL: I have no idea. I'm referencing Lillian's report to you guys of February 22. This is in the report where it mentions a patch test on Panel Book page 13 with reference to 56.

DR. MARKS: What panel book?

DR. ANSELL: Panel Book page 13 is where I'm seeing it. I'm searching for the word "patch" in the report. Here's a patch test of dermatitis patients.

DR. MARKS: That's not an HRIPT. I want a perspective. At any rate, I don't think it would inhibit us from moving forward, but that was my comment that I would have liked to see at least one HRIPT. I don't think it would cause me to say insufficient by any means, but it would be more robust. Lillian, your comment?

DR. BERGFELD: I made a comment earlier about the document and the headings. I'd like to draw your attention to this one in particular to the table of contents. I understand there's been a movement from animal to human as a topic heading to nonhuman and human. I understand that. But what I don't understand under "Irritation and Sensitization," you have irritation and then right in the middle of that you have dermal human and those are all animal and others where I think you need to isolate the human away from the nonhuman. It shouldn't be in the middle of two nonhuman studies or to follow it or have a separate heading as nonhuman and human. That's at your table of contents under "Irritation and Sensitization."

MS. BURNETT: You'd want the dermal nonhuman and the intradermal nonhuman together and then the human?

DR. BERGFELD: I think you should cluster your nonhuman together and your human together. You shouldn't be interspersing them.

MS. BURNETT: Our template had been whatever our test is, human/nonhuman, next test our data point, end point, human/nonhuman. We can change that.

DR. BERGFELD: I'd like to hear comments from other people because it happened in multiple documents. It wasn't just this one. I like the heading under irritation to put in the nonhuman and human. I like that. But the fact that you intermix them was a little bit problematic.

DR. MARKS: Are there any other comments? Rachel?

MS. WEINTRAUB: I had another comment and that's about footnote 52. It seemed like there was very little detail on the study. It just said Syrian hamsters. It didn't say how many. It seemed like it was a much less-detailed study than we normally have and I wanted to get the panel's interpretation about whether that was sufficient. It's on page 5 of the report, page 14 PDF.

DR. HILL: This is reference 52?

MS. WEINTRAUB: Yes, footnote 52.

DR. HILL: It's because the focus of the study was not on trimethylamine but, rather, benzo[a]pyrene.

MS. WEINTRAUB: Yes, I noticed that.

DR. HILL: That isn't informative to the lack of carcinogenicity of this compound that I think we probably have. Did we capture the wrong piece of data here?

DR. MARKS: What do you want to do with that, Ron? Do you want to leave that study out? Do you think it should stay in?

DR. HILL: What does Ron Shank think? Tom, what do you think?

DR. SHANK: This was in the control. Right? Tromethamine. So it's valid. Then we have some genotoxicity data at least in a bacterial assay not (inaudible) and the APD was not (inaudible). I have no concern over the carcinogenicity.

DR. SLAGA: I don't have any concern either.

DR. MARKS: Does that answer your question, Rachael?

DR. ANDERSEN: I think in fairness, the fact that that's a vehicle control arm could be added to the sentence to clarify just what it is we're dealing with here and that would make a lot more sense.

DR. MARKS: Thank you, Alan. Are there any other comments? Tomorrow I will be moving the tromethamine on to a tentative report with a conclusion of safe. Then a lot of our discussion, Lillian, will be captured in that.

Dr. BELSITO

DR. BELSITO: Okay. So, tromethamine. This is another first for us, and the first thing we're being asked is whether it was appropriate to look at data on amino ethylpropanediol and amino methylpropanediol to support safety.

So I guess I would ask Dan and Paul their comments on this.

DR. LIEBLER: Yes. So, in short, yes, I agree with the substitution of these two for the other one.

And particularly, the other one was particularly bad because there was not an alkyl group at the carbon that has the amine, and so the amine can undergo chemistry that gives rise to a whole bunch of other products that wouldn't happen with tromethamine.

So I think the other compound -- I don't remember the name of it, but the structure -- the carbon that had the amine just had a hydrogen on it. So that was a problem for me in terms of a valid analog.

So AMPD and AEPD strike me as very reasonable. And this is the report that had the funky floating labeling.

MS. BURNETT: Font.

DR. LIEBLER: Well, funky font. I think George Clinton cut that in 1975 -- funky font. (Laughter)

DR. BELSITO: So just looking at this report and even allowing for the use of data on other chemicals to support safety, I was a little concerned about the lack of sensitization data that we have for use of this up to 4 percent.

And I know that amino ethylpropanediol was negative at 10 percent, but tromethamine has two hydroxyl groups on it. So I think it's potentially more reactive, and I'm not sure that you can

predict -- Dan, correct me if I'm wrong -- predict the sensitization based upon the others where you have only one hydroxyl and then you have methyl groups that could be interfering with the stochiometric cooking-up of this molecule with a protein carrier.

So I just thought it's the first time we're looking at it. You know, can't we get some data at 4 percent?

That was my only comment. Dan, what do you think of that? Total dumbness?

DR. LIEBLER: No, not total dumbness, but I don't -- I mean, I think that if you're concerned -- I don't think there's a chemical reason to be concerned, really. But if we've got nothing on tromethamine, it would be great to have something on it.

I mean, having the data on these other two compounds is great in a supporting role, but if you had some sense -- you're looking for sensitization or irritation at that highest concentration of use.

DR. BELSITO: Sensitization, yes.

DR. SNYDER: So we have up to 4 percent on tromethane, but we have no data on tromethamine.

DR. BELSITO: Right.

DR. SNYDER: Okay.

DR. LIEBLER: Right. Yes. Okay, and that's not a valid substitute.

DR. BELSITO: And all we have is really irritation data. We have no sensitization data.

DR. BRESLAWEC: Irritation data.

DR. BELSITO: What?

DR. BRESLAWEC: Never mind.

DR. BELSITO: And, again, it's the first time we're looking at it. I think it would be nice.

My other comments really were since I won't be here tomorrow, if you guys do decide to go safe as used, we need the same type of language that they have on page 10 of the report about the regulation under Europe Annex 3 with nitrosamine content.

And then everything else was just -- it looks like really just things like, do you mean cellulites or cellulitis? Acidemia, not academia?

(Laughter)

DR. LIEBLER: I thought that was an impurity. It gave me a good laugh.

I do have a more serious point about this that I think throughout the report is important. Under impurities, you indicate that when tromethamine is heated at decomposition it emits toxic fumes. Totally irrelevant, I mean. So I don't think that needs to be there.

But there must be specifications for the material that's used to correct acidosis when administered to people.

And then there's, of course, enormous use of this material as a buffer in biochemistry and chemistry as TRIS.

So the question I would have is, what are the differences between the specs for the cosmetic ingredient and reagent grade TRIS, for example, that you'd buy from like Sigma or the material that's infused to correct acidosis?

So that information must be available from industry.

And then, when you describe the studies, particularly the in vitro studies but even some of the in vivo studies, where tromethamine is present in the cells, for example, the effects could be quite different depending on whether the free base is used or whether a salt was used, like a hydrochloride or so forth. It isn't clear from the descriptions that you paraphrase from the cited work whether or not that's even known or whether it was described in the paper.

If you add the free base, you're going to, you know, make the -- unless the system that was studied is well buffered, you're going to raise the pH and the effects could be just due to pH changes. And if you add the salt, it's less likely that that's going to happen.

And then the in vivo study mostly referred to controlling the pH of the blood when the

material was added.

It's very important that all of the citations are as specific as possible about the chemical form of tromethamine that was used.

DR. BELSITO: Okay. Have you made notes about these?

DR. LIEBLER: Yes, I flagged them all. I flagged them several places.

DR. BELSITO: Okay. Any other comments?

DR. SNYDER: So we're going to go insufficient for sensitization data.

DR. BELSITO: At concentration of use. See what they say -- the other team.

DR. SNYDER: What specific ingredient?

DR. BELSITO: It's only one ingredient -- tromethamine.

DR. SNYDER: Tromethamine, okay.

DR. EISENMANN: Concentration --

DR. BRESLAWEC: Concentration of use. I think you mean impurity data.

DR. BELSITO: No, sensitization at 4 percent.

DR. BRESLAWEC: Oh, at concentration of use.

DR. BELSITO: At concentration of use, yes.

DR. EISENMANN: Well, you know, you've already reviewed AMPD.

DR. BELSITO: Yes, I know.

DR. EISENMANN: AEPD is in the dictionary. I mean, I don't have -- it doesn't have any uses as far as I'm aware, but it is in the dictionary.

DR. SNYDER: Okay.

DR. EISENMANN: What I'm saying is --

DR. LIEBLER: So an analog is in the dictionary.

DR. EISENMANN: Yes. If you're putting the data in this report, if you want to put the ingredient in the report, that's the question.

DR. BELSITO: Sure.

DR. LIEBLER: Oh, I see.

DR. BELSITO: If the ingredient is in the dictionary, even if it has no uses, if we have data on it, put it in the report.

DR. EISENMANN: Right, and if you're reviewing it in this group.

DR. BELSITO: Yes. Fine.

DR. LIEBLER: So we're adding?

DR. SNYDER: We agreed. We already agreed to add those two -- AMPD and AEPD.

DR. BELSITO: No, we agreed to use the data --

DR. SNYDER: Data.

DR. BELSITO: -- to say safe.

DR. LIEBLER: So now we're adding which?

MS. BECKER: AMPD has been reviewed. So are you're talking about AEPD too?

DR. EISENMANN: It's in the dictionary.

DR. BELSITO: If it's in dictionary, add it.

MS. BECKER: You want to add it here, or should we add it with AMPD, or do you want all three together?

DR. EISENMANN: Well, if you're reviewing the data on all three, probably all three should be in there.

DR. BELSITO: Yes. Fine. You're looking -- what is it called, Halyna?

MS. BECKER: No.

DR. BELSITO: Okay.

MS. BECKER: It's processing.

DR. BELSITO: Okay. Any other comments? Carol?

DR. LIEBLER: And insufficient for impurities right now, or get the impurities?

DR. BELSITO: Insufficient for impurities and sensitization in concentration of use.

DAY 2

Dr. Marks presenting on tromethamine.

DR. MARKS: This is the first time the panel has reviewed this ingredient. It's a single ingredient, tromethamine, and there was the use of analogs in coming to the safety assessment, AEPD and AMPD aminomethyl propanediol, which the CIR had issued a safe conclusion back in 2009. Our team felt we could move forward and issue a tentative draft report with a conclusion of safe and I make that motion safe.

DR. BERGFELD: Paul?

DR. SNYDER: Yes, again, Don really was concerned about sensitization. We don't have sensitization on nitromethane methylamine. There was sensitization data for the AEPD analog, which was only up to I believe 1 percent, but we have concentration of use up to 4 percent for these and we also don't have impurities, and, so, we were proposing to go insufficient for sensitization data at concentration of use and impurities.

We also discussed it was raised about bringing the two analogs actually into this report. The AMPD has been reviewed and a report is published on that. AEPD is in the dictionary, but it has not been reviewed. And, so, we wanted to pursue or put on the table the potential to maybe bring all of the ingredients together into one report and then address the data needs and then I would take care of another ingredient that's out there that's in the dictionary that hasn't been reviewed.

SPEAKER: I like that.

DR. HILL: Well, our initial discussion yesterday was to wipe those other two ingredients out of the report as being not relevant, but actually in the part of the country where I now reside, we would call this crawfishing. Because I made those strong statements yesterday, I would at least like to say that in my mind if we consider sensitization mechanisms as most likely involving the amino group if they were to occur that it at least adds to the weight of evidence.

But I did make the statement that given the large number of uses with this, why don't we have it, and I think my comfort level is the fact that this molecule is used systemically and it has been used systemically for a long time, in fact parenteral dosage forms at relatively high levels. I'm not 100 percent sure that includes any possibility of dermal sensitization, but we don't have any literature that suggests that would be a problem, nor are there really any case report. But I still feel like maybe we ought to have it.

In terms of mechanisms, because there is that systemic use and a lot of data for that that we don't have for the other two, the only drawback I see for bringing these other two in is I'm not sure that any data on tromethamine helps to support the safety of these other two in my mind because in terms of sensitivity mechanisms, I mean, I just looked with a group of students the other afternoon about the difference between certain people with certain genotypes and actually the molecular mechanism of action which has kind of now been revealed, why those people react to a back genotypes react to abacavir versus other people that don't at the very detailed molecular level.

And, so, it's very subtle difference based on that genetic difference and coming up with mechanisms for sensitization that could apply in this particular case. So, I'm not sure a read-across would be appropriate, although there's no evidence that suggests that any of the three are sensitizers. So, I mean, combining them, don't combine them, I don't care, but I think we need data honestly.

DR. BERGFELD: Dan?

DR. LIEBLER: So, I thought these three compounds, actually, they belong together in a report. I think they're actually good analogs of each other and I'm not sure what specifics you're referring to with abacavir, but that's another molecule entirely, so --

DR. HILL: Well, but the point was --

DR. LIEBLER: I mean, the --

DR. HILL: Is what fits in the pocket of the complement presenting functionality, and there was just a very small variation in the pocket based on the amino acid difference. And, so, the point is to get sensitization, you need haptic information, and I felt like in tromethamine, we actually have stearic shielding, is not the right -- but occlusion of the amino group that isn't there in the other two. So, on the one hand, ABD and AEPD are a little more lipophilic and you'd predict a little better dermal penetration, I guess.

But I don't have a problem with lumping them; I'm just saying they need to be individually considered and I don't consider that read-across would be appropriate for sensitization on those three if you put them together and that was why I was arguing strongly at the beginning yesterday to take that data out as being irrelevant. But then what I thought about it some more, I thought well, if it's coming, the amino group would be involved; then it at least would add to the weight of evidence.

DR. LIEBLER: Well, I think the inclusion of the three together makes sense and if we have further discussion of the potential for read-across or reinforcing use of data for these compounds, we'll enjoy that discussion next time.

DR. MARKS: I withdraw my motion, and, Paul, would you go ahead and restate your motion?

DR. BERGFELD: Before you --

DR. MARKS: I guess the question is: Do we reopen? If we're going to combine them, obviously, we're reopening AMPD since that was already concluded to be safe. And I think our team supports moving forward as you did or proposed.

DR. SNYDER: So, I think rather than going insufficient, I propose Alan gives us his blessing that we would table this, we would reopen the one that's been reviewed, we would bring in the one that hasn't been reviewed but is in the dictionary, and then we would indicate to industry that we would like to have sensitization data at concentration of us and impurities.

DR. BERGFELD: And, so, you've made a motion to table. There's no discussion, but is there a second?

SPEAKER: Second.

DR. BERGFELD: Then all those in favor of tabling?

(Hands raised)

DR. BERGFELD: Okay, unanimous. Now we'll have discussion. Rachael is up and then Halyna.

MS. WEINTRAUB: I just wanted to mention that I raised the concern about the fact that an analog essentially was used for this ingredient and I thought there was insufficient rationale for that and I think when we use an analog, it's significant because so much of our work is based on providing data and evidence to support the safety of ingredients. So, I think we need to use analogs wisely and only with sufficient rationale where it truly makes sense and I think that this tabling and looking back in the way that we are, I think is actually a good course to go because it will give us other opportunities to find more data to support these.

DR. BERGFELD: Thank you. Halyna?

DR. BRESLAWEC: (off mic)

DR. BERGFELD: Okay. All right. So, we'll move forward then with those comments.

Cosmetic Ingredient Review

Commitment & Credibility since 1976

May 17, 2013

MEMORANDOM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Subject: Data Submitted for Tromethamine, Aminomethyl Propanediol, and Aminoethyl Propanediol As Used In Cosmetics

Attached you will find data from the Council which includes updated use data for tromethamine as well as new irritation/ sensitization data. This data has been incorporated into the report. It also includes 2013 VCRP data.

1. HRIPT of a mascara containing 1.8% tromethamine,
2. HRIPT of a mascara containing 2% tromethamine,
3. Updated concentration of use data for tromethamine,
4. 2013 VCRP data, and
5. Three HRIPTs of products containing tromethamine up to 2%.

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(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: March 25, 2013

SUBJECT: HRIPT on a Product Containing Tromethamine

Consumer Product Testing Co. 2011. Repeated insult patch test of a mascara containing 1.8% Tromethamine. Experiment Reference Number C11-2402.03.

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

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Consumer Product Testing Co

FINAL REPORT

CLIENT:

ATTENTION:

TEST: Repeated Insult Patch Test
Protocol No.: 1.01L

TEST MATERIAL: MASCARA -

EXPERIMENT REFERENCE NUMBER: C11-2402.03

Trometnamine 1.8%

Reviewed by: Richard R. Eisenberg, M.D.
Medical Director
Board Certified Dermatologist

Approved by: Michael Caswell, Ph.D., CCRC, CCRA
Director, Clinical Evaluations

Approved by: Joy Frank, R.N.
Executive Vice President, Clinical Evaluations

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

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

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Consumer Product Testing Co

QUALITY ASSURANCE UNIT STATEMENT

Study Number: C11-2402.03

The Consumer Product Testing Company, Incorporated (CPTC) Quality Assurance Unit (QAU) is responsible for monitoring the conduct, content and reporting of all clinical laboratory studies that are conducted at CPTC.

This study has been conducted in accordance with ICH Guideline E6 for *Good Clinical Practice*, the requirements of 21 CFR Parts 50 and 56, other applicable regulations, CPTC Standard Operating Procedures, and the approved Study Protocol.

The CPTC QAU has reviewed all data, records, and documents relating to this study and also this Final Report. The following QAU representative signature certifies that all data, records, and documents relating to this study and also this Final Report have been reviewed and are deemed to be acceptable, and the study conforms to all of the requirements as indicated above.

All records and documents pertaining to the conduct of this study shall be retained in the CPTC archives for a minimum of ten (10) years. At any time prior to the completion of the tenth archival year, a Sponsor may submit a written request to the CPTC QA Department to obtain custody of study records once the CPTC archive period has been completed. This transfer shall be performed at the Sponsor's expense. In the absence of a written request, study-related records shall be destroyed at the end of the CPTC archive period in a manner that renders them useless.

Quality Assurance Representative

Date

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

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

Participants: One hundred fifteen (115) qualified subjects, male and female, ranging in age from 18 to 70 years, were selected for this evaluation. One hundred one (101) subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

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

Exclusion Criteria:

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

Test Material: MASCARA -

Study Schedule:

Panel #	Initiation Date	Completion Date
20110182	June 6, 2011	July 14, 2011
20110186	June 6, 2011	July 15, 2011

[a]With parental or guardian consent

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Methodology:

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

Induction Phase:

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

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

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

Challenge Phase:

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

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Methodology (continued):

Evaluation Criteria (Erythema and additional Dermal Sequelae):

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

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

Results:

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

Observations remained negative throughout the test interval.

Subject demographics are presented in Table 2.

Summary:

Under the conditions of this study, test material, MASCARA - , did not indicate a potential for dermal irritation or allergic contact sensitization.

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Table 1
Panel #20110182

Individual Results

MASCARA -

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

24* = Supervised removal of 1st Induction and Challenge Patch
DNC = Did Not Complete Study
m = Additional make up day granted at the discretion of the clinic supervisor

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Table 1
(continued)
Panel #20110182

Individual Results

MASCARA -

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	-----DNC---	
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	----------DID NOT COMPLETE STUDY----------											
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0[m]	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
DNC = Did Not Complete Study
m = Additional makeup day granted at the discretion of the clinic supervisor

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Table I
(continued)
Panel #20110186

Individual Results

MASCARA -

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

24* = Supervised removal of 1st Induction and Challenge Patch
DNC = Did Not Complete Study
m = Additional Makeup day granted at the discretion of the clinic supervisor

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Table 1
(continued)
Panel #20110186

Individual Results

MASCARA -

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	----------DNC----------			
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	----------DID NOT COMPLETE STUDY----------							
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	----------DNC----------			
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0

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

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: March 26, 2013

SUBJECT: HRIPT on a Product Containing Tromethamine

TKL Research. 2009. Repeated insult patch test of a mascara containing 2% Tromethamine.

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

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TKL RESEARCH

SUMMARY REPORT

TKL Study No.: [redacted]

Date of Report: June 19, 2009

Study Title:	Repeated Insult Patch Test Mascara Containing 2% Trometnamine
Study Sponsor:	[redacted]
TKL Protocol No.:	TKL-1000
Sponsor Reference No.:	
Study Objective:	To assess the sensitization potential of topically applied study material.
Study Design:	Standard RIPT methodology with nine 24-hour induction applications and a single 24-hour challenge application following a 10-15 day rest period.
Principal Investigator:	Jonathan S. Dosik, MD – Dermatologist
Director, Dermatologic Safety Testing:	Kathleen Georgeian
Corporate Office:	TKL Research, Inc. 365 W. Passaic Street Rochelle Park, NJ 07662
Study Site:	TKL Research, Inc. 48 Franklin Turnpike Ramsey, NJ 07446
Study Dates:	Date Study Initiated: April 24, 2009 Date Study Completed: May 29, 2009

Study Material:

SPL Code and Category	Amount Applied	Patch Condition
Mascara	0.2 g	Occlusive

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Number of Subjects:	Enrolled: 112	Completed: 102
	Discontinued: 10	
	Lost to follow-up: 6	
	Voluntary withdrawal: 4	

Listing of Attached Tables:

Appendix I	Summary Tables
Appendix II	Data Listings

SUMMARY AND CONCLUSION:

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

There were no adverse events (AE) reported on this study.

Under the conditions employed in this study, there was no evidence of sensitization to SPL Code

STATEMENT OF QUALITY CONTROL:

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

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SIGNATURES:

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Jonathan S. Dosik, MD
Dermatologist/Principal Investigator

6/18/09
Date

Kathleen Georgeian
Clinical Research Coordinator and
Director, Dermatologic Safety Testing

6/19/09
Date

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APPENDIX I

SUMMARY TABLES

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Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	112
Subjects completed induction phase	103 (92.0)
Subjects completed all phases	102 (91.1)
Total subjects discontinued	10 (8.9)
Lost to follow-up	6 (5.4)
Voluntary withdrawal	4 (3.6)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	35 (31.3)
N (%) 45 to 64	56 (50.0)
N (%) 65 and up	21 (18.8)
Mean (SD)	52.3 (13.0)
Median	51.4
Range	18.7 to 75.1
Gender	
N (%) Male	20 (17.9)
N (%) Female	92 (82.1)
Race	
Asian	3 (2.7)
Black	2 (1.8)
Caucasian	102 (91.1)
Hispanic	3 (2.7)
Other	2 (1.8)

See data listing 2 for further detail.

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TKL Study No

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product =

	Induction Reading										Challenge Phase		
Response	1	2	3	4	5	6	7	8	9	Make Up	48hr	72hr	96hr(*)
-	110	98	99	100	103	98	102	101	100	0	102	102	
Total evaluable	110	98	99	100	103	98	102	101	100	0	102	102	
Number absent	0	0	0	1	1	1	0	0	0		0	0	
Number absent	0	11	9	3	0	5	1	2	3		0	0	
Number discontinued	2	3	4	8	8	8	9	9	9		10	10	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=103)

Response	n(%) Subjects
-	103 (100.0%)

(*) when required

Key to Symbols:
- = No reaction ? = Minimal or doubtful response, slightly / different from surrounding normal skin
+ = Definite erythema, no edema ++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation
D = Damage to epidermis: oozing, crusting and/or superficial erosions
p = Papular response >50%

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APPENDIX II

DATA LISTINGS

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
002	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
003	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
004	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
005	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
006	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
007	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
008	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
009	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
010	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
011	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
012	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
013	04/24/09	04/24/09	--	05/04/09	I3	S	11
014	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
015	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
016	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
017	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
018	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
019	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
020	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
021	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
022	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
023	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
024	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
025	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
026	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
027	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
028	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
029	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
030	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
031	04/24/09	04/24/09	--	04/29/09	I0	L	6

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocnl violation, AE=Adverse event, O=Other)

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Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	04/24/09	04/24/09	--	04/27/09	I0	S	4
033	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
034	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
035	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
036	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
037	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
038	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
039	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
040	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
041	04/24/09	04/24/09	--	05/26/09	I9	L	33
042	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
043	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
044	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
045	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
046	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
047	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
048	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
049	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
050	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
051	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
052	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
053	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
054	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
055	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
056	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
057	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
058	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
059	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
060	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
061	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
062	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 1: Subject Enrollment and Disposition

Subject No.	Study Dates: Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
063	04/24/09	04/24/09	--	05/06/09	I3	L	13
064	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
065	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
066	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
067	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
068	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
069	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
070	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
071	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
072	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
073	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
074	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
075	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
076	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
077	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
078	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
079	04/24/09	04/24/09	--	05/04/09	I3	L	11
080	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
081	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
082	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
083	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
084	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
085	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
086	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
087	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
088	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
089	04/24/09	04/24/09	--	04/29/09	I2	S	6
090	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
091	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
092	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
093	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
094	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
095	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
096	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
097	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
098	04/24/09	04/24/09	--	05/04/09	I3	S	11
099	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
100	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
101	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
102	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
103	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
104	04/24/09	04/24/09	--	05/01/09	I1	L	8
105	04/24/09	04/24/09	--	05/11/09	I6	L	18
106	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
107	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
108	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
109	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
110	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
111	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36
112	04/24/09	04/24/09	05/26/09	05/29/09	C	C	36

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product =

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	-	-	-	-	-		-	-	
002	-	-	-	-	-	-	-	-	-		-	-	
003	-	-	-	-	-	-	-	-	-		-	-	
004	-	-	-	-	-	-	-	-	N9G		-	-	
005	-	-	-	-	-	-	-	-	-		-	-	
006	-	-	-	-	-	-	-	-	-		-	-	
007	-	-	-	X	-	-	-	-	-	N9G	-	-	
008	-	-	-	-	-	-	-	-	-		-	-	
009	-	-	-	-	-	-	-	-	-		-	-	
010	-	-	-	-	-	-	-	-	-		-	-	
011	-	-	-	-	-	-	-	-	-		-	-	
012	-	-	-	-	-	-	-	-	-		-	-	
013	-	X	-	X	X	X	X	X	X		X	X	
014	-	-	X	-	-	-	-	-	-	N9G	-	-	
015	-	-	-	-	-	-	-	-	-		-	-	
016	-	-	-	-	-	-	-	-	-		-	-	
017	-	X	-	-	-	-	-	-	-	N9G	-	-	
018	-	X	-	-	-	-	-	-	-	N9G	-	-	
019	-	-	X	-	-	-	-	-	-	N9G	-	-	
020	-	-	-	-	-	-	-	-	-		-	-	
021	-	-	-	-	-	-	-	-	-		-	-	
022	-	X	-	-	-	-	-	-	-	N9G	-	-	
023	-	-	-	-	-	-	-	-	-		-	-	

Key to Symbols:
- = No reaction ? = Minimal or doubtful response, slightly different from surrounding normal skin
+ = Definite erythema, no edema ++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation
N9G = No ninth grading NA = Not applied NP = Not patched due to reaction achieved
X = Reading not performed due to missed visit or subject discontinuation
D = Damage to epidermis: oozing, crusting and/or superficial erosions
p = Papular response >50% NR=Data not recorded
MU = Make-up reading for missed induction visit

(*) When required
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Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product =

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	-		-	-	
025	-	X	-	-	-	-	-	-	-	N9G	-	-	
026	-	-	-	-	-	-	-	-	N9G		-	-	
027	-	-	-	-	-	-	-	-	-		-	-	
028	-	-	-	-	-	-	-	-	-		-	-	
029	-	-	-	-	-	X	-	-	-	N9G	-	-	
030	-	-	-	-	-	-	-	-	-		-	-	
031	X	X	X	X	X	X	X	X	X		X	X	
032	X	X	X	X	X	X	X	X	X		X	X	
033	-	-	-	-	-	-	-	-	-		-	-	
034	-	-	-	-	-	-	-	-	-		-	-	
035	-	-	-	-	-	-	-	-	-		-	-	
036	-	-	-	-	-	-	-	-	-		-	-	
037	-	-	-	--	--	--	-	-	-		-	-	
038	-	-	X	-	-	-	-	-	-	N9G	-	-	
039	-	-	-	-	-	-	-	-	-		-	-	
040	-	-	-	-	-	-	-	-	-		-	-	
041	-	-	-	-	-	-	-	-	-		X	X	
042	-	-	-	-	-	-	-	X	-	N9G	-	-	
043	-	-	X	-	-	-	-	-	-	N9G	-	-	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	-	-	-	-	N9G		-	-	
046	-	-	-	-	-	X	-	-	-	N9G	-	-	

(*) When required
Generated on 06/09/09:12:33 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product =

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	-	X	-	-	-	-	-	-	-	N9G	-	-	
048	-	-	-	-	-	-	-	-	-		-	-	
049	-	-	X	-	-	-	-	-	-	N9G	-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	-	-		-	-	
052	-	-	-	-	-	-	-	-	-		-	-	
053	-	-	-	-	-	-	-	-	-		-	-	
054	-	-	-	-	-	-	-	-	-		-	-	
055	-	-	-	-	-	-	-	-	-		-	-	
056	-	-	-	-	-	X	-	-	-	N9G	-	-	
057	-	-	-	X	-	-	-	-	-	N9G	-	-	
058	-	-	-	-	-	-	-	-	-		-	-	
059	-	-	-	-	-	-	-	-	-		-	-	
060	-	-	-	-	-	-	X	-	-	N9G	-	-	
061	-	-	-	-	-	-	-	-	-		-	-	
062	-	-	-	-	-	-	-	-	-		-	-	
063	-	-	-	X	X	X	X	X	X		X	X	
064	-	-	-	-	-	-	-	-	-		-	-	
065	-	X	-	-	-	-	-	-	-	N9G	-	-	
066	-	-	-	-	-	-	-	-	-		-	-	
067	-	-	X	-	-	-	-	-	-	N9G	-	-	
068	-	-	-	-	-	-	-	-	-		-	-	
069	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 06/09/09:12:33 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product =

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
070	-	-	-	-	-	-	-	-	-		-	-	
071	-	-	-	-	-	-	-	-	-		-	-	
072	-	-	-	-	-	-	-	-	-		-	-	
073	-	-	X	-	-	-	-	-	-	N9G	-	-	
074	-	-	-	-	-	-	-	X	-	N9G	-	-	
075	-	-	-	-	-	-	-	-	-		-	-	
076	-	X	-	-	-	-	-	-	-	N9G	-	-	
077	-	-	-	-	-	X	-	-	-	N9G	-	-	
078	-	-	-	-	-	-	-	-	-		-	-	
079	-	-	-	X	X	X	X	X	X		X	X	
080	-	-	-	-	-	-	-	-	-		-	-	
081	-	-	-	X	-	-	-	-	-	N9G	-	-	
082	-	-	-	-	-	-	-	-	-		-	-	
083	-	-	-	-	-	-	-	-	-		-	-	
084	-	-	-	-	-	-	-	-	-		-	-	
085	-	-	-	-	-	-	-	-	-		-	-	
086	-	-	-	-	-	-	-	-	-		-	-	
087	-	-	-	-	-	-	-	-	-		-	-	
088	-	X	-	-	-	-	-	-	-	N9G	-	-	
089	-	-	X	X	X	X	X	X	X		X	X	
090	-	-	-	-	-	-	-	-	-		-	-	
091	-	-	-	-	-	-	-	-	-		-	-	
092	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 06/09/09:12:33 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product =

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
093	-	-	-	-	-	-	-	-	-		-	-	
094	-	-	-	-	-	-	-	-	-		-	-	
095	-	-	X	-	-	-	-	-	-	N9G	-	-	
096	-	-	-	-	-	-	-	-	-		-	-	
097	-	-	-	-	-	-	-	-	-		-	-	
098	-	-	-	X	X	X	X	X	X		X	X	
099	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	-	-	-	-	-	-	-		-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	-	-	X	-	-	-	N9G	-	-	
103	-	-	-	-	-	-	-	-	-		-	-	
104	-	X	X	X	X	X	X	X	X		X	X	
105	-	X	-	-	-	-	X	X	X		X	X	
106	-	X	-	-	-	-	-	-	-	N9G	-	-	
107	-	-	-	-	-	-	-	-	-		-	-	
108	-	-	-	-	-	-	-	-	-		-	-	
109	-	-	-	-	-	-	-	-	-		-	-	
110	-	-	-	-	-	-	-	-	-		-	-	
111	-	-	X	-	-	-	-	-	-	N9G	-	-	
112	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 06/09/09:12:33 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: March 26, 2013

SUBJECT: Updated Concentration of Use by FDA Product Category: Tromethamine

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Concentration of Use by FDA Product Category - Tromethamine

Product Category	FDA Code†	Maximum Concentration of Use
Eye brow pencil	03A	2%
Eye liner	03B	1-2%
Eye shadow	03C	0.8%
Eye lotion	03D	2%
Mascara	03F	2%
Perfumes	04B	0.02%
Powders (dusting and talcum)	04C	0.0002-0.05%
Other fragrance preparations	04E	0.2%
Hair conditioners	05A	0.01%
Shampoos (noncoloring)	05F	0.001%
Tonics, dressings and other hair grooming aids	05G	0.8%
Blushers (all types)	07A	2%
Face powders	07B	0.05%
Foundations	07C	0.3-2%
Lipstick	07E	0.3%
Makeup bases	07F	0.4%
Nail creams and lotions rinse-off	08C	 3.7%
Dentifrices (aerosol, liquid, pastes and powders)	09A	0.002%
Bath soaps and detergents	10A	0.00009%
Aftershave lotions	11A	2%
Shaving cream (aerosol, brushless and lather)	11E	1%
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	12A	0.5%

Face and neck creams, lotions and powders not spray	12C	1-2%
Body and hand creams, lotions and powders not spray	12D	0.05-2%
Moisturizing creams, lotions and powders not spray	12F	1%
Paste masks and mud packs	12H	3.1%
Skin fresheners	12I	0.3%
Other skin care preparations rinse-off	12J	2%
Suntan gels, creams and liquids not spray	13A	0.2-2%
Other suntan preparations	13C	0.5%

†Product category codes used by FDA

Information collected in 2012
Table prepared September 24, 2012
Updated March 26, 2013: nail creams and lotions rinse-off product changed to 3.7%; paste masks and mud packs changed to 3.1%

FDA VCRP Use Data 2013 for Tromethamine, AMPD, and AEPD

03A - Eyebrow Pencil	TROMETHAMINE	1
03B - Eyeliner	TROMETHAMINE	15
03C - Eye Shadow	TROMETHAMINE	2
03D - Eye Lotion	TROMETHAMINE	24
03E - Eye Makeup Remover	TROMETHAMINE	2
03F - Mascara	TROMETHAMINE	14
03G - Other Eye Makeup Preparations	TROMETHAMINE	17
04B - Perfumes	TROMETHAMINE	2
04E - Other Fragrance Preparation	TROMETHAMINE	2
05A - Hair Conditioner	TROMETHAMINE	1
05F - Shampoos (non-coloring)	TROMETHAMINE	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	TROMETHAMINE	7
05H - Wave Sets	TROMETHAMINE	1
07A - Blushers (all types)	TROMETHAMINE	2
07C - Foundations	TROMETHAMINE	9
07D - Leg and Body Paints	TROMETHAMINE	1
07E - Lipstick	TROMETHAMINE	1
07F - Makeup Bases	TROMETHAMINE	8
07I - Other Makeup Preparations	TROMETHAMINE	8
08C - Nail Creams and Lotions	TROMETHAMINE	1
10A - Bath Soaps and Detergents	TROMETHAMINE	9
10E - Other Personal Cleanliness Products	TROMETHAMINE	3
11A - Aftershave Lotion	TROMETHAMINE	11
11D - Preshave Lotions (all types)	TROMETHAMINE	1
11E - Shaving Cream	TROMETHAMINE	1
11G - Other Shaving Preparation Products	TROMETHAMINE	2
12A - Cleansing	TROMETHAMINE	42
12C - Face and Neck (exc shave)	TROMETHAMINE	71
12D - Body and Hand (exc shave)	TROMETHAMINE	65
12F - Moisturizing	TROMETHAMINE	173
12G - Night	TROMETHAMINE	25
12H - Paste Masks (mud packs)	TROMETHAMINE	7
12I - Skin Fresheners	TROMETHAMINE	1
12J - Other Skin Care Preps	TROMETHAMINE	21
13A - Suntan Gels, Creams, and Liquids	TROMETHAMINE	1
13B - Indoor Tanning Preparations	TROMETHAMINE	3
13C - Other Suntan Preparations	TROMETHAMINE	2
		558

03B - Eyeliner	AMINOMETHYL PROPANEDIOL	1
03F - Mascara	AMINOMETHYL PROPANEDIOL	117
03G - Other Eye Makeup Preparations	AMINOMETHYL PROPANEDIOL	3
07C - Foundations	AMINOMETHYL PROPANEDIOL	1
07I - Other Makeup Preparations	AMINOMETHYL PROPANEDIOL	2
12A - Cleansing	AMINOMETHYL PROPANEDIOL	2
12C - Face and Neck (exc shave)	AMINOMETHYL PROPANEDIOL	3
12F - Moisturizing	AMINOMETHYL PROPANEDIOL	4
		133

No uses for aminoethyl propanediol were reported to the VCRP.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 22, 2013

SUBJECT: HRIPTs on a Products Containing Tromethamine

Clinical Research Laboratories, Inc. 2007. Repeated insult patch test of a mascara containing 2% Tromethamine.

Product Investigations, Inc. 2010. Determination of the irritating and sensitizing propensities of water-based eyeliner stick containing 2% Tromethamine on human skin.

Consumer Product Testing Co. 2007. Repeated insult patch test of a fragranced body lotion containing 1.8% Tromethamine.

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Clinical
Research
Laboratories, Inc.

Cream Mascara - RIPT
(0/102) 2% Tromethamine

Final Report

Repeated Insult Patch Test

[redacted]

AUTHORIZED SIGNATURES:

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

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

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

REPORT DATE: [redacted]

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

Clinical Research Laboratories, Inc.

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: [redacted]

Start Date: October 3, 2007

Completion Date: November 9, 2007

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

Eileen Voigt
Signature of QA Auditor

11/21/2007
Date

[redacted]

Clinical Research Laboratories, Inc.

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

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

INVESTIGATIVE SITE

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

TEST MATERIAL

The following test material was provided by [redacted] and was received by Clinical Research Laboratories, Inc. on September 28, 2007:

Test Material	Test Condition	Patch Type
[redacted]	Test as received	Semi-occlusive*

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

[redacted]

STUDY DATES

This study was initiated on October 3, 2007 and was completed on November 9, 2007.

* Semi-occlusive Strip (TruMed Technologies Inc., Burnsville, Minnesota)

Clinical Research Laboratories, Inc.

[redacted]

PANEL SELECTION

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

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

TEST METHOD

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

[redacted]

TEST METHOD (Continued)

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

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

The sites were graded according to the following scoring system:

Dermal Scoring Scale

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

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

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

[redacted]

RESULTS

This study was initiated with 110 subjects. Eight subjects discontinued study participation for reasons unrelated to the test material. A total of 102 subjects completed the study.

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

CONCLUSION

Based on the test population of 102 subjects and under the conditions of this study, the test material identified as [redacted] did not demonstrate a clinically significant potential for eliciting dermal irritation or sensitization.

RETENTION

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

Clinical Research Laboratories, Inc.

[redacted]

TABLE I

Summary of Dermal Scores

Test Material:	[redacted]

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

Clinical Research Laboratories, Inc.

[redacted]

TABLE I
(Continued)

Summary of Dermal Scores

Test Material: [redacted]

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

Clinical Research Laboratories, Inc.

[redacted]

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted]

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

Clinical Research Laboratories, Inc.

[redacted]

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted]

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

Clinical Research Laboratories, Inc.

[redacted]

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted]

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

PRODUCT INVESTIGATIONS, INC.

151 East Tenth Avenue
Conshohocken, PA 19428
610-825-5855 • fax 610-825-7288

Water-based Eyeliner Stick RIPT
(0/102) 2% Tromethamine

[redacted]

DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF [redacted] ON HUMAN SKIN

PREPARED FOR

[redacted]

[redacted]

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DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF [redacted] ON HUMAN SKIN

1.00 OBJECTIVES:

.01 To identify and characterize the skin-damaging propensities that [redacted] can be induced to exercise under the conditions of this modified patch test procedure.

.02 To adjudge whether the exercise of such propensities under the test conditions contraindicates the kind of skin contact that would be occasioned during the appropriate use of the product.

2.00 DESIGN:

.01 A modified version of the Repeated Insult Patch Test [redacted] was conducted under double blind conditions on a panel composed of more than one hundred subjects at the outset.

.02 The regimen comprised nine sequential 24-hour induction applications and two concurrently conducted 24-hour challenge applications, one on the initial induction site and one on a naive site.

.03 During the initial phase, the skin of the contact sites was graded and the grades recorded on Wednesdays, Fridays (i.e. twenty-four hours after patches had been removed), and Mondays (i.e. forty-eight hours after patches had been removed).

.04 During the challenge phase, the skin of the contact sites was graded within moments after the patches had been removed (24 hours post application) and again twenty-four hours later. Follow-up examinations were conducted thereafter only if adverse effects were present.

.05 This study was conducted in compliance with the standards of good clinical practices generally applicable for the protection of the privileges and well-being of individuals who participate in patch test procedures.

3.00 SPONSOR: [redacted]

Project Director:

Authorization:

Purchase Order:

4.00 STUDY PRODUCT:

Type of Product:	Eyeliner
Sponsor Identification:	[redacted]
Date received:	2/22/10
Quantity rec'd:	>439 g. gross wt.
Form used in study:	Volatilized
PI Nº	[redacted]

5.00 SITE OF STUDY:

Product Investigations, Inc.
142 North Ninth Street
Suite 16
Modesto, CA 95350

Study Personnel:

Medical Director:	Morris V. Shelanski, MDCM
Dir. Derm. Services:	Joseph E. Nicholson III
Dermatologist:	Clinton E. Prescott Jr., MD
Technicians:	Lisa Cortez, Henry Cortez
Quality Assurance:	Samuel J. Charles III

6.00 DATES OF STUDY:

Started:	22 February 2010
Completed:	26 March 2010

7.00 SELECTION OF SUBJECTS:

.01 RECRUITING:

Prospective subjects were recruited from surrounding localities via phone, posters and personal contact.

.02 INFORMED CONSENT:

All individuals who expressed interest in participating were given an informed consent document to read. This document, which each candidate had to read and sign before being entered into the study, presented the following information:

a. How many subjects were to be enrolled in the study;
b. The intended use of the product;
c. Why the product was being tested;
d. How the test was to be performed;
e. That the regimen was not intended to benefit a subject's health, well being, or quality of life.
f. The different ways that participation may be detrimental to a subject's health, well being, or quality of life.
g. That not all detrimental effects could be foreseen and made known at the time the informed consent was presented for the prospective subject's signature.
h. What commitments a subject had to make to be in compliance; and
i. What considerations a subject was entitled to receive and the conditions for receiving them.

.03 DETERMINATION OF ELIGIBILITY:

Information concerning a prospective subject's qualifications was obtained from the answers the subject gave in filling out a medical history form and in responding to specific questions. Those who did not meet the following criteria were rejected.

a. **Inclusion Criteria: Satisfaction of all the following items was obligatory:**
   i. The candidate was at least eighteen years old, and
   ii. agreed to comply fully with the scheduled study regimen, and
   iii. expressed awareness that a participant would incur risks that would affect her/his well-being, and
   iv. denied that the amount of the stipend had induced her/him to participate against her/his better judgment, and
   v. had read the informed consent agreement, and
   vi. had assured the interviewer that she/he had no questions about the informed consent's contents that had not been answered to her/his satisfaction, and
   vii. had signed the consent form willingly and without reservation.

b. **Exclusion Criteria:** Any one of the following items was cause for rejection:
   i. The candidate had an illness that contraindicated participation; or
   ii. a condition that rendered the skin unsuitable for use in this study; or
   iii. was using dosages of medications that could alter the skin's tolerance; or
   iv. had a documented history of intolerance to the category of products submitted for study; or
   v. was a female who was pregnant or was breast feeding an infant.

.04 PANEL INFORMATION:

a. **Panel N^{o}:** [redacted]

b. **Demographics:**

SEX	Number	Age Range
Female	70	18 - 83
Male	40	19 - 66

c. **Dedication:** This was a shared panel, i.e. the subjects were engaged in the evaluation of materials submitted by sponsors other than [redacted]

8.00 SITE INFORMATION:

.01 LOCATION:

[redacted] was assigned Band #4 on the right side of the back of each subject.

.02 IDENTIFICATION OF A CONTACT SITE:

At each visit the skin around the contact site was marked to facilitate examinations after the device was removed and positioning of subsequently-applied devices as precisely as was feasible on the same site.

9.00 PATCHING DEVICES:

.01 TYPE OF DEVICE:

Partially-occlusive patching devices consisting of a 2 cm x 2 cm absorbent pad centered on the adhesive-coated surface of a 2 cm x 4 cm plastic film were used to convey and maintain the product on the skin.

.02 PREPARATION OF A PATCHING DEVICE:

The webril pad of a patching device was evenly coated with 200mg of the test material. Prepared devices were exposed to ambient air for at least 30 minutes prior to application.

.03 POSITIONING AND REMOVING A PATCHING DEVICE:

a. A prepared device was positioned on its designated site on each subject with the product-treated surface of the pad in contact with the skin.
b. Firm pressure was applied to the backing of the device to effect intimate contact of the pad with the skin and to bond the flanges of the device securely to the skin.
c. When the time came for removing the device, the device was peeled off the skin as gently as was feasible under the circumstances.

10.00 DATA ACQUISITION:

.01 GRADING PROCEDURE:

a. Examinations of the contact sites to grade the effects elicited by the product were conducted on Mondays, Wednesday and Fridays. When a subject came in on a scheduled examination day, the technician examined the skin of the contact site.
   i. If no adverse effect was detected, a "0" was recorded in the subject's Case Report Form.
   ii. If an adverse effect was detected, the technician entered a grade indicating her assessment of the response's intensity.
b. The subject was then sent into the patching room where the site was examined again by a second technician to ascertain independently whether or not the site should be used again. If she disagreed with the first technician's assessment, the application was held in abeyance until the issue could be resolved with the help of the supervisor and/or the investigator.
c. The supervisor or the investigator was called in not only when a disagreement had to be resolved, but also to validate substantial sudden changes, e.g. when a response is deemed to merit a grade ≥3 or when a response has been judged to have decreased by two or more points from the previous day's status.

.02 CRITERIA FOR GRADING RESPONSE INTENSITY:

The following scale was used in this procedure to designate the intensities of those gross skin changes that may be occasioned by exposing the surface of the skin to a product.

Morphology	Visible Change	Grade
Subclinical Stage	None	0
Inflammation		
Vascular Dilation:	Faint redness with poorly defined margins	1
	Redness with well-defined margins	2
Infiltration:	Redness plus well-defined edema	3
	Redness plus papules, or vesicles or ulceration	4

.04 SITE CHANGES:

a. Switch to a Naive Site:
   i. If the product had elicited a Grade 2 response on a subject, application of the product would have been switched immediately to a naive site on the subject.
b. Discontinuation of Applications:
   i. If the product had elicited a second Grade 2 on a subject, application of the product would have been discontinued immediately for the remainder of the initial phase on the affected subject.
   ii. If the product had elicited a Grade 3 response on a subject, application of the product would have been discontinued immediately for the remainder of the initial phase on the affected subject.

11.00 OVERVIEW OF STUDY REGIMEN:

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week #1	Apply	Remove	Grade/Apply	Remove	Grade/Apply	(Removed)	–
Week #2	Grade/Apply	Remove	Grade/Apply	Remove	Grade/Apply	(Removed)	–
Week #3	Grade/Apply	Remove	Grade/Apply	Remove	Grade/Apply	(Removed)	–
Week #4	Grade	–	–	–	–	–	–
Week #5	Apply	Remove/Grade	Grade	Grade*	Grade*	–	–

*If necessary

12.00 STUDY REGIMEN:

.01 INITIAL/INDUCTION PHASE-

Week #1:

Monday:

i. As each subject presented herself/himself at the clinic, the skin of the contact site assigned to the product submitted for study was examined and ascertained to be suitable before applications were begun.
ii. A freshly-prepared patching device was applied on its assigned site.
iii. The skin around the device was marked and the subject was instructed to return on Tuesday.

Tuesday:

i. As each subject returned, the site-identifying marks were reinforced.
ii. The patching device was removed by a technician and the subject was instructed to return on Wednesday.

Wednesday:

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. A freshly-prepared patching device was applied on the same site.
iii. The site-identifying marks were reinforced and the subject was instructed to return on Thursday.

Thursday:

i. As each subject returned, the site-identifying marks were reinforced.
ii. The patching device was removed by a technician and the subject was instructed to return on Friday.

Friday:

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. A freshly-prepared patching device was applied on the same site.
iii. The site-identifying marks were reinforced.
iv. The subject was dismissed with instructions to remove the patching device on Saturday, to record the time of removal, and to return to the clinic on the following Monday for resumption of the regimen.

Week #2:

Monday:

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. The time at which the patch was removed on Saturday was recorded.
iii. A freshly-prepared patching device was applied on the same site.
iv. The site-identifying marks were reinforced and the subject was instructed to return on Tuesday.

Tuesday, Wednesday, Thursday, Friday:

The procedures followed were the same as those followed on corresponding days during Week 1.

Week #3:

Monday:

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. The time at which the patch was removed on Saturday was recorded.
iii. A freshly-prepared patching device was applied on the same site.
iv The site-identifying marks were reinforced and the subject was instructed to return on Tuesday.

Tuesday, Wednesday, Thursday, Friday:

The procedures followed were the same as those followed on corresponding days during Week 1.

Week #4:

Monday:

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. The time at which the patch was removed on Saturday was recorded.
iii. a) If the subject had undergone all nine induction applications, she/he was dismissed after being instructed as follows:
i) to report back to the clinic on the following Monday to receive the challenge applications, and
ii) to notify the investigator without delay should any significant changes occur in the skin of the contact site before Monday of the challenge week.

b) If the subject had not received the required number of induction applications and was deficient without valid reason, applications were continued. As many as two missed applications could be made up during this week. When the subject had undergone the required number of make up applications, she/he was dismissed after being instructed as in section a) ii, above.

.02 HIATUS/MAKE UP PHASE-

Week # 4:

After the examination on Monday of Week 4, no procedures other than make-up cycles were scheduled during this period.

.03 CHALLENGE PHASE-

Week #5:

Monday:

i. As each subject returned, the skin of the initial induction site was examined and ascertained to be free of any conditions that would have rendered it unfit for undergoing the challenge applications.
ii. A prepared device was applied on the initial induction site.
iii. A second prepared device was applied on a naive site.
iv. The skin around both devices was marked and the subject was instructed to return on Tuesday.

Tuesday: (Note: If a subject was absent on Monday, she/he was patched on Tuesday.)

i. As each subject returned, the site-identifying marks around both contact sites were reinforced.
ii. Both patching devices were removed by a technician.
iii. The skin of both contact sites was graded; the grades were recorded.
iv. The subject was instructed to return on Wednesday.

Wednesday:

i. As each subject returned, the skin of both contact sites was graded; the grades were recorded.
ii. If follow-up was indicated, the subject was instructed to return on Thursday, otherwise the subject was dismissed from the study of this material.

.04 FOLLOW-UP PHASE:

Week No. 6 and Week No. 7:

During the two weeks following the exit examination, the subjects were given the opportunity to relay any information concerning effects that were relevant to the characterization of the product as well as to communicate the need for treatment of persistent or newly-occurring responses.

13.00 PROCEDURE DEVIATIONS:

No deviations in procedure were necessary.

14.00 COMPLIANCE

	No. Of AEC's		COMPLIANT	
PHASE	Required	EXCUSED	YES	NO
Induction	8	0	104	6
Challenge	1/1	0	102	8

104 of the 110 Subjects were in compliance with the number of required application/examination cycles during induction
102 of the 110 Subjects were in compliance with the number of required application/examination cycles during challenge

15.00 INCIDENCE OF RESPONSES:

Grade	Type of Response	Induction Phase	Challenge Phase	
			Original Contact Site	Naive Contact Site
0	No visible change	110 subjects	102 subjects	102 subjects
1	Faint redness, undefined border	0 "	0 "	0 "
2	Intense redness, defined border	0 "	0 "	0 "
3	Redness + definite edema	0 "	0 "	0 "
4	Redness + papules, or vesicles, etc.	0 "	0 "	0 "
	No. of Responders	0 subjects	0 subjects	0 subjects
	No Data Acquired	0 subjects	8 subjects	8 subjects

16.00 SIGNIFICANCE OF THE RESPONSES:

.01 Initial/Induction Phase:

No responses were noted on any of the 110 subjects who underwent at least one post-application examination. The absence of responses characterizes the product as one which is devoid of clinically significant skin-irritating propensities.

.02 Challenge Phase:

a. **Original Contact Sites:**
No responses were noted on any of the 102 subjects who participated in this phase of the study. The absence of responses characterizes the product as one which is devoid of clinically significant skin sensitizing propensities.

b. **Naive Contact Sites:**
No responses were noted on any of the 102 subjects who participated in this phase of the study. The absence of responses characterizes the product as one which is devoid of clinically significant skin sensitizing propensities.

17.00 CONCLUSIONS:

.01 [redacted] was found to be neither a clinically significant skin irritant nor a skin sensitizer under the conditions of this study.

.02 [redacted] is not contraindicated for usages entailing repeated applications on human skin under conditions appropriate for such products.

PRODUCT INVESTIGATIONS, INC.

4/20/16
Date

Joseph E. Nicholson III
Director, Dermatological Studies

18.00 COMPLIANCE WITH GOOD QUALITY ASSURANCE STANDARDS:

I have audited the results presented in this report and believe that, to the best of my knowledge, they accurately reflect the raw data acquired during the course of this study.

Samuel J. Charles III
Director, Quality Assurance

[redacted]

Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE PHASE					
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5					
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	
1	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
2	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
3	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
4	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
5	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
6	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
7	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
8	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
9	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
10	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
11	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
12	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
13	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
14	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
15	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
16	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
17	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
18	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
19	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
20	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
21	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
22	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
23	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
24	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
25	B		0		0	0		0		Dropped																
26	B		0		0	0		A		Dropped																
27	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
28	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
29	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
30	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			

(Grade) / (Grade) = Original SIte / Naive Site

[redacted]

Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE PHASE					
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5					
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	
31	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
32	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
33	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
34	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
35	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
36	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
37	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
38	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
39	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
40	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
41	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
42	B		0		0	0		0		0	0		0		0	0					A	A	A			
43	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
44	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
45	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
46	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
47	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
48	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
49	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
50	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
51	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
52	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
53	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
54	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
55	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
56	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
57	B		0		0	A		A		Dropped																
58	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
59	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
60	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			

(Grade) / (Grade) = Original SIte / Naive Site

[redacted]

Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE PHASE					
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	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	
61	B		0		0	A		A		Dropped																
62	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
63	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
64	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
65	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
66	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
67	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
68	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
69	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
70	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
71	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
72	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
73	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
74	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
75	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
76	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
77	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
78	B		0		0	0		A		Dropped																
79	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
80	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
81	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
82	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
83	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
84	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
85	B		0		0	0		0		0	0		0		Dropped											
86	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
87	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
88	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
89	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
90	B		0		Dropped																					

(Grade) / (Grade) = Original Site / Naive Site

[redacted]

Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE PHASE					
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5					
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	
91	B	[redacted]	0	[redacted]	0	0	[redacted]	0	[redacted]	0	0	[redacted]	0	[redacted]	0	0					B	0/0	0/0			
92	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
93	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
94	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
95	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
96	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
97	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
98	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
99	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
100	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
101	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
102	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
103	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
104	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
105	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
106	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
107	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
108	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
109	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			
110	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0			

(Grade) / (Grade) = Original Site / Naive Site

Consumer Product Testing Co.

EST. 1975

Fragranced Body Lotion RIPT
(0/85) 1.8% Tromethamine

FINAL REPORT

CLIENT: [redacted]

ATTENTION:

TEST:

TEST MATERIAL:

EXPERIMENT REFERENCE NUMBER:

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

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

[redacted]

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

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

Consumer Product Testing Co.

EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: [redacted]

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

Quality Assurance personnel involved:

Quality Assurance

9.24.07
Date

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

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

[redacted]

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

Participants: One hundred seventeen (117) qualified subjects, male and female, ranging in age from 16 to 77 years, were selected for this evaluation. Eighty-five (85) subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

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

Exclusion Criteria:

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

Test Material: [redacted]

Study Schedule:

Panel #	Initiation Date	Completion Date
20070251	July 30, 2007	September 8, 2007
20070252	August 1, 2007	September 13, 2007

[a]With parental or guardian consent

[redacted]

Methodology:

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

Induction Phase:

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

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

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

Challenge Phase:

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

*Manufactured by TruMed Technologies, Inc., Burnsville, MN

[redacted]

Methodology (continued):

Evaluation Criteria (Erythema and additional Dermal Sequelae):

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

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

Results:

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

Observations remained negative throughout the test interval.

Subject demographics are presented in Table 2.

Summary:

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

[redacted]

Table 1

[redacted]

Individual Results

[redacted]

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

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

[redacted]

Table 1
(continued)

[redacted]

Individual Results

[redacted]

Subject Number	Induction Phase										Virgin Challenge Site	
	24*hr	1	2	3	4	5	6	7	8	9	24*hr	72 hr
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0[m]	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	----------DID NOT COMPLETE STUDY----------										
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	----------DID NOT COMPLETE STUDY----------										
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	----------DID NOT COMPLETE STUDY----------								
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	----------DID NOT COMPLETE STUDY----------											
55	0	0	----------DID NOT COMPLETE STUDY----------									
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	----------DID NOT COMPLETE STUDY----------							
58	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
m = Additional makeup day granted at the discretion of the clinic supervisor

[redacted]

Table 1
(continued)

[redacted]

Individual Results

[redacted]

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

24* = Supervised removal of 1st Induction and Challenge Patch
m = Additional makeup day granted at the discretion of the clinic supervisor
DNC = Did not complete study

[redacted]

Table 1
(continued)

[redacted]

Individual Results

[redacted]

Subject Number	Induction Phase										Virgin Challenge Site	
	24*hr	1	2	3	4	5	6	7	8	9	24*hr	72 hr
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	----------DID NOT COMPLETE STUDY----------											
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	DID NOT COMPLETE STUDY			
38	0	0	0	0	0	0	0	0	0	0	---DNC--	
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	----------DID NOT COMPLETE STUDY----------								
42	0	0	0	----------DID NOT COMPLETE STUDY----------								
43	0	----------DID NOT COMPLETE STUDY----------										
44	0	----------DID NOT COMPLETE STUDY----------										
45	0	----------DID NOT COMPLETE STUDY----------										
46	0	0	0	0	----------DID NOT COMPLETE STUDY----------							
47	0	0	0	0	0	0	0	0	0	0	---DNC--	
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0[m]	----------DID NOT COMPLETE STUDY----------							
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	DNC
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
m = Additional makeup day granted at the discretion of the clinic supervisor
DNC = Did not complete study

[redacted]

Table 2

[redacted]

Subject Data

Subject Number	Initials	Age	Sex
1	SP	39	M
2	AA	54	F
3	JM	61	M
4	CT	49	F
5	PP	24	F
6	EV	34	M
7	MM	58	F
8	ER	26	M
9	PC	59	F
10	JM	16	M
11	DD	54	M
12	JV	27	F
13	AD	42	M
14	RT	27	F
15	MF	31	M
16	NE	63	F
17	MV	53	F
18	AW	63	F
19	SC	59	F
20	NR	35	F
21	DL	21	M
22	CP	52	F
23	LA	74	F
24	SM	19	F
25	JY	56	M
26	CB	71	M
27	JM	77	F
28	TB	58	M
29	AG	44	F

[redacted]

Table 2
(continued)

[redacted]

Subject Data

Subject Number	Initials	Age	Sex
30	JB	60	M
31	PM	45	F
32	AA	60	F
33	ES	48	F
34	DD	20	F
35	FD	66	F
36	JF	69	F
37	EA	44	F
38	SN	68	F
39	RL	75	M
40	MK	54	F
41	PN	71	M
42	AT	42	F
43	CM	31	F
44	LT	41	F
45	JC	74	F
46	CS	61	F
47	EP	59	F
48	GV	34	F
49	DG	50	F
50	LP	41	F
51	AR	67	F
52	JC	69	M
53	EM	47	F
54	IR	36	F
55	JS	27	M
56	AS	63	F
57	RS	40	F
58	JR	17	F

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: March 12, 2013

SUBJECT: Comments on the Draft Report on Tromethamine Prepared for the March 18-19, 2013 CIR Expert Panel Meeting

This report does not have report page numbers. Therefore, the numbers provided below are the Panel Book numbers.

Key Issues

p.8, Introduction - The Introduction should provide some information on the methods used to justify the read-across approach, e.g., similarities in physico-chemical properties, use of the OECD QSAR Toolbox profiling for mammalian toxicity. The Introduction should also mention that amino propanediol (APD) was also considered an appropriate analog, and why it is not included in the CIR report.

Additional Comments

Memo - Comments on the Scientific Literature Review on Tromethamine were provided by the Council, not the CIR Science and Support Committee as stated in the memo.

Data Profile, p.16, Table 1 - The Data Profile incorrectly indicates that log Kow values are not available for Tromethamine and the two analogs, Aminomethyl Propanediol (AMPD) and Aminoethyl Propanediol (AEPD). This is not correct. Log Kow values are found in the Physico-Chemical Parameters table in the analogue approach document provided by The Dow Chemical Company. The log Kow value presented in Table 1 of the CIR report is not correct. Table 1 gives the value as "2.31" while the value in the information provided by Dow is "-2.31".

p.8 - Please include the maximum use concentration of AMPD reported in the 2009 CIR safety assessment.

p.8 - The statement that Tromethamine "is used as an[d] emulsifying agent for cosmetic creams and lotions" should not be in the Non-Cosmetic Use section. Please move the information from the European Union Cosmetics Directive to the Cosmetic Use section.

p.8, last line - Please correct: "to treat academia in humans"

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p.9 - In the toxicokinetics section, please indicate what was recovered at a rate of 64% and 77% after 2 and 3 days, and in what was it found?

p.9 - In the description of the *in vitro* dermal penetration study, please clarify what is meant by "dermal absorption". Is this the amount found in the receptor fluid? Or the amount in the receptor fluid plus the amount left in the skin? More details about this study would be helpful. How much was found in the skin compared to the receptor fluid?

p.9 - The following sentence is not complete: "In a second experiment, when administered i.p. to rats, the largest amount of ^{14}C-tromethamine collected in skeletal and heart muscle at 12 and 24 h."

p.11, 12 - It is not correct to state that the number of males used in the reproduction/ developmental toxicity screening test (OECD 421) of Tromethamine is not known. The submission says the animals were mated 1 to 1, and on p.126 of the Dow submission, Table 2, Results of clinical parameters indicates that 10 males per dose group were examined.

p.12 - Please revise the following sentence: "One dog died on day 3, but was attributed to heartworms." (dog is the subject of this sentence, so the sentence is saying dog was attributed to heartworms).

p.13 - Please include the duration of the patch test of the cosmetic product containing 3.1% Tromethamine.

p.13 - Please provide more details about the peptide reactivity assay. What peptide was used? What were the negative and positive (diethyl maleate) controls? What were the peptide depletion values for the test compound compared to the positive and negative controls?

p.13 - In the description of the study of subjects with exposure to metal working fluid, the section heading is AMPD, but the paragraph indicates that "AEPD" produced a positive response in one subject. Which is correct, AMPD or AEPD? Rather than using "dermatitis patients", please use "subjects with dermatitis".

p.14 - In the Summary of the AMPD safety assessment, please indicate the route and duration of the study of the hair spray containing 0.5% AMPD. Because the hair spray tested only contained 0.135% AMPD, please change "compound-related" to "treatment-related".

p.14 - In the Summary, please include the study type and duration for the dermal penetration study. Please add the species used in the intravenous study. Please add the type of study in which no reproductive effects were observed, e.g., OECD 421.

p.15 - Please complete the following sentences. "At 40%, pH unknown, was not irritating." "A cosmetic product containing 3.1% tromethamine was not irritating a patch test."

p.17, Table 2 - For reports with only one ingredient, please present the information in a table by FDA product category. The tables that summarize the use information by duration and type of exposure are helpful when there are many ingredients in a report, but for only one ingredient, it is a shame to not include information that would be helpful to someone reading the report who wants to know the use concentration of the ingredient in a specific FDA product category.