Safety Assessment of *Butyrospermum parkii* (Shea)-Derived Ingredients as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	September 2, 2016
Panel Meeting Date:	September 26-27, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, DPA. This safety assessment was prepared by Christina L. Burnett, Scientific Analyst/Writer and Bart Heldreth, Ph.D., Chemist CIR.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina Burnett, Senior Scientific Writer/Analyst
Date: September 2, 2016
Subject: Draft Tentative Report of the Safety Assessment of *Butyrospermum parkii* (Shea)-Derived Ingredients

Enclosed is the draft tentative report of the Safety Assessment of *Butyrospermum parkii* (Shea)-Derived Ingredients as Used in Cosmetics. (It is identified as *shea092016rep* in the pdf document.)

At the June 2016 meeting, the Panel issued an Insufficient Data Announcement for the 13 *Butyrospermum parkii* (shea)-derived ingredients described in the safety assessment. Data needs included:

- Method of manufacturing for Butyrospermum Parkii (Shea) Nut Extract, Butyrospermum Nut Shell Powder, Butyrospermum Parkii (Shea) Seedcake Extract, and Hydrolyzed Shea Seedcake Extract
- Additional information on method of manufacturing, composition and impurities data, and sensitization data on Butyrospermum Parkii (Shea) Butter Unsaponifiables.
- Composition and impurities data on the above listed nut and seedcake ingredients
- Sensitization data on the above listed nut and seedcake ingredients

Since the June meeting, unpublished human irritation and sensitization studies of Butyrospermum Parkii (Shea) Butter Extract at concentrations up to 5% in formulation were received. These data have been incorporated into the report and highlighted in tables. No other requested data have been received by CIR staff. Comments received from the Council prior to the June meeting have been considered. The comments and the unpublished data can be found in this report's package (*shea092016pcpc and shea092016data, respectively).*

At the June meeting, the Panel added Butyrospermum Parkii (Shea) Butter and Butyrospermum Parkii (Shea) Oil to the report. The use tables have been updated with the 2016 VCRP data and the Council's surveys on these two ingredients. With this new data, Butyrospermum Parkii (Shea) Butter has the most reported uses of the ingredients listed in this safety assessment in cosmetic products, with a total of 4358; nearly three-fourths of the uses are in leave-on formulations. Butyrospermum Parkii (Shea) Butter has the highest reported maximum concentration of use; it is used at up to 100% in moisturizers. According to data reported in 2011, Butyrospermum Parkii (Shea) Oil is used at up to 11% in lipsticks.

The Panel should carefully consider and discuss the data presented in this report and issue a Tentative Report with a safe, safe with qualifications, or insufficient data conclusion.

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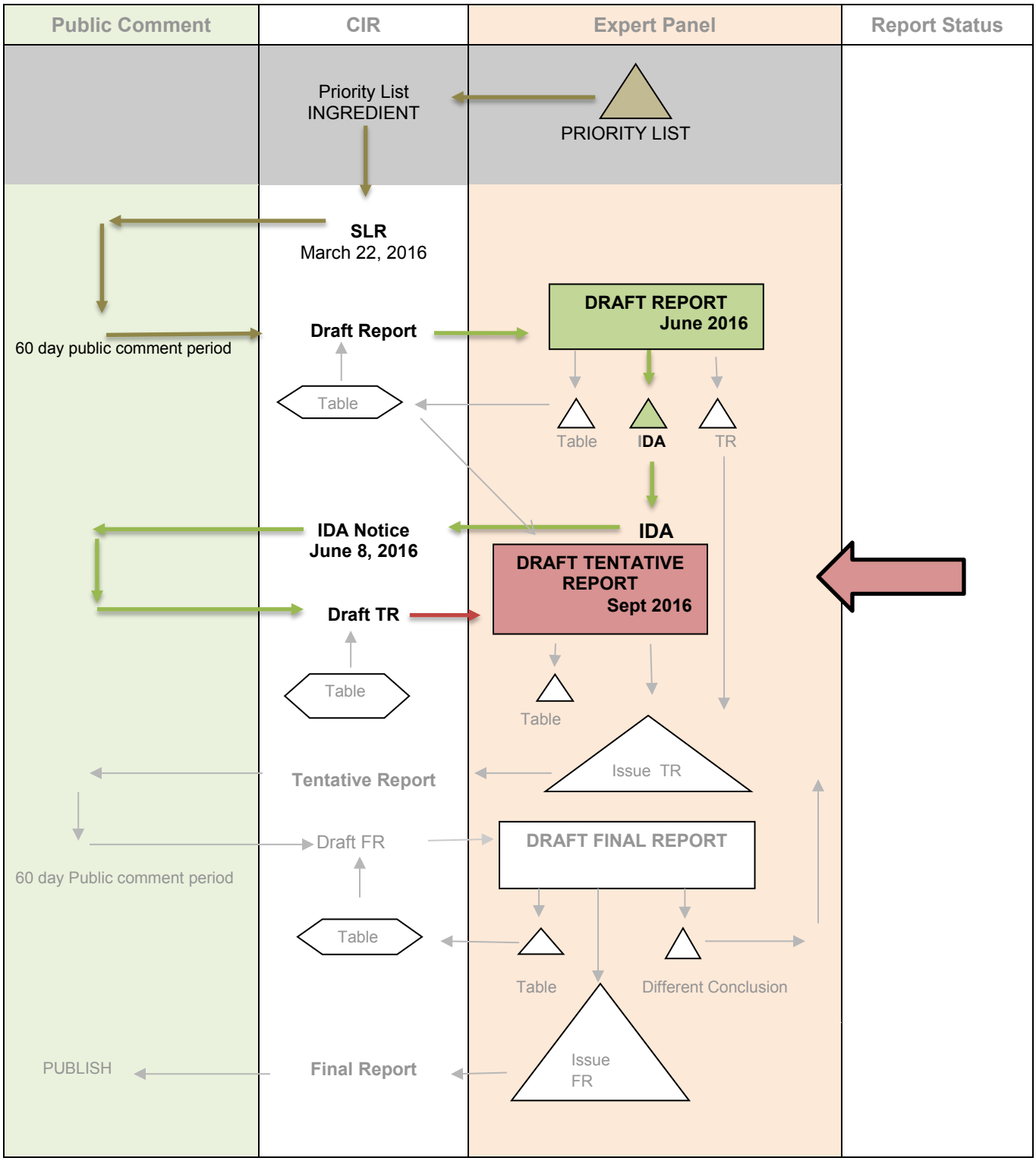
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Butyrospermum Parkii* (Shea)-Derived Ingredients

MEETING Sept 2016



***Butyrospermum parkii* (Shea)-Derived Ingredients History**

March 2016 – Scientific Literature Review announced.

June 2016 - The Panel issued an Insufficient Data Announcement for the 13 *Butyrospermum parkii* (shea)-derived ingredients described in the safety assessment. Data needs included:

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- Composition and impurities data on the above listed nut and seedcake ingredients
- Sensitization data on the above listed nut and seedcake ingredients

***Butyrospermum parkii* (Shea)-Derived Ingredients Data Profile – September 2016 – Writer, Christina Burnett**															
	In-Use	**Physical/Chemical Properties**	**Method of Manufacturing**	**Composition/Impurities**	**Toxicokinetics**	**Acute Toxicity**	**Repeated Dose Toxicity**	**Reproductive and Developmental Toxicity**	**Genotoxicity**	**Carcinogenicity**	**Irritation/Sensitization - Nonhuman**	**Irritation/Sensitization - Clinical**	**Ocular/Mucosal**	**Phototoxicity**	**Case Studies**
Butyrospermum Parkii (Shea) Butter	X	X	X	X							X	X	X	X	
Butyrospermum Parkii (Shea) Butter Extract	X											X			
Butyrospermum Parkii (Shea) Butter Unsaponifiables	X		X	X					X		X		X	X	
Butyrospermum Parkii (Shea) Nut Extract	X														
Butyrospermum Parkii (Shea) Nut Shell Powder	X														
Butyrospermum Parkii (Shea) Oil	X	X	X	X			X	X		X					
Butyrospermum Parkii (Shea) Seedcake Extract	X														
Hydrogenated Shea Butter	X														
Hydrogenated Shea Oil															
Hydrolyzed Shea Seedcake Extract															
Shea Butter Glyceride	X														
Shea Butter Glycerides	X														
Shea Oleine (not an INCI ingredient)	X		X	X	X		X	X		X					

"X" indicates that data were available in the category for that ingredient.

Search Strategy for *Butyrospermum parkii* (Shea)-Derived Ingredients
(Performed by Christina Burnett)

- SciFinder – January 2016
  - Search for ingredients by INCI names, only Shea Glyceride(s) in system –0 reference hits

Search Terms	TOXLINE Hits (excluding PUBMED)	PUBMED Hits	SCCS/SCCP Opinion	ECHA Hits	NICNAS
Butyrospermum parkii	5	9	0	0	0
Vitellaria paradoxa	1	37	0	0	0
Shea	*	*	0	0	0

*Reference searches for "shea" were not very successful because hits with authors named "Shea" would come up, even with qualifiers.

Total references ordered or downloaded: 24
Search updated April 15, 2016 = 0 relevant references found.

Search updated August 2, 2016 = 0 relevant references found.

Butyrospermum parkii (Shea)-Derived Ingredients
June 6-7, 2016

Dr. Marks' Team

DR. MARKS: We are to shea. This is the first review of these ingredients. However, the oil, butter, butter unsaponsifiables and hydrogenated butter were found to be safe in 2011. Actually, it isn't quite the first time we have seen all these ingredients. We have seen some of them before.
Tom and Ron, are the ingredients okay that we have listed, including adding the two below, the oil and butter? What needs do you have?

DR. SHANK: The only needs I had were for nut extract, nut shell powder, seedcake extract, and hydrogenated seedcake. The rest were fine.

MS. BURNETT: Nuts and seeds?

DR. SHANK: The ones I just mentioned, HRIPT, highest use concentrations.

DR. MARKS: Let me go back.

MS. BURNETT: Nut extract?

DR. SHANK: Nut extract, its highest use concentration is 1 percent. Nut shell powder --

DR. MARKS: Do that again, Ron. I'm sorry. Insufficient?

DR. SHANK: Insufficient for nut extract, nut shell powder, seedcake extract, hydrogenated seedcake extract, so four.

DR. MARKS: Hydrolyzed or hydrogenated?

MS. BURNETT: Hydrogenated.

DR. SHANK: Hydrogenated.

DR. HELDRETH: There is only a hydrolyzed seedcake extract.

MS. BURNETT: They are right next to each other.

DR. HILL: Say it again? I'm looking at the read across table, so there are some that are not in use.

MS. BURNETT: Those are all included.

DR. HILL: I see hydrolyzed seedcake extract but not hydrogenated seedcake extract.

MS. BURNETT: Insufficient data.

DR. MARKS: All those are for sensitization, HRIPT, is that right?

DR. SHANK: That's correct.

DR. MARKS: The nut extract, do we have uses?

MS. BURNETT: Yes.

DR. MARKS: It must have been low because I didn't highlight that.

MS. BURNETT: Nut extract has concentration use. (Inaudible). Nut shell powder has 2 VCRPs, used up to 1 percent. Seedcake extract has two uses, used up to 5.5 percent.

DR. MARKS: 50 percent okay for the oil. I guess what you're saying is because the ingredients may vary, the composition may vary, that is why you would like the HRIPT. I guess I was reassured when I saw the oil, that sensitization up to 60 percent were safe or no sensitization, and then we had the oil butter, butter unsaponifiables, no concern about sensitization.

DR. HILL: But the difference is you are looking at shell and you are looking at seedcake which are then extracting, and those things probably are not showing up in your oils or butters or glycerides. Composition and method of manufacturing for those, and clarification.

DR. MARKS: This would be an insufficient data notice, since it is the first review.

DR. HILL: Composition and method of manufacturing for the same ones he listed, and also for the writer, if we could recapture what we had from shea butter and shea oil from the other report into this one for reference.

MS. BURNETT: The data is summarized in there.

DR. HILL: Yes, okay.

MS. BURNETT: I take it the Panel would like -- we did not officially have those in this list since we had already re-reviewed them, but we can pull them over officially. I do have concentration and use data for the butter, and can incorporate it into this report, so it would be available at the next meeting.

DR. HILL: I also wanted a clarification, is the nut oil in the scheme essentially the same as shea oil or is it something different. It's not clear from the way that figure is written or what's described, whether or not oil is the same as shea oil or essentially the same.

MS. BURNETT: Nut extract is the same as the butter extract?

DR. HILL: Where is Figure 1. You start with the tree nut, and then there is a boiling step, and then it says shea nut oil. Is that the same as shea oil or something, a new and improved shea oil, or something completely different and we get shea oil another way.

MS. BURNETT: I believe it's the same, it's the nomenclature they use. I will 100 percent check that. From what I remember, it is the same. Shea nut oil and shea oil are the same thing.

DR. HILL: We have a lot of data for shea oleine that informs in terms of informing one ingredient to another. I hate to use the term "read across," but that is what it is.

DR. MARKS: Okay. We are going to include the shea oil and the shea butter, and add a paragraph down below, correct? Next to the last paragraph.

DR. HILL: I wanted a clarification when we have butter extract, where we don't have method of manufacture, it is important because is it consistent with the lipstick ingredient that is used at 2 percent, and then 5 percent -- in general, is the butter extract consistent with the lipstick ingredient where we have data. I know it's definition. We don't know from the definition.

MS. BURNETT: I'm sorry. I'm not following you.

DR. HILL: Okay. We have safety test data on the lipstick, does that inform all the butter extract stuff? Do you see what I'm asking? In other words, can I read from the lipstick where I do have data to all of the butter uses, there isn't data on anything other than the lipstick.

Do you get what I'm saying? It's a natural preparation, just because there is something called shea butter extract in the lipstick, is that consistent -- you may not be able to get that information. That is an industry question, actually.

I guess what I'm saying is when we have tested the lipstick, have we tested shea butter broadly enough to --

MS. BURNETT: I can't --

DR. HILL: I know you can't answer it. It's an information need.

DR. MARKS: Okay.

MS. BURNETT: Before we completely move off shea, this one had delayed, that included the in vitro sensitization. That was just summary data. That's all I got, that little summary sheet.

DR. SLAGA: (off mic)

MS. BURNETT: Yes.

DR. MARKS: That was the shea butter.

DR. HILL: Then I had a question, before we move on, I had a couple of questions for the toxicologists.

DR. MARKS: What is the butter made out of? Is it made out of the nut?

MS. BURNETT: Yes.

DR. MARKS: Ron Shank, you don't think butter would represent the nut extract, certainly not the shell.

DR. HILL: The scheme shows the shea butter is coming from the oil by hexane extraction, which probably means you're picking up almost all -- the oleine is going to be very similar to that.

I had a question for the toxicology people. In the studies of the hydrogenated oleine, grant you, they were given fairly high doses in most of these studies, we are frequently seeing ALT values go up, AOK levels go up. Do we have any concerns related to that whatsoever? They are all high dose, if I'm not mistaken.

MS. BURNETT: 15 percent.

DR. HILL: I was concerned that we were always seeing -- what is causing that to happen in those hydrogenated oleine.

MS. BURNETT: Page 12.

DR. HILL: On the other hand, you are not seeing it on the ones that aren't hydrogenated, as best I can tell.

DR. SLAGA: I didn't have any trouble --

DR. SHANK: High level --

DR. HILL: That's what I thought.

DR. SHANK: It didn't concern me.

DR. MARKS: Tomorrow, let me summarize where I think our team is at. I'll move that we issue an insufficient data notice, that we want the method of manufacture, composition and sensitization data for nut extract, nut shell powder, seedcake extract, and hydrolyzed seedcake extract. Does that sound good?

DR. SHANK: Uh-huh.

DR. HILL: I was particularly noting one of those seedcake extracts because I saw uses in baby oils, for example.

DR. MARKS: Okay.

MS. BURNETT: Wave 2 in vitro. We just need to discuss it.

DR. MARKS: In terms of -- reactivity assay, is that what you're talking about?

MS. BURNETT: Yes, right.

DR. MARKS: That was on the butter unsaponifiables.

MS. BURNETT: This is the first time we have seen an in vitro skin sensitization study come in. All of them have been HRIPTs. This is new. Part of the wave of the future, so we just wanted to get the Panel's feel on inclusion and weight of importance, I guess.

DR. MARKS: This ingredient we had concluded was safe prior, correct?

MS. BURNETT: On the unsaponifiables, yes.

DR. MARKS: This was that 2011 report, so this is just new data that has arrived?

MS. BURNETT: Yes, additional data.

DR. MARKS: Is this from the P&G and Frank Gerberick's work on using direct peptide reactivity? Does anybody know that?

DR. BJERKE: Yes.

DR. HILL: The Europeans consider HRIPT to -- they think it is unethical, they don't like to see it done or something along those lines.

MS. BURNETT: I think Dr. Belsito said something like that, yes.

DR. ANSELL: Yes.

DR. MARKS: I heard Frank present this, and what they do is compare it to data already known and it appeared this was substantiated to be valid.

DR. BJERKE: (Inaudible) Whether it is predictive of the (Inaudible).

DR. HILL: The dog ate my homework here.

DR. SLAGA: They look at it versus the HRIPT, right?

DR. BJERKE: I can't really (Inaudible).

DR. HILL: What I was going to ask is in our previous report, did we actually have data on the unsaponifiables, and I didn't get a chance to check that before sitting here. That was on my punch list.

MS. BURNETT: If I had it, it should have been summarized, and I'm not seeing it.

DR. HILL: The reason I asked the question is because if you look at the method of manufacture for the unsaponifiables, you're going to get a very different cut of compounds than you get in the butter, the oil, because you are getting -- what is the word I'm looking for -- platanoides. There is one other class I'm missing, sorry.

DR. SLAGA: Triterpenoids?

DR. HILL: Triterpenoids, thank you. In the unsaponifiables, you are getting a lot of those at a considerably high concentration. Thank you. I hang my head in shame.

DR. MARKS: What is the ECVAM?

DR. ANSELL: European Centre for Validation of Alternative Methods. Japan –VAM.

DR. LORETZ: Korean-VAM.

DR. MARKS: The comment was do we know enough about the DPRA, the direct peptide reactivity assay, and the ECVAM protocol to say yes, we feel comfortable that this is a valid tool in predicting sensitivity.

DR. HILL: I'm not prepared to comment today.

MS. BURNETT: A discussion item for our purposes, we had a feeling this is not going to be the last, new generations of --

DR. MARKS: I'd be very interested to hear if it is being used in RIFM, and Dan and Don's comment on this. They may have heard a presentation on it, or used the data already. We are not using this data at this point to make a conclusion of it being safe. It does bring up the issue of a new test.

DR. SHANK: Many years ago, we asked to find out exactly what the assay was and how it compared with HRIPT. I think this is going to be coming up again and again, we need the same kind of information, how does this stack up

DR. ANSELL: It is a topic of great interest to the industry as well.

DR. HILL: It also dovetails into something I heard today, I think it was Dan or actually Don was asking first, when they develop these computational models and then validate them with data, the predictive models are going to use data from whatever tests, these would be input in there as well. Knowing the model, it is important to understand whether the computations is going to give you confidence or not because the question is what weight is being put on those models in terms of prediction and now.

DR. BJERKE: The DPRA is not a replacement for other existing tests, but part of the integrated assessment approach and part of (Inaudible). We are marching along this future of non-animal (Inaudible). This is one piece of the puzzle. (Inaudible) It is one of the mechanistic steps for skin sensitization.

DR. SHANK: We get a comparison of results from the peptide assay, compounded or possibly the negative of that assay versus (Inaudible).

DR. BJERKE: Yes.

DR. SHANK: Thank you.

MS. DEWAN: (Inaudible). There are different endpoints.

DR. BJERKE: Yes, that is one of the necessary points of the adverse outcomes, you get the skin sensitization.

DR. HILL: Yes, not all sensitization (Inaudible).

MS. DEWAN: Yes.

DR. ANSELL: We do see the DPRA comparison against HRIPT when used in conjunction with (Inaudible). The HRIPT is not 100 percent accurate either. This actually was a presentation to another group from IBS, Dr. Norman gave it, and compared three of the methods and then compared against HRIPT and then compared against other material.

This whole issue, as you pointed out, is of great interest to us right now.

MS. BURNETT: It was a nice presentation.

DR. MARKS: Team, do we want to ask somebody to come in and present to us?

DR. SLAGA: It would be nice.

DR. SHANK: It would be helpful.

DR. MARKS: It would be helpful to me also.

DR. SLAGA: It would be helpful to us.

DR. MARKS: I think it would be helpful to all of us. This is the wave of the future. If you are going to avoid animal testing, I'm not quite sure in terms of humans. Is that going to be banned in Europe in the future?

DR. ANSELL: They consider it unethical.

DR. BJERKE: But they use it.

MR. STEINBERG: In the early part of the 2000s, I was moderating a conference in Tokyo. One of the speakers was a toxicologist from Europe whose paper basically said you are asking for a 100 percent correlation between a non-animal test to an animal test, when we don't have 100 percent correlation between an animal test and human tests, and we are never going to get it. So, where are we going?

DR. MARKS: Maybe that can be one of the points the speaker makes, I guess. I think we need to be brought up to date with the direct peptide reactivity assay. I heard Frank Gerberick present it. He's with P&G. I believe, is it true, he's the one who essentially developed it. The problem there is he obviously had a bias in favor. (Laughter)

DR. BJERKE: Right. Industry is looking at integrated testing strategy, and there are three or four different ways that industry is approaching this, so we are going to see who wins. It is a combination of a wide variety of in vitro tests, and one of them will rise to the top as being the most predictive.

DR. SHANK: One usually isn't enough, you need the battery.

DR. BJERKE: Right.

DR. ANSELL: That's what they are looking at now. I think ultimately where we are going is if we can identify the molecular trigger, then all the tests become irrelevant.

DR. HILL: I'm sure it seemed perfectly relevant at the time, some meetings ago, some humans are much more susceptible than other humans because of their genotype, eventually we will work our way to that, too, until such time that every insurance company everywhere is paying for genotyping.

The pharmaceutical industry has been looking at this for at least 20 years as an index of we don't want that compound, and one of the conclusions that came out more recently was in some cases we are paring out perfectly good and useful drugs because that is not the be all end all, there are limitations to interpretation. In this case, it was safety.

I do think we need to hear about it because in particular the presenter from Alto Mira this morning mentioned this is one of the indices that is still going to be a predictive model looking at sensitization earlier. We can't expect that to be the 100 percent of the time criteria, and that is important to know.
DR. MARKS: I hate to belabor shea ingredients any longer. What happened in the 2011 review of those four ingredients which now is part of this report? In my mind, why aren't we reopening and adding all these?

DR. SLAGA: I felt the same.

MS. BURNETT: The plant oil report that had the 200 and some ingredients.

DR. SLAGA: It would be better.

DR. MARKS: I see what you're saying.

MS. BURNETT: They are not quite all related. In that report, it was hydrolyzed oil, and this has extracts in it. It would have to be reopened for all the --

DR. MARKS: I got you. The idea is this will be duplicated from that 2011.

MS. BURNETT: Yes.

DR. MARKS: This is the first review of these ingredients, and I might say with the exception of the oil, butter, butter unsaponifiables, and hydrogenated butter, which were found to be safe in the 2011 report, and I would move tomorrow that we issue an insufficient data notice. We would like the method of manufacture, composition and sensitization data for nut extract, nut shell powder, seedcake extract, hydrolyzed seedcake extract, and presumably that will be seconded, and when we start discussing it, I will mention the direct peptide reactivity assay to detect sensitivity, we would like to know more about the specificity and sensitivity and perhaps invite a speaker, such as Frank Gerberick.

Does that sound good, team?

DR. SLAGA: Sounds good.

Dr. Belsito's Team

DR. BELSITO: Okay, the next one is shea derived ingredients. It's the first time we're looking at this. And we've received a good amount of data and then, the question is is it sufficient?

And basically, the first thing I thought was that we really don't have composition and impurities for any of the seed cake or nut shell and nut extract and thought that we needed those. We don't have any photosensitization. We have a phototoxicity study but I really didn't think based upon the molecular structures that these would be absorbing materials but do we need a UV spectra or should we ask for photosensitization data?

DR. LIEBLER: Well, these are complicated mixtures so I mean, I don't think a UV spectra will be useful at all.

DR. BELSITO: Okay.

DR. LIEBLER: I think we would handle these like we would handle other botanicals or, you know, plant extracts essentially. So I don't see, unless they were photosensitizing constituents of concern identified in any of these, I don't think we need a photosensitization phototox evaluation.

DR. BELSITO: Okay, but then, that should eventually go in our discussion as to why we didn't request it?

DR. LIEBLER: Right, right. Well, what about the issue of bringing the other ingredients in from the other report that was brought up in the introduction letter?

MS. BURNETT: We brought half not all and --

DR. LIEBLER: So we --

MS. BURNETT: We do the use concen -- use and concentration data. It's not in this report but I can readily put it in. In the data supplement you have the concentration data.

DR. EISENMANN: For shea butter but not for the oil

MS. BURNETT: The shea butter, yeah, the oil but if you want to use the old data, we have that from the 2010 report and I do have some of the data, the composition data came from -- is for the butter.

DR. LIEBLER: From the 2011 report?

MS. BURNETT: Yes, and available literature that I have found since.

DR. LIEBLER: So that would help us with like the hydrogenated shea butter, the shea butter extract, shea butter unsaponifiables. Probably is not going to help us with the nut extract, shell powder or seed cake.

DR. BELSITO: Right. Because I actually thought that if you were okay with the olein to -- with a 13-week feeding study of the olein in terms of systemic toxicity we could go sufficient for the butter-derived ingredients. And then, sufficient for nut and seed cake-derived ingredients for composition impurities and depending upon the sensitization and irritation, photoabsorption and if absorbed then more systemic tox effects. But I thought the butter-derived or the butter ingredients were safe as used based upon the information we had here?

DR. LIEBLER: Yeah, I agree.

DR. BELSITO: Curt? Paul?

DR. SNYDER: I was just looking to see if is the shea nut oil used as a standalone or is it -- shea nut oil is broad.

DR. BELSITO: Is it -- it's not listed under what we're looking at. It just says shea oil.

DR. SNYDER: I assume that's the nut oil, right?

DR. LIEBLER: There is not a nut oil listed, there's shea oil. There's a nut extract, a nut shell powder.

DR. BELSITO: And the definition of shea oil is I see hydrogenated. Where is shea oil?

MS. BURNETT: Because it's not in this report yet it -- the definition's not there yet.

DR. BELSITO: Okay. So presumable the hydrogenated shea oil is well it just says it's the controlled hydrogenization, (inaudible) butter.

DR. SNYDER: Because if we have that then that makes everything after that, right? Because everything else is derived from that, right?

DR. BELSITO: From the oil?

DR. SNYDER: I guess in the flow chart, flow diagram that she has at the beginning --

DR. BELSITO: Well, the butter -- the butter is not defined here but in everything else it's from the butter. But is the butter derived from the --

DR. SNYDER: Well, but a simple diagram she has everything is derived from the shea nut oil where it either -- it goes acetone fractionation to the --

DR. LIEBLER: Yeah, acetone fractionation gives you the oleins, the stearins and then, the hexane extraction gives you the shea butter. And when you mentioned shea nut oil, Paul, you had to go -- I realize you were looking at the scheme and I was looking at the list.

DR. SNYDER: Yeah, okay.

DR. LIEBLER: That's what the difference --

DR. BELSITO: Yeah.

DR. SNYDER: But we have data on the shea nut oil, right?

DR. BELSITO: We don't how much data is. That just came from the seed oil report, right?

MS. BURNETT: Right.

DR. BELSITO: That was put in that report.

MS. BURNETT: Correct.

DR. BELSITO: So we could have cleared it simply on the basis that we had no data for that particular seed oil but had it for other seed oils. We don't know.

DR. LIEBLER: Right.

DR. EISENMANN: In this report a couple of the shea oleins that is used shea oil as their control, correct?

MS. BURNETT: I believe so, yes.

DR. EISENMANN: And you might have -- if you put in a little bit more information on those you might have a little bit more data on them.

DR. BELSITO: Where are you, Carol? What page? Is that genotox with the olein?

DR. EISENMANN: I think it was more of the longer term study or the reproductive study that might have --

MS. BURNETT: I think it's the Kuroso geneste study if I remember. I know they did a palm oil.

DR. BELSITO: Right, and they did olein.

DR. EISENMANN: And they did something called shea nut oil.

DR. BELSITO: So they -- under carcinogenicity oral, under in four weeks --

DR. SNYDER: Shea nut oil, yeah.

DR. BELSITO: -- shea nut oil and palm oil.

DR. EISENMANN: Also reproductive and developmental tox's also in there.

DR. BELSITO: So they did shea nut oil 15 percent and that was negative as well.

DR. SNYDER: Yeah.

DR. BELSITO: So what is your point there, Paul? Then we don't need --

DR. SNYDER: Well, if we have the composition for shea nut oil I think we would -- we could --

DR. BELSITO: Yeah, but we don't know -- that still doesn't give us composition. It just says that it doesn't have a carcinogenic effect.

DR. SNYDER: No, but if we had -- I -- what's that other -- we don't know what that other point is in regards to the seed oil composition --

DR. BELSITO: Right.

DR. SNYDER: So that may provide us data for the composition issue, correct?

DR. BELSITO: Well, let's pop up the seed oil report.

MS. BURNETT: Sorry, my computer --

DR. BELSITO: Has that been published?

MS. BURNETT: Yes, I think so. Sorry, my computer died so I'm trying to get it back up to speed here.

DR. BELSITO: If it's been published I should be able to get it off the Columbia PubMed.

MS. BECKER: Or you can go to cir.org and go to ingredients, cr-safety.org.

MS. BURNETT: No, it hasn't been published yet, I'm sorry, I thought it had.

DR. BELSITO: So it's not been published?

MS. BURNETT: No.

DR. BELSITO: So I'm not going to be able to get it. Does anyone have the --

MS. BURNETT: Yeah, we have it. It's on our Web site. What's -- I'm sorry, what end point are we looking for?

DR. BELSITO: We're looking did we get a composition for shea nut oil or we were just reading across from other oils?

MS. BURNETT: I have the oil.

DR. SNYDER: Oil or the extract?

MS. BURNETT: Oil. I have the butter and the oil. Oh, wait, that's sorry, wrong thing. We had physical and chemical properties. Yes, I have shea oil and shea butter. The oil has up to 4 percent palmitic acid, up to 56 percent stearic, up to 47 percent oleic, up to 6.5 percent linoleic and up to 2 percent arachidonic.

DR. BELSITO: So I think that, between that and our usual botanical boilerplate, that should cover the butters.

DR. SNYDER: And it's not that much different from table four for the butter and the -- or the -- yeah, the butter and the -- we do have an oil here, too, so we don't know whether that's -- there's composition data that's listed in table four as the shea oil.

DR. BELSITO: Right. So this must be -- actually it's the same isn't it?

MS. BURNETT: I carried it over from the other report I believe.

DR. BELSITO: Yeah. So this covers the butter ingredients but it still doesn't do anything for the nut or and seed cake derived ingredients, right? It just clears the butter?

DR. LIEBLER: Right, yeah, I think the butter, oil and the extracts from the butter and oil are all, you know, covered I think. It's the nut and seed cake stuff that we don't have.

DR. BELSITO: Right.

DR. LIEBLER: The seed cake. I'm not even sure what that is.

MS. BURNETT: So I know we're not supposed to officially look at Wikipedia but shea butter is extracted from the nut so --

DR. LIEBLER: Right.

MS. BURNETT: -- it might two entries for the same ingredient, nut extract and --

DR. LIEBLER: The nut is -- the nut being the seed?

DR. EISENMANN: Usually what the seed cake is is what's left over after you take the oil out.

DR. LIEBLER: Okay. So that's going to be a whole lot of cellulose.

DR. EISENMANN: In general when they use that term.

DR. LIEBLER: Yeah. It's the crunchy stuff that's left, yeah.

DR. BERGFELD: Would that be a problem to you, the cellulose?

DR. BELSITO: No, but we need composition and impurities. I mean, we can guess composition but we can't guess impurities if we're not told how it's manufactured. So sufficient for the butter and oil-derived ingredients, insufficient for the nut and seed cake derived ingredients and at this point, we're asking for composition and impurities. And depending upon this additional data, including 28-day dermal absorption, sensitization, irritation and if absorbed, repro genotoxicity may be necessary. Is that what we're asking for?

DR. SNYDER: Yes, but you need to add the nut shell extract.

DR. LIEBLER: The nut shell powder it can be.

DR. BELSITO: That's what I said.

DR. SNYDER: Oh, I'm sorry.

DR. BELSITO: We need for the nut and seed cake derived ingredients.

DR. SNYDER: Yeah.

DR. BELSITO: Oh, but you're saying the oil is from the nut so --

DR. SNYDER: We have the nut shell --

DR. BELSITO: -- we need to specifically say nut shell.

DR. SNYDER: Yeah. I assume that's different than - -

DR. BELSITO: So insufficient for the nut shell and seed cake.

DR. SNYDER: Right.

DR. BELSITO: Okay. Okay. Anything else? Okay. So the butter and oils are fine. The nut shell and seed cake ingredients we need composition impurities and then, depending upon those perhaps other data needs.

MS. BURNETT: Okay. And before we leave the topic, we posed a question in the wave two data on the in vitro assay for skin sensitivity?

DR. BELSITO: Oh, yeah, that's --

MS. BURNETT: Just want a little dis --

DR. BELSITO: That is irritation. It's not sensitization.

MS. BURNETT: It's irritation?

DR. BELSITO: Yes.

MS. BURNETT: Okay.

DR. BELSITO: I mean, they -- it was one application so that's an irritation study. Anything else?
…
Christina?

MS. BURNETT: Yes?

DR. BELSITO: Before you leave just if we can move - - are we done with this ingredient because I forgot to raise something about shea butter?

MS. BURNETT: Oh, sure, sorry.

DR. BELSITO: Okay. So we were asked whether, for the shea butter report, we wanted to include direct peptide reactivity and we never addressed that. And my answer to that was yes, right? Were we not in wave two? CR receive concentration of use data?

MS. BURNETT: Yes.

DR. BELSITO: And it says should be noted that direct peptide reactivity to assess skin sensitization, does the panel wish to include this new type of in vitro study in our safety assessments? So my answer to that is yes.

MS. BURNETT: We were looking for a discussion since this is a new data.

DR. BELSITO: To know --

MS. BURNETT: We'll be getting new -- more data like this and --

DR. BELSITO: Yeah.

MS. BURNETT: -- since this is --

DR. BELSITO: So this is just one part of looking at sensitization. Well, to answer your question it really was driven by work that was done at the University of Manchester in conjunction with Frank Gerberick and Procter & Gamble. So basically it's looking at binding to cysteine and lysine. And if it doesn't bind it's thought not to be a sensitizer. If it does bind then there are all sorts of other things you look at. So we can -- I think we can use it.

MS. BURNETT: Okay.

DR. BELSITO: If it binds and it depletes cysteine and lysine then it's a potential sensitizer depending upon a lot of other things. So it's just it's an in vitro method and people still don't know how to -- when it does bind, how to integrate it into H class and must assays and other assays that have been OECD validated for different classes of compounds. But it's a cut. If it's negative, it's negative and we don't need to worry further about sensitization. If it's positive it doesn't answer our question but I think we should know what the data is.

MS. BURNETT: Okay.

DR. BERGFELD: How does that relate to the molecular size of say wheat?

DR. BELSITO: Well, it doesn't relate in any way to molecular size. Molecular size takes into account that if it's reactive then if it's a molecular size or it's a log Kow that doesn't get absorbed then you can eliminate it based upon that, you know. It's just one of the --

DR. BERGFELD: So it's two different --

DR. BELSITO: Yeah, it's just one of the many decision trees you go down in terms of dermal toxicity as to how far you want to dig into the system.

DR. BERGFELD: Okay.

DR. BELSITO: But I mean, it's OECD validated. I think we should use it.

DR. BERGFELD: I think we should have it described, too, what it is.

DR. BELSITO: Well, I mean, what, you know --

DR. BERGFELD: Well, I mean, you described it but I think officially it should be described.

DR. BELSITO: Yeah, I mean, I think as these new tools get validated for safety assessments and it's all being driven because of the European regulation that you can't use animal models anymore for cosmetic chemicals, you know, it probably is not a bad idea to have a little session where people, you know, someone comes in. You know, John Lauco who's now with Estee Lauder is actually the person who did most of the rec-peptide research with the people at Manchester. You know, perhaps he could come down and while he didn't do the H class or the must work, I'm sure he's very familiar with that and give us an overview of those in vitro methods and where industry specifically the cosmetic industry is going since he's with Lauder.

MS. BURNETT: Right. The same suggestion was made in the other group to have a little -- the same suggestion --

DR. BELSITO: Yeah.

MS. BURNETT: -- was made to have someone come in and --

DR. BELSITO: Yeah, because Dan and I are familiar with it because the fragrance industry has been driving those models so we hear about it all the time but everyone else --

DR. LIEBLER: And that was John's PhD project.

MS. BURNETT: Okay.

DR. BELSITO: Yeah. Yeah. Direct peptide was John's PhD at Manchester. So sorry I forgot, I had a note with my shea butter and I totally missed it. Okay.

Full Panel Meeting

DR. BERGFELD: Okay. Then moving on to the next ingredient. Dr. Marks, the shea butter.

DR. MARKS: So this is the first time we've seen this draft safety assessment of the parkii or -- is it shea or shea? I say shea but. Shea-derived ingredients. Some of these ingredients; the oil, butter, butter unsponifiables, and hydrogenated butter were reviewed previously in a 2011 report and found to be safe. We added some more ingredients to this report. And we felt that we should move forward with an insufficient data notice, that one, we needed a method of manufacturer. Two, composition. Three; sensitization data for the nut extract, the nut shell powder, the seed cake extract, and the hydrolyzed seed cake extract. So that's a motion that we issue an insufficient data notice for those three data needs for these nut products and then, also, the seed cake. And then we can discuss about the Direct Peptide Reactivity assay afterward.

DR. BELSITO: Okay, so I think we're in agreement, but let me just put it another way. We thought all of the butter and oil and glycerides were safe as used, but we needed exactly what you said for the nut -- for four of the materials. The nut extract, the nut shell powder, the seed cake extract, and the hydrolyzed seed cake extract. Is that correct?

DR. MARKS: Yes.

DR. BELSITO: We're just looking at those four. Yes, so we agree.

DR. MARKS: Yes. And so the three needs again are method of manufacturer, composition, and sensitization data.

DR. BERGFELD: And you're seconding the motion? Any other comments? Ron Hill?

DR. HILL: I had made the request noting that the unsponifiables is a very different beast than some of these other ingredients, that we go back and look in detail at we had from those in that previous report and make sure that's all captured in here before we make that final decision.

DR. BERGFELD: Okay.
MS. BURNETT: Dr. Hill, I'm pretty sure all the data that was in the plant oil report has been carried over. I don't think there was any data for the unsponifiables other than the concentrations.

DR. HILL: Okay, so that's -- see for me, that's an insufficiency if that's the case, but we didn't talk about that yesterday because I thought perhaps we had it, so. I didn't research overnight to be sure.

MS. BURNETT: Right. I summarized all the data from that report.

DR. BERGFELD: So would you like to purpose that that would be one of the needs that we would ask for?

DR. HILL: For me it is.

DR. BERGFELD: Insufficient. Okay.

DR. MARKS: I agree with that.

DR. BERGFELD: Okay. Any other comments or suggested --

DR. HILL: Are there five now, we add the butter unsaponifiable also?

DR. LIEBLER: Right, unsaponifiable content. I was under the same impression as Ron that that had been carried in from the -- or that was in the report. So if it's not, we should have those (inaudible).

DR. BELSITO: So for method of manufacturer and impurities --

DR. LIEBLER: Correct.

DR. BELSITO: -- is that your -- okay.

DR. BERGFELD: Any other? Ron?

DR. HILL: Yeah, I wanted to -- either composition or enough about -- from the method of manufacturer, that we have a better idea what would be in there. I think we have a decent idea.

DR. LIEBLER: That shouldn't be hard to (inaudible).

DR. HILL: No, I don't think so.

DR. LIEBLER: -- at all.

DR. HILL: No.

DR. BERGFELD: Okay. Move the question then. All of us in favor of an insufficient report? Thank you. Unanimous.

DR. MARKS: Actually, it's a data notice. Yeah.

DR. BERGFELD: Insufficient data notice. Thank you. The next one is your saccharides. Dr. Belsito? Oh, you
want to talk --

DR. BELSITO: Actually, I wanted to discuss the
(inaudible).

DR. BERGFELD: -- about the new --

DR. DR. MARKS: Yeah, this new sensitivity test called the Direct Peptide Reactivity Assay. That was in wave II data mentioned. And we got, actually, a very nice discussion and came around to what really is the sensitivity and specificity. And our team felt it might be helpful to invite a speaker to review this and put in prospective to our previous test for sensitivity like a local lymph node assay, HRIPT. And I had suggested Frank Gerberick. I heard him present this at a meeting earlier this year. But it could be somebody else. But Frank's an immunologist who's been at P&G for a number of years and has been involved with sensitivity testing for decades now and helped develop some of those others or validate some of those other tests, particularly, the local lymph node assay. He helped validate that.

DR. BELSITO: I mean it -- I'm fine with Frank. This was -- the DPRA came out of Proctor and Gamble combined with work with Kimbull at University of Manchester. It was actually John Lavco's Ph.D., and John was with (Griffin?), now with Estee Lauder. So he would be another person. I think this was actually his research in collaboration with Frank. And it's approved. I mean if it's negative, it's fine. If it's positive, it doesn't mean it's a sensitizer, it simply means that it could be a sensitizer. And then you need other studies. So it's not like an HRIPT. It just the first cut when you're looking. But it was clean here, so suggesting that it's not a sensitizer.

DR. BERGFELD: I think that you heard in the introductory remarks from Lillian, that that was the intent --

DR. BELSITO: Right.

DR. BERGFELD: -- to invite a speaker. Any other additions, comments? Okay, then we -- time to move on? All right then.

Safety Assessment of *Butyrospermum parkii* (Shea)-Derived Ingredients as Used in Cosmetics

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The 2016 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, DPA. This safety assessment was prepared by Christina L. Burnett, Scientific Analyst/Writer and Bart Heldreth, Ph.D., Chemist CIR.

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DRAFT ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 13 *Butyrospermum parkii* (shea)-derived ingredients, which are most frequently reported to function in cosmetics as skin and hair conditioning agents. The Panel reviewed the available data to determine the safety of these ingredients. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Industry should use good manufacturing practices to limit impurities that could be present in botanical ingredients. The Panel concluded…(to be determined).

INTRODUCTION

The *Butyrospermum parkii* (shea)-derived ingredients detailed in this report function mainly as skin and hair conditioning agents in personal care products according to the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*).[1] This report assesses the safety of the following 13 *Butyrospermum parkii* (shea)-derived ingredients:

Butyrospermum Parkii (Shea) Butter
Butyrospermum Parkii (Shea) Butter Extract
Butyrospermum Parkii (Shea) Butter Unsaponifiables
Butyrospermum Parkii (Shea) Nut Extract
Butyrospermum Parkii (Shea) Nut Shell Powder
Butyrospermum Parkii (Shea) Oil
Butyrospermum Parkii (Shea) Seedcake Extract
Hydrogenated Shea Butter
Hydrogenated Shea Oil
Hydrolyzed Shea Seedcake Extract
Shea Butter Glyceride
Shea Butter Glycerides
Shea Oleine

The Panel previously reviewed the safety of Butyrospermum Parkii (Shea) Oil, Butyrospermum Parkii (Shea) Butter, Butyrospermum Parkii (Shea) Butter Unsaponifiables, and Hydrogenated Shea Butter in the 2011 safety assessment of plant-derived fatty acid oils and found these ingredients to be safe as used in cosmetics.[2] Because data from the previous assessment may help to inform the safety of the ingredients listed in this current assessment, the relevant information has been summarized here in italics.

Botanicals such as *Butyrospermum parkii* (shea)-derived ingredients may contain hundreds of constituents, some of which may have the potential to cause toxic effects. In this assessment, CIR is reviewing the potential toxicity of each of the *Butyrospermum parkii* (shea)-derived ingredients as a whole, complex mixture. Except for specific constituents of concern, CIR will not review the potential toxicity of the individual constituents found in *Butyrospermum parkii* from which the ingredients in this report are derived.

The ingredient names, according to the *Dictionary,* are written as listed above, without italics and without abbreviations. When referring to the tree from which these ingredients are derived, the standard scientific practice of using italics will be followed (e.g., *Butyrospermum parkii*). The shea tree is also known taxonomically as *Vitellaria paradoxa* and is referred to as such by many references and by the Food and Drug Administration (FDA).

While shea oleine ("oleine" is an oleate triglyceride) is not an ingredient listed in the *Dictionary*, toxicity data for this substance may be useful for assessing the safety of the *Butyrospermum parkii* (shea)-derived ingredients, using an inference approach. Shea oleine is listed as a cosmetic ingredient in the FDA Voluntary Cosmetic Registration Program (VCRP) database.

CHEMISTRY

Definition

The definitions and functions of the *Butyrospermum parkii* (shea)-derived ingredients included in this report are provided in Table 1.

Plant Identification

The raw materials for the *Butyrospermum parkii* (shea)-derived ingredients found in this report are obtained from the tree *Butyrospermum parkii,* which grows in mainly in equatorial Africa.[3-5]

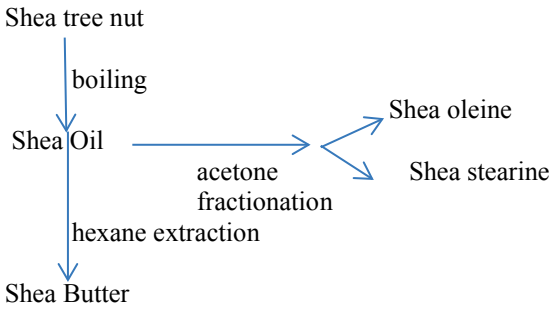
Physical and Chemical Properties

Butyrospermum Parkii (Shea) Butter is a grey, tallow-like solid, with a specific gravity of 0.918 at 15°C and a melting point of 32-46 °C.[2] Butyrospermum Parkii (Shea) Oil is a pale yellow liquid. No other relevant

published physical and chemical properties data on *Butyrospermum parkii* (shea)-derived ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted.

Method of Manufacture

The general description of the method of manufacturing of several *Butyrospermum parkii* (shea)-derived ingredients is described in the following schematic:[6]



Butyrospermum Parkii (Shea) Butter Unsaponifiables

Butyrospermum Parkii (Shea) Butter Unsaponifiables is obtained by molecular distillation and supercritical carbon dioxide extraction of Butyrospermum Parkii (Shea) Butter.[7]

Composition/Impurities

The mean tocopherol concentrations and fatty acid compositions of *Butyrospermum parkii* (shea)-derived ingredients are provided in Table 2 and Table 3, respectively. While *Butyrospermum parkii* grows mainly in equatorial Africa, subtle differences in geographic location and climate affect the levels of the natural compounds, such as tocopherol and fatty acids, in *Butyrospermum parkii* (shea)-derived ingredients.[3,4]

A study of Butyrospermum Parkii (Shea) Butter (described as kernel fats; n-hexane extraction) from 36 samples from seven different countries found the principal triacylglycerols to be stearic-oleic-stearic (mean 31.2% of total triacylglycerols), stearic-oleic-oleic (27.7%), and oleic-oleic-oleic (10.8%).[8] Triterpene ester contents ranged from 0.5% to 6.5% and consisted of α-amyrin cinnamate (mean 29.3% of total triterpene esters), butyrospermol cinnamate (14.8%), α-amyrin acetate (14.1%), lupeol cinnamate (9.0%), β-amyrin cinnamate (7.6%), lupeol acetate (7.2%), butyrospermol acetate (5.8%, and β-amyrin acetate (4.9%) (Figure 1).

The same researchers identified the content and composition of triterpene alcohol fractions of the non-saponifiable lipids of Butyrospermum Parkii (Shea) Butter from 36 samples.[9] The shea kernels contained 30%-54% fat, of which 2%-12% were non-saponifiable lipids. Triterpene alcohol content in the non-saponifiable lipids was 22%-72%. The triterpene alcohol fractions contained α-amyrin, β-amyrin, lupeol, and butyrospermol with minor or trace amounts of ψ-taraxasterol, taraxasterol, parkeol, 24-methylene-24-dihydroparkeol, 24-methylenecycloartanol, dammaradienol, and 24-methylenedammarenol.

An analysis of the phenolic constituents of shea kernels by liquid chromatography-mass spectrometry (LC-MS) identified the following catechin compounds: gallic acid, catechin, epicatechin, epicatechin gallate, gallocatechin, epigallocatechin, gallocatechin gallate, and epigallocatechin gallate.[5] Quercetin and *trans*-cinnamic acid were also identified. The mean kernel content of the catechin compounds was 4000 ppm with a range of 2100-9500 ppm.

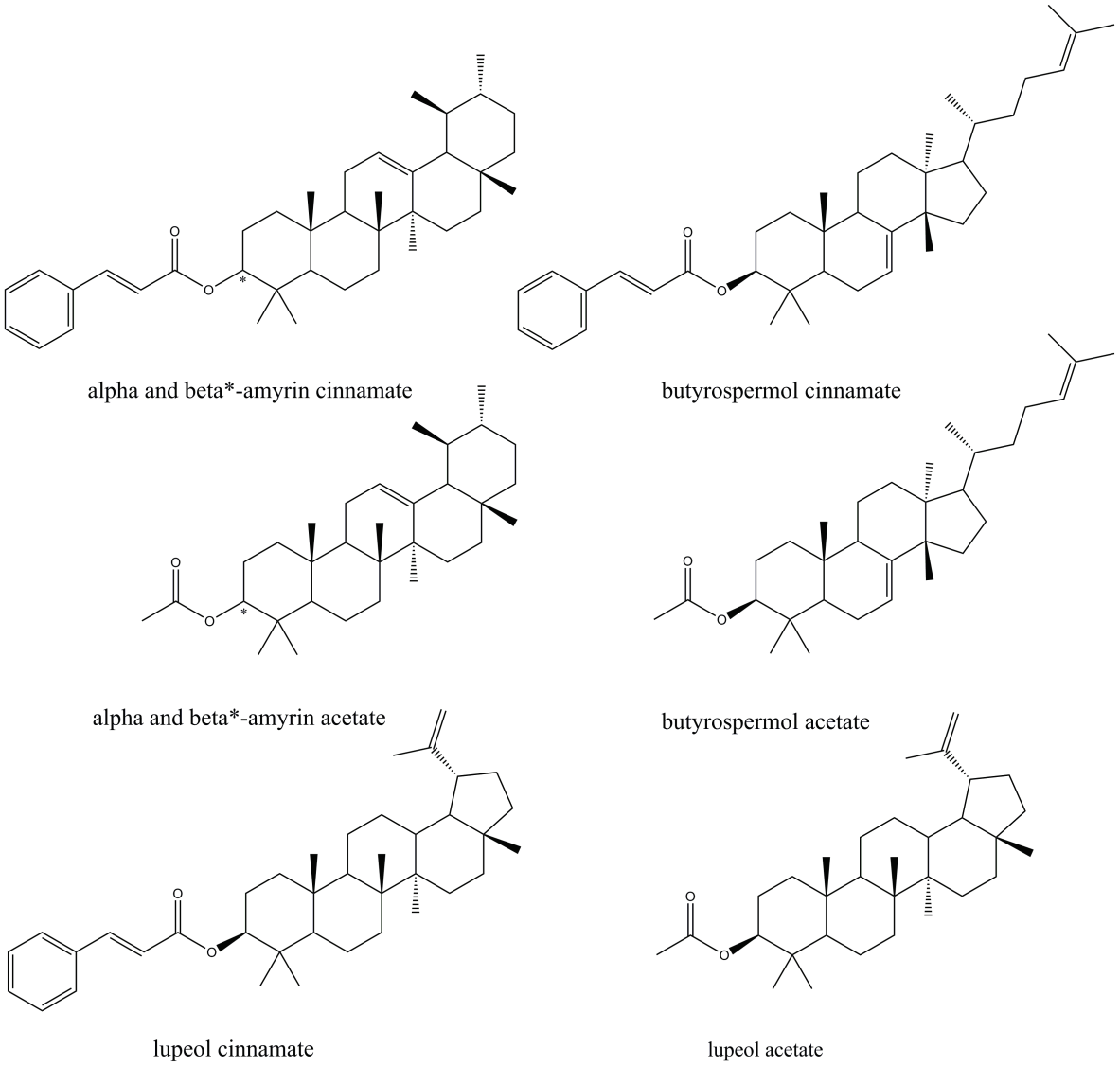


Figure 1. Triterpene esters.

Butyrospermum Parkii (Shea) Butter Unsaponifiables

Butyrospermum Parkii (Shea) Butter Unsaponifiables mainly contain terpene alcohols present in the butter in the form of cinnamic acid esters (including α- and β-amyrin lupeol, butyrospermol, and cycloartenol) and phytosterols including α-spinasterol, Δ7-stigmasterol, and stigmasterol).[7]

Shea Oleine

The primary component of shea oleine is the oleate triglyceride.

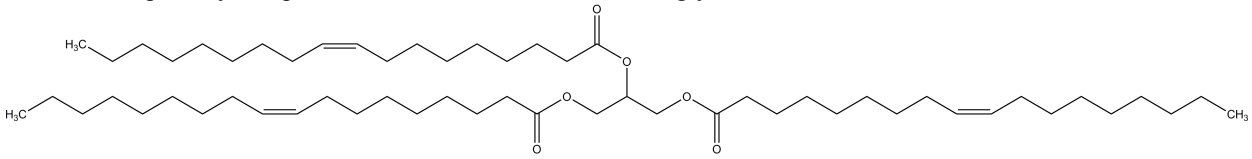


Figure 2. Oleate triglyceride.

However, the sterol component of shea oleine is approximately 8% (w/w), of which approximately 97% is 4,4-dimethylsterols (mostly as esters of cinnamic acid), 2% is 4-demethylsterols and 0.5% is 4-α-methylsterols.[6]

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by Industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2016 VCRP data, Butyrospermum Parkii (Shea) Butter has the most reported uses of the ingredients listed in this safety assessment in cosmetic products, with a total of 4358; nearly three-fourths of the uses are in leave-on formulations (Table 4).[10,11] Butyrospermum Parkii (Shea) Butter Extract has the second greatest number of overall uses reported, with a total of 468; two-thirds of the uses are in leave-on formulations. The results of the concentration of use survey conducted in 2016 by the Council indicate Butyrospermum Parkii (Shea) Butter has the highest reported maximum concentration of use; it is used at up to 100% in moisturizers.[12] Butyrospermum Parkii (Shea) Oil is used at up to 11% in lipsticks.[13] No uses were reported for Hydrogenated Shea Oil or Hydrolyzed Shea Seedcake Extract.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided. For example, Hydrogenated Shea Butter is reported to be used in 22 formulations, but no use concentration data were provided. In other cases, no uses were reported to the VCRP, but a maximum use concentration was provided in the industry survey. For example, Shea Butter Glyceride was not reported in the VCRP database to be in use, but the industry survey indicated that it is used at concentrations up to 0.49%. It should be presumed that Shea Butter Glyceride is used in at least one cosmetic formulation.

Some of these ingredients may be used in products that can be incidentally ingested or come into contact with mucous membranes. For example, Butyrospermum Parkii (Shea) Oil is used in lipsticks at up to 11%.[13] Additionally, some of these ingredients were reported to be used in hair sprays, face powders, fragrances and body and hand sprays and could possibly be inhaled. For example, Butyrospermum Parkii (Shea) Seedcake Extract was reported to be used in fragrance preparations at a maximum concentration of 4% and Butyrospermum Parkii (Shea) Unsaponifiables was reported to be used in a face powder at 0.06%.[12] In practice, 95% to 99% of the droplets/ particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays. 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. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[14-16]

The *Butyrospermum parkii* (shea)-derived ingredients described in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[17]

Non-Cosmetic

Butyrospermum Parkii (Shea) Oil (sheanut oil), from which many of the ingredients of this report are derived, is generally recognized as safe (GRAS) in the U.S. as a direct food additive (21CFR§184.1702). It is used in confections and frostings, coatings of soft candy, and sweet sauces and toppings.

Refined sheanut oil is described as a component of a mixture of oils used as a cocoa butter substitute, as a coating agent, and in margarine and shortening in the *Food Chemicals Codex*, a compendium of internationally recognized standards published by the United States Pharmacopeia (USP) for the purity and identity of food ingredients.[18]

A triterpene-rich extract of *Butyrospermum parkii* has been reported to be used as a dietary supplement for the treatment of osteoarthritis.[19] Other studies have found that components of shea extracts potentially have anti-inflammatory, antioxidant, and anti-tumor effects.[20-23]

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

Oral

Shea Oleine

In an oral absorption and excretion study, groups of Colworth Wistar male rats were fed shea oleine in a semisynthetic diet.[24] In a low-dose experiment, groups of 24 rats received control feed, feed containing 0.5% shea oleine, or feed containing 5% shea oleine for 1 week, with control feed administered to all rats the week prior and the week following the exposure week. In a high-dose experiment, 2 groups of 15 male and 15 female rats received either 10% or 20% shea oleine in the feed for 3 weeks. In the first experiment, feces were collected and pooled weekly for each treatment group throughout weeks 2 and 3. In the second experiment, feces were collected and pooled for each treatment group in week 3 only. The dried fecal matter of the rats was then analyzed with thin-layer and gas-liquid chromatography for fecal lipid, total sterol, differential sterol levels, and, specifically, 4,4-dimethyl-sterols (the main sterol constituent (~ 97%) of shea oleine). Excretion of 4,4-dimethylsterols increased with the consumption of shea oleine. Apparent absorption was 27% to 52% and was estimated from the disappearance of 4,4-dimethylsterols from the feces. The majority of the 4,4-dimethylsterols was excreted unchanged.

Human

Oral

Shea Oleine

The oral absorption and excretion of shea oleine was studied in 4 male volunteers.[24] On day 3 of an 8 day period, the subjects consumed a single 25 g portion (approximately 0.4 g/kg) of shea oleine in mayonnaise. No other vegetable fats were consumed during the course of the study. Feces were collected on days 3 to 8 inclusively, freeze-dried, and weighed. The dried fecal matter was analyzed in the manner described above. Excretion of 4,4-dimethylsterols increased with the consumption of shea oleine, with a marked increase from baseline on days 4 and 5 and a return to approximate baseline on day 8. Absorption of 4,4-dimethylsterols was estimated to be 13% to 49%. The majority of the 4,4-dimethylsterols was excreted unchanged.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

No relevant published acute toxicity studies on *Butyrospermum parkii* (shea)-derived ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted.

Subchronic Toxicity Studies

Shea Oleine

In a 13-week rat feeding study, Colworth-Wistar rats received a diet containing 20% (w/w; 10 to 15 g/kg/day) shea oleine or hydrogenated shea oleine.[25] Groups of 15 male and 15 female rats were fed either 20% (w/w) palm oil, soy bean oil, or the hydrogenated equivalents. During the exposure period, body weight, food and water consumption, urine chemistry, and clinical pathology were assessed. Gross necropsy and microscopic examination of select tissues and organs were performed at study completion.

Results showed that shea oleine diets produced biological effects similar to those of palm oil and soy bean oil diets. Slightly reduced body weight gain was observed in rats fed either of the shea oleine diets when compared to diets with palm oil and soy bean oil. No significant differences in body weight gains were observed between rats fed hydrogenated shea oleine versus non-hydrogenated shea oleine. Slightly reduced cholesterol levels, increased aminotransferase levels, and lower triglyceride and alanine aminotransferase values were observed in rats fed non-hydrogenated diets, as were increased liver weights and reduced liver-lipid values. These changes were not considered to be biologically significant. Also considered biologically insignificant by the authors were raised alkaline phosphatase levels and increased food consumption in rats fed hydrogenated shea oleine. The authors concluded that all diets were well tolerated in the rats and considered none of the findings in this study to be adverse.[25]

Chronic Toxicity Studies

Butyrospermum Parkii (Shea) Oil and Shea Oleine

See Carcinogenicity section below.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Oral

Butyrospermum Parkii (Shea) Oil and Shea Oleine

The reproductive toxicity potential of shea oleine and hydrogenated shea oleine was assessed in two dietary studies in rats.[26] In study 1, groups of 20 male and 20 female Colworth-Wistar rats received 7% (w/w; 3.5 g/kg/day) of either type of shea oleine in their diet for 20 weeks (breeding began at week 12 and lasted for 2 weeks). In study 2, groups of 50 male and 50 female Colworth-Wistar rats received 15% (w/w; 7.5 g/kg/day) of either type of shea oleine in their diets for 10 weeks (breeding began at week 2 and lasted for 1 week). Both studies also evaluated other commercially available materials, such as Butyrospermum Parkii (Shea) Oil (15% w/w, in study 2), palm oil, and cocoa butter. The rats received the test materials during pre-mating, mating, pregnancy and offspring weaning. Reproduction was assessed by counting the number of litters, pups born, and pups surviving, and measuring body weights at birth and at weaning on day 21. Skeletal evaluation using X-ray, clinical pathology and macroscopic examination were performed on F_1 rats. Parental animal parameters assessed were body weight, food consumption, clinical pathology, organ weights and macroscopic examination. Fatty acids and hydrocarbon levels were measured, and various tissues were evaluated in F_0 animals for lipogranulomata in Study 2.

Slightly reduced body weight gain, reduced cholesterol, and increased alkaline phosphatase levels were observed in rats treated with either shea oleine or hydrogenated shea oleine. No adverse effects on reproduction from any shea materials were observed in either study for any parameter. Results showed that shea oleine and hydrogenated shea oleine were toxicologically comparable to the other commercially available materials used in this study. The authors concluded that there was no evidence of reproductive toxicity following dietary exposure to shea oleine and hydrogenated shea oleine in rats at concentrations equating to greater than 15% (7.5 g/kg/day).[26]

GENOTOXICITY

In Vitro

Butyrospermum Parkii (Shea) Butter Unsaponifiables

Butyrospermum Parkii (Shea) Butter Unsaponifiables was not mutagenic in an Ames test.[7] The test material was tested at 50 to 5000 μg/plate, with and without metabolic activation. No further details were provided.

CARCINOGENICITY

Oral

Butyrospermum Parkii (Shea) Oil and Shea Oleine

The carcinogenic potential of shea oleine was evaluated in a dietary study in Colworth-Wistar rats for 104 weeks.[6] The study also evaluated Butyrospermum Parkii (Shea) Oil and palm oil. Groups of 50 male and 50 female rats received diets containing 15% (w/w; approximately equivalent to 7.5 g/kg/day) shea oleine, 15% (w/w) Butyrospermum Parkii (Shea) Oil, or 15% (w/w) palm oil. The rats were the offspring of the animals used in the reproduction study described above (study 2) and the test diets began at weaning (21 days of age). The following parameters were assessed: mortality, clinical signs of toxicity, body weight, food intake, clinical pathology, organ weights and macroscopic and histopathological changes plus tumor type and incidence evaluation.

Final mortality rates for both sexes for shea oleine and Butyrospermum Parkii (Shea) Oil were in the range of 28% to 30% each, while the mortality rates for both sexes exposed to palm oil was 40%. No clinical signs of toxicity were found after exposure to either shea test material. Reduced body weight gain and increased feed intake were observed in rats of both sexes fed either shea diets, while reduced cholesterol was observed in females fed the shea oleine diet. Increased alkaline phosphatase levels were observed in both sexes fed the Butyrospermum Parkii (Shea) Oil diet, but this value was only increased in females fed the shea oleine diet. Reduced heart weight and an increased incidence of pulmonary lipidosis were observed in rats of both sexes fed either shea diet. In females fed either shea diet, an increase in the number of hepatomas was observed, while in males fed shea oleine, increases in pancreatic exocrine adenomas and skin keratoacanthomas were observed. The increase in the incidence of hepatomas was thought to be related to the high fat content of the diets. The authors concluded that none of the findings in this study were adverse effects and that shea oleine showed no tumorigenic potential in the rat at 15% in the diet (7.5 g/kg/day) when compared to Butyrospermum Parkii (Shea) Oil and palm oil.[6]

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Dermal irritation studies are summarized in Table 5. [7,27,28] Butyrospermum Parkii (Shea) Butter Unsaponifiables was non-irritating in an EpiSkin™ assay when tested undiluted and in a human primary cutaneous tolerance test at 30% diluted in paraffin oil. Butyrospermum Parkii (Shea) Butter Extract at 5% in a moisturizer was not irritating in human irritation studies.

Butyrospermum Parkii (Shea) Butter

In an EpiSkin™ in vitro assay, 24.1% Butyrospermum Parkii (Shea) Butter in a lip wax was not an irritant.[2] In animal study, Butyrospermum Parkii (Shea) Butter (concentration not reported) produced very slight erythema with or without edema in 2/3 rabbits exposed to the test material for 4 h in an irritation study utilizing occlusive patches. The erythema was resolved 3 or 4 days after patching. Butyrospermum Parkii (Shea) Butter did not cause primary cutaneous irritation when tested at up to 2%. No irritation to Butyrospermum Parkii (Shea) Butter was observed in human volunteers for in-use studies of lip gloss or body/hand massage oils at concentrations up to 45%.

Sensitization

Dermal sensitization studies are summarized in Table 6. [7,29-32] Undiluted Butyrospermum Parkii (Shea) Butter Unsaponifiables was considered non-sensitizing in a direct peptide reactivity assay. Butyrospermum Parkii (Shea) Butter Extract was non-sensitizing in human repeat insult patch tests (HRIPTs) at up to 5% in formulation.

Butyrospermum Parkii (Shea) Butter

Butyrospermum Parkii (Shea) Butter was not sensitizing in a guinea pig maximization study.[2] The induction concentration was 75% and the challenge concentrations were 20% and 50%. No sensitization was observed in multiple HRIPTs with products containing Butyrospermum Parkii (Shea) Butter. Concentrations tested were up to 60%.

Phototoxicity and Photosensitization

In Vitro

Butyrospermum Parkii (Shea) Butter Unsaponifiables

Butyrospermum Parkii (Shea) Butter Unsaponifiables was considered non-phototoxic in a 3T3 NRU assay when tested at 0.005 to 1 mg/ml.[7] No further details were provided.

Animal

Butyrospermum Parkii (Shea) Butter

Butyrospermum Parkii (Shea) Butter was not phototoxic in guinea pigs when tested at 10 and 20% in acetone.[2] The test sites were irradiated with UV-B light for 80 seconds followed by UV-A light for 80 min.

OCULAR IRRITATION STUDIES

In Vitro

Butyrospermum Parkii (Shea) Butter Unsaponifiables

A balm containing 0.00405% to 0.00675% Butyrospermum Parkii (Shea) Butter Unsaponifiables was considered non-irritating in a Skinethic reconstituted mucous model.[7] Approximately 10 µl of the balm was applied undiluted for 24 h. The negative control was phosphate buffer saline and the positive control was 0.1% and 3% sodium dodecyl sulfate). No further details were provided.

Animal

Butyrospermum Parkii (Shea) Butter

While mild conjunctival reactions were observed, undiluted Butyrospermum Parkii (Shea) Butter was considered not irritating when tested in the eyes of male rabbits.[2]

SUMMARY

The 13 *Butyrospermum parkii* (shea)-derived ingredients detailed in this report function mainly as skin and hair conditioning agents in personal care products.

According to 2016 VCRP data, Butyrospermum Parkii (Shea) Butter has the most reported uses of the ingredients listed in this safety assessment in cosmetic products, with a total of 4358; nearly three-fourths of the uses are in leave-on formulations. Butyrospermum Parkii (Shea) Butter Extract has the second greatest number of overall reported, with a total of 468; about two-thirds of the uses are in leave-on formulations. The results of the concentration of use survey conducted in 2016 by the Council indicate Butyrospermum Parkii (Shea) Butter has the highest reported maximum concentration of use; it is used at up to 100% in moisturizers. Butyrospermum Parkii (Shea) Oil is used at up to 11% in a lipstick. No uses were reported for Hydrogenated Shea Oil or Hydrolyzed Shea Seedcake Extract.

Butyrospermum Parkii (Shea) Oil is a GRAS direct food additive in the U.S. It is used as a cocoa butter substitute in confections and frostings, coatings of soft candy, and sweet sauces and toppings. It is also used as a margarine or shortening. Components of shea extracts have potential anti-inflammatory, antioxidant, and anti-tumor effects.

Oral absorption and excretion studies of rats fed up to 20% shea oleine in a semisynthetic diet found excretion of 4,4-dimethylsterols increased with the consumption of shea oleine. Apparent absorption of shea oleine was 27% to 52%, as measured by 4,4-dimethylsterols. The majority of the 4,4-dimethylsterols was excreted unchanged. The findings for the absorption and excretion of approximately 0.4 g/kg in a single dose study of human volunteers were similar, with the absorption of shea oleine estimated to be 13% to 49%, as measured by 4,4-dimethylsterols.

In a 13-week rat feeding study, shea oleine or hydrogenated shea oleine (20% w/w, equivalent to 10-15 g/kg/day, for both test materials) did not produced adverse effects. No reproductive effects were observed in rats fed shea oleine or hydrogenated shea oleine (up to 15% w/w, equivalent to 7.5 g/kg/day, for both test materials) for up to 20 weeks. No tumorigenic potential or adverse effects to shea oleine (15% w/w, equivalent to 7.5 g/kg/day) was observed in a carcinogenicity study in the offspring of the rats from the reproductive study.

Butyrospermum Parkii (Shea) Butter Unsaponifiables was not mutagenic in an Ames test.

Butyrospermum Parkii (Shea) Butter Unsaponifiables was non-irritating in an EpiSkin™ assay when tested undiluted and in a human primary cutaneous tolerance test at 30% diluted in paraffin oil. Butyrospermum Parkii (Shea) Butter Extract at 5% in a moisturizer was not irritating in human irritation studies.

Undiluted Butyrospermum Parkii (Shea) Butter Unsaponifiables was considered non-sensitizing in a direct peptide reactivity assay. Butyrospermum Parkii (Shea) Butter Extract was non-sensitizing in human repeat insult patch tests (HRIPTs) at up to 5% in formulation.

Butyrospermum Parkii (Shea) Butter Unsaponifiables was considered non-phototoxic in a 3T3 NRU assay when tested at 0.005 to 1 mg/ml.

A balm containing 0.00405% to 0.00675% Butyrospermum Parkii (Shea) Butter Unsaponifiables was considered non-irritating in a Skinethic reconstituted mucous model.

No relevant published acute toxicity or clinical studies on *Butyrospermum parkii* (shea)-derived ingredients were identified in a literature search for these ingredients and no unpublished data were submitted.

DRAFT DISCUSSION

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients in one formulation may each contribute to the final concentration of a single constituent. Therefore, when formulating products, manufacturers should avoid reaching levels in final formulation of botanical constituents that may cause sensitization or other adverse effects.

The Panel discussed the issue of incidental inhalation exposure from hair sprays, fragrance preparations, body and hand sprays, and face powders. There were no inhalation toxicity data available. The Panel noted that droplets/particles from spray and loose-powder cosmetic products would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the 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. 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 expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

The Panel issued an insufficient data announcement for the 13 *Butyrospermum parkii* (shea)-derived ingredients in this safety assessment. The additional data needed to evaluate the safety of these ingredients are:

- Method of manufacturing for Butyrospermum Parkii (Shea) Nut Extract, Butyrospermum Nut Shell Powder, Butyrospermum Parkii (Shea) Seedcake Extract, and Hydrolyzed Shea Seedcake Extract
- Additional information on method of manufacturing, composition and impurities data, and sensitization data on Butyrospermum Parkii (Shea) Butter Unsaponifiables.
- Composition and impurities data on the above listed nut and seedcake ingredients
- Sensitization data on the above listed nut and seedcake ingredients

CONCLUSION

To be determined…

TABLES AND FIGURES

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

Ingredient/CAS No.	Definition	Function
Butyrospermum Parkii (Shea) Butter	Butyrospermum Parkii (Shea) Butter is a fat obtained from the fruit of *Butyrospermum parkii*. The accepted scientific name for *Butyrospermum parkii* is *Vitellaria paradoxa*.	skin-conditioning agents – miscellaneous; skin-conditioning agents – occlusive; viscosity increasing agents - nonaqueous
Butyrospermum Parkii (Shea) Butter Extract CAS No. 91080-23-8	Butyrospermum Parkii (Shea) Butter Extract is the extract of Butyrospermum Parkii (Shea) Butter. The accepted scientific name for *Butyrospermum parkii* is *Vitellaria paradoxa*.	skin-conditioning agents - miscellaneous
Butyrospermum Parkii (Shea) Butter Unsaponifiables CAS No. 194043-92-0; 225234-14-0	Butyrospermum Parkii (Shea) Butter Unsaponifiables is the fraction of shea butter which is not saponified in the refining recovery of shea butter fatty acids. The accepted name for *Butyrospermum parkii* is *Vitellaria paradoxa*.	hair conditioning agents; skin-conditioning agents - miscellaneous
Butyrospermum Parkii (Shea) Nut Extract CAS No. 91080-23-8	Butyrospermum Parkii (Shea) Nut Extract is the extract of the nuts *of Butyrospermum parkii*. The accepted name for *Butyrospermum parkii* is *Vitellaria paradoxa*.	skin-conditioning agents - emollient
Butyrospermum Parkii (Shea) Nut Shell Powder CAS No. 91080-23-8	Butyrospermum Parkii (Shea) Nut Shell Powder is the powder obtained from the dried, ground nut shells of *Butyrospermum parkii*. The accepted scientific name for *Butyrospermum parkii* is *Vitellaria paradoxa*.	abrasives
Butyrospermum Parkii (Shea) Oil	Butyrospermum Parkii (Shea) Oil is the liquid fraction obtained from Butyrospermum Parkii (Shea) Butter. The accepted name for *Butyrospermum parkii* is *Vitellaria paradoxa*.	skin-conditioning agents – miscellaneous; skin-conditioning agents - occlusive
Butyrospermum Parkii (Shea) Seedcake Extract CAS No. 91080-23-8	Butyrospermum Parkii (Shea) Seedcake Extract is the extract of the seedcake of *Butyrospermum parkii*. The accepted name for *Butyrospermum parkii is Vitellaria paradoxa*.	skin protectants
Hydrogenated Shea Butter	Hydrogenated Shea Butter is the end product of the controlled hydrogenation of Butyrospermum Parkii (Shea) Butter.	skin-conditioning agents – occlusive; viscosity increasing agents - nonaqueous
Hydrogenated Shea Oil CAS No. 93333-83-6	Hydrogenated Shea Oil is the product obtained by the hydrogenation of Butyrospermum Parkii (Shea) Oil.	skin conditioning agents – emollient; skin-conditioning agents - occlusive
Hydrolyzed Shea Seedcake Extract	Hydrolyzed Shea Seedcake Extract is the hydrolysate of an extract of shea seedcake derived by acid, enzyme, or other method of hydrolysis.	not reported
Shea Butter Glyceride	Shea Butter Glyceride is the monoglyceride derived from Butyrospermum Parkii (Shea) Butter.	skin-conditioning agents – emollient; surfactants – emulsifying agents
Shea Butter Glycerides CAS No. 194043-92-0; 1016637-12-9	Shea Butter Glycerides are a mixture of mono-, di-, and triglycerides derived from Butyrospermum Parkii (Shea) Butter.	emulsion stabilizers; hair conditioning agents; skin-conditioning agents – miscellaneous; slip modifiers; surfactants – emulsifying agents; viscosity increasing agents - aqueous
Shea Oleine	Not in *Dictionary*.	Not in *Dictionary*.

Table 2. Mean concentrations of tocopherols in 102 Butyrospermum Parkii (Shea) Butter samples by HPLC analysis (μg/g)[3]

α-tocopherol	β-tocopherol	γ-tocopherol	δ-tocopherol	total tocopherol
112	16	38	34	208

Table 3. Total fatty acid composition of *Butyrospermum parkii* (Shea)-derived ingredients (%) [2,4,33]

Fatty Acids	Butyrospermum Parkii (Shea) Oil	Butyrospermum Parkii (Shea) Butter
Myristic (C14)	NR	0.5
Palmitic (C16)	3.8-4.1	2.6-9
Stearic (C18)	41.2-56.8	25.6-50.2
Oleic (C18:1)	34.0-46.9	37.1-62.1
Linoleic (C18:2)	3.7-6.5	0.6-10.8
Linolenic (C18:3)	NR	0.5 max
Arachidic (C20)	1-2	0-3.5

NR-Not reported.

Table 4. Frequency and concentration of use according to duration and type of exposure for shea ingredients.[10-13]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Butyrospermum Parkii (Shea) Butter		**Butyrospermum Parkii (Shea) Butter Extract**		**Butyrospermum Parkii (Shea) Butter Unsaponifiables**		**Butyrospermum Parkii (Shea) Nut Extract**	
Totals[†]	**4358**	**0.0001-100**	**468**	**0.0000095-5**	**69**	**0.01-4.5**	**NR**	**0.0003-1**
Duration of Use								
Leave-On	3370	0.001-100	324	0.0000095-5	66	0.015-4.5	NR	0.01-1
Rinse Off	971	0.0001-10	140	0.00028-0.96	3	0.01-2	NR	0.0003-0.51
Diluted for (Bath) Use	17	0.05-3	4	0.05	NR	NR	NR	NR
Exposure Type								
Eye Area	227	0.1-8	19	0.5	38	0.16-0.5	NR	NR
Incidental Ingestion	382	0.01-9.4	36	0.075-1.9	3	0.25-2.5	NR	NR
Incidental Inhalation -Sprays	12; 1510[a]; 846[b]	0.1-0.33; 0.001-8[a]; 0.59[b]	10; 111[a]; 92[b]	0.001-0.025; 0.001-0.8[a]; 0.0001[b]	6[a]; 5[b]	0.5[a]	NR	NR
Incidental Inhalation - Powders	9; 26[c]; 846[b]	3; 0.59[b]; 0.05-8[c]	2; 8[c]; 92[b]	0.015; 0.0000095-5[c]; 0.0001[b]	3; 1[c]; 5[b]	0.06	NR	NR
Dermal Contact	3652	0.0004-100	409	0.0001-5	61	0.051-4.5	NR	0.0003-1
Deodorant (underarm)	16[a]	NR	1[a]	0.05	NR	NR	NR	NR
Hair - Non-Coloring	286	0.0001-8	23	0.001-0.96	5	0.01-0.5	NR	0.01
Hair-Coloring	23	0.004-3.5	NR	NR	NR	NR	NR	NR
Nail	8	0.1-5	NR	0.01	NR	NR	NR	NR
Mucous Membrane	1029	0.0004-9.4	116	0.00028-1.9	3	0.051-2.5	NR	0.0003-0.51
Baby Products	32	0.005-7	10	0.1	1	4	NR	NR

	Butyrospermum Parkii (Shea) Nut Shell Powder		**Butyrospermum Parkii (Shea) Oil**		**Butyrospermum Parkii (Shea) Seedcake Extract**		**Hydrogenated Shea Butter**	
Totals[†]	**2**	**0.00028-1**	**58**	**0.001-11**	**2**	**0.0002-5.5**	**22**	**NR**
Duration of Use								
Leave-On	2	0.01-1	28	0.01-11	2	0.0002-5.5	11	NR
Rinse Off	NR	0.00028-0.5	27	0.001-2.5	NR	0.0003-2	11	NR
Diluted for (Bath) Use	NR	NR	3	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	2	0.5-8	NR	0.0002-5.5	NR	NR
Incidental Ingestion	NR	NR	1	0.5-11	NR	3	1	NR
Incidental Inhalation -Sprays	1[b]	NR	18[a]; 4[b]	1; 0.2[a]	2[a]	0.0095-4; 0.01[a]	1; 5[a]; 3[b]	NR
Incidental Inhalation - Powders	1[b]	NR	1; 4[b]	0.95-8[c]	NR	0.0012-5[c]	3[b]	NR
Dermal Contact	2	0.00028-1	54	0.005-8	2	0.0002-5.5	14	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.01	3	0.001-0.4	NR	0.001-0.99	7	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	0.1-2	NR	3-5	NR	NR
Mucous Membrane	NR	0.00028-0.0011	25	0.005-11	NR	0.0003-3	4	NR
Baby Products	NR	NR	NR	NR	NR	5	NR	NR

Table 4. Frequency and concentration of use according to duration and type of exposure for shea ingredients.[10-13]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Shea Butter Glyceride		**Shea Butter Glycerides**		**Shea Oleine**			
Totals†	**NR**	**0.49**	**31**	**0.49-6.5**	**3**	**NR**		
Duration of Use								
Leave-On	NR	NR	24	6.5	3	NR		
Rinse Off	NR	0.49	7	0.49-2	NR	NR		
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR		
Exposure Type								
Eye Area	NR	NR	4	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	NR	NR	NR		
Incidental Inhalation -Sprays	NR	NR	13[a]; 3[b]	NR	1; 1[a]	NR		
Incidental Inhalation - Powders	NR	NR	3[b]	0.49-6.5	NR	NR		
Dermal Contact	NR	0.49	27	NR	1	NR		
Deodorant (underarm)	NR	NR	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	4	NR	2	NR		
Hair-Coloring	NR	NR	NR	NR	NR	NR		
Nail	NR	NR	NR	NR	NR	NR		
Mucous Membrane	NR	NR	2	2	NR	NR		
Baby Products	NR	NR	1	NR	NR	NR		

NR = No reported use

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a.] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[b.] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c.] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

Table 5. Dermal irritation studies for *Butyrospermum parkii* (shea)-derived ingredients.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
In Vitro					
Butyrospermum Parkii (Shea) Butter Unsaponifiables	undiluted	N/A	EpiSkin™ assay; no further details provided	Non-irritating	[7]
Human					
Butyrospermum Parkii (Shea) Butter Extract	5% in a moisturizer	46 subjects	Single-blind, 4-week clinical use study; test material applied twice daily in place of regular moisturizer; study supervised by a dermatologist who conducted baseline, 2-week interim, and final exams.	No irritation	[27]
Butyrospermum Parkii (Shea) Butter Extract	5% in a moisturizer	18 subjects	24-h single insult patch test; no further details provided	No irritation	[28]
Butyrospermum Parkii (Shea) Butter Unsaponifiables	30% diluted in paraffin oil	10 subjects	48-h primary cutaneous tolerance test; single patch; no further details provided	No irritation	[7]

Table 6. Dermal sensitization studies for *Butyrospermum parkii* (shea)-derived ingredients.

Test Article	Concentration/Dose	Test Population	Procedure	Results	References
			In Vitro		
Butyrospermum Parkii (Shea) Butter Unsaponifiables	undiluted	N/A	Direct peptide reactivity assay; performed in accordance with the European Centre for the Validation of Alternative Methods (ECVAM) protocol; reactivity of test material evaluated by monitoring peptide depletion following 24-h contact between test material and synthetic cysteine and lysine peptides; no further details were provided.	Non-reactive and considered non-sensitizing	[7]
			Human		
Butyrospermum Parkii (Shea) Butter Extract	2% in a body lotion	28 healthy subjects	HRIPT; 0.05ml test material applied neat under an occlusive dressing to a sodium lauryl sulfate (SLS) pre-treated site on the upper arm	Not sensitizing	[29]
Butyrospermum Parkii (Shea) Butter Extract	2% in a body lotion	26 healthy subjects	HRIPT; 0.05ml test material applied neat under an occlusive dressing to a SLS pre-treated site on the upper arm	Not sensitizing	[30]
Butyrospermum Parkii (Shea) Butter Extract	5% in a face cream	25 healthy subjects	HRIPT; 0.05ml test material applied neat under an occlusive dressing to a SLS pre-treated site on the upper arm	Not sensitizing	[31]
Butyrospermum Parkii(Shea) Butter Extract	1.7975% in a lipstick	104 subjects	HRIPT; 0.2 g test material applied to area 1 in^2 on upper back ; semi-occluded	Not a dermal irritant or dermal sensitizer	[32]

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2016 FDA VCRP RAW DATA

04E - Other Fragrance Preparation	HYDROGENATED SHEA BUTTER	1
05A - Hair Conditioner	HYDROGENATED SHEA BUTTER	7
07C - Foundations	HYDROGENATED SHEA BUTTER	1
07E - Lipstick	HYDROGENATED SHEA BUTTER	1
10A - Bath Soaps and Detergents	HYDROGENATED SHEA BUTTER	3
12C - Face and Neck (exc shave)	HYDROGENATED SHEA BUTTER	3
12F - Moisturizing	HYDROGENATED SHEA BUTTER	5
12H - Paste Masks (mud packs)	HYDROGENATED SHEA BUTTER	1
01A - Baby Shampoos	SHEA BUTTER GLYCERIDES	1
03C - Eye Shadow	SHEA BUTTER GLYCERIDES	4
05A - Hair Conditioner	SHEA BUTTER GLYCERIDES	3
07I - Other Makeup Preparations	SHEA BUTTER GLYCERIDES	1
10A - Bath Soaps and Detergents	SHEA BUTTER GLYCERIDES	1
10E - Other Personal Cleanliness Products	SHEA BUTTER GLYCERIDES	1
11A - Aftershave Lotion	SHEA BUTTER GLYCERIDES	1
12A - Cleansing	SHEA BUTTER GLYCERIDES	1
12C - Face and Neck (exc shave)	SHEA BUTTER GLYCERIDES	1
12D - Body and Hand (exc shave)	SHEA BUTTER GLYCERIDES	2
12F - Moisturizing	SHEA BUTTER GLYCERIDES	12
12J - Other Skin Care Preps	SHEA BUTTER GLYCERIDES	2
13B - Indoor Tanning Preparations	SHEA BUTTER GLYCERIDES	1
04E - Other Fragrance Preparation	SHEA OLEINE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	SHEA OLEINE	1
05I - Other Hair Preparations	SHEA OLEINE	1
01A - Baby Shampoos	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	1
01B - Baby Lotions, Oils, Powders, and Creams	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	8
01C - Other Baby Products	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	1
02B - Bubble Baths	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	3
02D - Other Bath Preparations	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	1
03A - Eyebrow Pencil	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	1
03C - Eye Shadow	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	6
03D - Eye Lotion	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	7
03G - Other Eye Makeup Preparations	VITELLARIA PARADOXA (SHEA) BUTTER	5

	EXTRACT	
04A - Cologne and Toilet waters	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	4
04E - Other Fragrance Preparation	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	6
05A - Hair Conditioner	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	12
05F - Shampoos (non-coloring)	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	7
05I - Other Hair Preparations	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	3
07A - Blushers (all types)	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	1
07B - Face Powders	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	2
07C - Foundations	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	4
07E - Lipstick	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	36
07G - Rouges	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	1
07I - Other Makeup Preparations	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	11
10A - Bath Soaps and Detergents	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	48
10B - Deodorants (underarm)	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	1
10E - Other Personal Cleanliness Products	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	28
11E - Shaving Cream	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	8
11G - Other Shaving Preparation Products	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	4
12A - Cleansing	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	20
12B - Depilatories	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	8
12C - Face and Neck (exc shave)	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	36
12D - Body and Hand (exc shave)	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	56
12F - Moisturizing	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	82
12G - Night	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	22
12H - Paste Masks (mud packs)	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	4
12I - Skin Fresheners	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	4
12J - Other Skin Care Preps	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	24
13B - Indoor Tanning Preparations	VITELLARIA PARADOXA (SHEA) BUTTER EXTRACT	3

01B - Baby Lotions, Oils, Powders, and Creams	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	1
03B - Eyeliner	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	6
03C - Eye Shadow	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	32
05A - Hair Conditioner	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	1
05F - Shampoos (non-coloring)	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	2
05I - Other Hair Preparations	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	2
07A - Blushers (all types)	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	4
07B - Face Powders	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	3
07C - Foundations	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	1
07E - Lipstick	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	3
07I - Other Makeup Preparations	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	2
12C - Face and Neck (exc shave)	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	1
12D - Body and Hand (exc shave)	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	4
12F - Moisturizing	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	5
12G - Night	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	1
12J - Other Skin Care Preps	VITELLARIA PARADOXA (SHEA) BUTTER UNSAPONIFIABLES	1
12D - Body and Hand (exc shave)	VITELLARIA PARADOXA (SHEA) NUT SHELL POWDER	1
12J - Other Skin Care Preps	VITELLARIA PARADOXA (SHEA) NUT SHELL POWDER	1
12F - Moisturizing	VITELLARIA PARADOXA (SHEA) SEEDCAKE EXTRACT	2
01B - Baby Lotions, Oils, Powders, and Creams	VITELLARIA PARADOXA (SHEA) BUTTER	26
01C - Other Baby Products	VITELLARIA PARADOXA (SHEA) BUTTER	6
02A - Bath Oils, Tablets, and Salts	VITELLARIA PARADOXA (SHEA) BUTTER	10
02B - Bubble Baths	VITELLARIA PARADOXA (SHEA) BUTTER	3
02C - Bath Capsules	VITELLARIA PARADOXA (SHEA) BUTTER	1
02D - Other Bath Preparations	VITELLARIA PARADOXA (SHEA) BUTTER	3
03A - Eyebrow Pencil	VITELLARIA PARADOXA (SHEA) BUTTER	3
03B - Eyeliner	VITELLARIA PARADOXA (SHEA) BUTTER	19
03C - Eye Shadow	VITELLARIA PARADOXA (SHEA) BUTTER	33

03D - Eye Lotion	VITELLARIA PARADOXA (SHEA) BUTTER	114
03E - Eye Makeup Remover	VITELLARIA PARADOXA (SHEA) BUTTER	1
03F - Mascara	VITELLARIA PARADOXA (SHEA) BUTTER	7
03G - Other Eye Makeup Preparations	VITELLARIA PARADOXA (SHEA) BUTTER	50
04E - Other Fragrance Preparation	VITELLARIA PARADOXA (SHEA) BUTTER	12
05A - Hair Conditioner	VITELLARIA PARADOXA (SHEA) BUTTER	118
05C - Hair Straighteners	VITELLARIA PARADOXA (SHEA) BUTTER	17
05E - Rinses (non-coloring)	VITELLARIA PARADOXA (SHEA) BUTTER	2
05F - Shampoos (non-coloring)	VITELLARIA PARADOXA (SHEA) BUTTER	43
05G - Tonics, Dressings, and Other Hair Grooming Aids	VITELLARIA PARADOXA (SHEA) BUTTER	65
05I - Other Hair Preparations	VITELLARIA PARADOXA (SHEA) BUTTER	41
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	VITELLARIA PARADOXA (SHEA) BUTTER	22
06D - Hair Shampoos (coloring)	VITELLARIA PARADOXA (SHEA) BUTTER	1
07A - Blushers (all types)	VITELLARIA PARADOXA (SHEA) BUTTER	7
07B - Face Powders	VITELLARIA PARADOXA (SHEA) BUTTER	9
07C - Foundations	VITELLARIA PARADOXA (SHEA) BUTTER	22
07E - Lipstick	VITELLARIA PARADOXA (SHEA) BUTTER	382
07F - Makeup Bases	VITELLARIA PARADOXA (SHEA) BUTTER	4
07G - Rouges	VITELLARIA PARADOXA (SHEA) BUTTER	1
07I - Other Makeup Preparations	VITELLARIA PARADOXA (SHEA) BUTTER	83
08B - Cuticle Softeners	VITELLARIA PARADOXA (SHEA) BUTTER	4
08C - Nail Creams and Lotions	VITELLARIA PARADOXA (SHEA) BUTTER	2
08G - Other Manicuring Preparations	VITELLARIA PARADOXA (SHEA) BUTTER	2
10A - Bath Soaps and Detergents	VITELLARIA PARADOXA (SHEA) BUTTER	522
10B - Deodorants (underarm)	VITELLARIA PARADOXA (SHEA) BUTTER	16
10E - Other Personal Cleanliness Products	VITELLARIA PARADOXA (SHEA) BUTTER	108
11A - Aftershave Lotion	VITELLARIA PARADOXA (SHEA) BUTTER	42
11B - Beard Softeners	VITELLARIA PARADOXA (SHEA) BUTTER	3
11D - Preshave Lotions (all types)	VITELLARIA PARADOXA (SHEA) BUTTER	1
11E - Shaving Cream	VITELLARIA PARADOXA (SHEA) BUTTER	8
11F - Shaving Soap	VITELLARIA PARADOXA (SHEA) BUTTER	3
11G - Other Shaving Preparation Products	VITELLARIA PARADOXA (SHEA) BUTTER	3
12A - Cleansing	VITELLARIA PARADOXA (SHEA) BUTTER	73
12B - Depilatories	VITELLARIA PARADOXA (SHEA) BUTTER	5
12C - Face and Neck (exc shave)	VITELLARIA PARADOXA (SHEA) BUTTER	275
12D - Body and Hand (exc shave)	VITELLARIA PARADOXA (SHEA) BUTTER	564
12E - Foot Powders and Sprays	VITELLARIA PARADOXA (SHEA) BUTTER	7
12F - Moisturizing	VITELLARIA PARADOXA (SHEA) BUTTER	1,251
12G - Night	VITELLARIA PARADOXA (SHEA) BUTTER	144
12H - Paste Masks (mud packs)	VITELLARIA PARADOXA (SHEA) BUTTER	44

12I - Skin Fresheners	VITELLARIA PARADOXA (SHEA) BUTTER	5
12J - Other Skin Care Preps	VITELLARIA PARADOXA (SHEA) BUTTER	126
13A - Suntan Gels, Creams, and Liquids	VITELLARIA PARADOXA (SHEA) BUTTER	8
13B - Indoor Tanning Preparations	VITELLARIA PARADOXA (SHEA) BUTTER	32
13C - Other Suntan Preparations	VITELLARIA PARADOXA (SHEA) BUTTER	5
02A - Bath Oils, Tablets, and Salts	VITELLARIA PARADOXA (SHEA) OIL	1
02B - Bubble Baths	VITELLARIA PARADOXA (SHEA) OIL	2
03D - Eye Lotion	VITELLARIA PARADOXA (SHEA) OIL	1
03G - Other Eye Makeup Preparations	VITELLARIA PARADOXA (SHEA) OIL	1
05A - Hair Conditioner	VITELLARIA PARADOXA (SHEA) OIL	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	VITELLARIA PARADOXA (SHEA) OIL	1
05I - Other Hair Preparations	VITELLARIA PARADOXA (SHEA) OIL	1
07B - Face Powders	VITELLARIA PARADOXA (SHEA) OIL	1
07E - Lipstick	VITELLARIA PARADOXA (SHEA) OIL	1
10A - Bath Soaps and Detergents	VITELLARIA PARADOXA (SHEA) OIL	21
12A - Cleansing	VITELLARIA PARADOXA (SHEA) OIL	5
12C - Face and Neck (exc shave)	VITELLARIA PARADOXA (SHEA) OIL	4
12F - Moisturizing	VITELLARIA PARADOXA (SHEA) OIL	14
12G - Night	VITELLARIA PARADOXA (SHEA) OIL	2
12I - Skin Fresheners	VITELLARIA PARADOXA (SHEA) OIL	1
12J - Other Skin Care Preps	VITELLARIA PARADOXA (SHEA) OIL	1

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: June 8, 2016

SUBJECT: Butyrospermum Parkii (Shea) Butter Extract

KGL Inc. 2009. An evaluation of the contact-sensitization potential of a topical coded product (body lotion containing 2% Butyrospermum Parkii (Shea) Butter Extract) in human skin by means of the maximization assay. (6925)

KGL Inc. 2009. An evaluation of the contact-sensitization potential of a topical coded product (body lotion containing 2% Butyrospermum Parkii (Shea) Butter Extract) in human skin by means of the maximization assay. (6736)

KGL Inc. 2009. An evaluation of the contact-sensitization potential of a topical coded product (face cream containing 5% Butyrospermum Parkii (Shea) Butter Extract) in human skin by means of the maximization assay.

Anonymous. 2009. Four week use study of a moisturizer containing 5% Butyrospermum Parkii (Shea) Butter Extract.

Anonymous. 2009. Clinical evaluation report: Human patch test (moisturizer containing 5% Butyrospermum Parkii (Shea) Butter Extract.

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KGL INC

FINAL REPORT dated December 22, 2009

KGL Protocol: #6925

Sample: Body Lotion Contains 2% Butyrospermum Parki. (Shea) Butter Extract

www.kgl-inc.com or www.ivylabs.com

Ivy Laboratories (KGL, INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)

Telephone: [215] 387-8400
FAX: [215] 387-1046

E-mail address: ivystudies@verizon.net

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

Sponsor: Commitment Letter dated: November 11, 2009

Principal Investigator: Kays Kaidbey, M.D. (Board Certified Dermatologist)

Testing Facility: KGL INC.
505 Parkway
Broomall, PA 19008-4204 (USA)
(Phone: 215-387-8400)
(FAX: 215-387-1046)

Final Report Date: **December 22, 2009**

Kays Kaidbey, M.D.
Principal Investigator

December 22, 2009
Date

FINAL REPORT

STUDY TITLE:

An assessment of the contact-sensitizing potential of a coded topically-applied test agent using a Human Maximization Assay.

KGL PROTOCOL:

KGL Protocol **#6925**

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) (21 CFR 50, 56, 312) ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register) and in accordance with KGL's Standard Operating Procedures (SOP's).

STUDY OBJECTIVE:

The objective of this study was to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

DESIGN RATIONALE:

A repeat insult patch test wherein the test product was applied under an occlusive dressing to an SLS (sodium lauryl sulfate) pre-treated site on the upper outer arm repeatedly to the same designated area for five 48-hour induction periods followed 7-10 days later by a single challenge to a naïve skin site on the opposite outer arm.

STUDY SPONSOR:

SPONSOR STUDY:

Commitment Letter dated November 11, 2009

TESTING FACILITY:

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KGL ADMINISTRATIVE STRUCTURE:

Linda Haid (Panel Recruitment/Initial Screening)
Angelit Barnes (Technician /Patch Applications/Removals/Recognize/Report AE's)
John B. Chicchi (Evaluator)
Mary J. Massing (Quality Assurance)

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study. Each interviewed panelist who qualified was then asked to read and sign the consent form prior to enrollment. Copies of all consent forms are on file at KGL, Inc.

CONDUCTION DATES:

This study was conducted between November 16, 2009 through December 17, 2009.

TEST MATERIAL:

The test product, supplied by the sponsor, was labeled Body Lotion , and tested as supplied viz. neat.

TEST PRODUCT ACCOUNTABILITY:

The test sample was received in good condition by our Quality Assurance Department. The test material was checked for (1) amount (2) product number or code (3) material container etc. The material was individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). The test sample was stored under ambient conditions in an inaccessible location under the supervision of the investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test material(s) will be disposed of in accordance with applicable governmental regulations following submission of the final written report or returned to the Sponsor via a traceable method, if requested.

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. Panelists had no blemishes, excess hair or other marks on their upper outer arms that would obscure grading of the test site. Both male and female panelists were eligible. None of the subjects had a medical or dermatological illness and none were sensitive to sunscreens or to topical preparations and/or cosmetics. A completed subject was a subject who satisfied the admission criteria and who completed the scheduled study procedures.

Inclusion Criteria:

1. Healthy adult male and female volunteers between the ages of 18 and 65 years.
2. All subjects who were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. Subjects with any significant internal diseases e.g., cardiac, pulmonary, renal, hepatic, etc.
2. History of allergy or hypersensitivity to cosmetics, toiletries or other dermatological products
3. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticaria
4. Pregnancy or mothers who are breastfeeding or planning a pregnancy
5. Scars, moles or other blemishes over the upper arm(s) or back which can interfere with the study
6. Subjects receiving systemic or topical drugs or medications which can interfere with delayed immunologic responses e.g., corticosteroids, non-steroidal anti-inflammatories, retinoids, immunosuppressants
7. Other conditions considered by the investigator as sound reasons for disqualification from enrollment into the study

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each subject accepted into the study were recorded sequentially as they were enrolled.

RECORDING OF DATA:

The case report forms (CRF's) for this study were provided by the Investigator. All case report forms were completed in actual time, during each subject's visit. Copies of the CRF's will be retained by the investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS:

All study related documents, case report forms (CRF's), original informed subject consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

STUDY PROCEDURES:

Method and Procedures[1,2]

Patches were applied to the upper outer arm of each subject. The entire test was composed of three distinct phases: (1) an Induction phase and (2) a Rest Phase and (3) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material was applied to the same site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Rest Period**:

No exposure to the test material was made during this rest period, which lasted for 10 days after the last induction patch.

(3) **Challenge Phase**:

After a ten day rest period, the subjects were challenged with a single application of the test material to a new skin site on the opposite upper outer arm in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and 0.05ml of the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded, and again 24 hours later for any reactions.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	GRADES:	CLASSIFICATION:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

ADVERSE EXPERIENCES:

No adverse experiences or unanticipated reactions were encountered or reported by any of the panelists.

RESULTS:

A total of twenty-eight (28) healthy, adult volunteers of both sexes who satisfied the inclusion criteria were enrolled into this study. There were 23 females and 5 males. Their ages ranged from 20 to 65 years. Subjects #11 and #22 failed to maintain the scheduled study visits, as instructed. Both subjects were subsequently dropped from the study for lack of compliance. The remaining 26 subjects completed this investigation, as outlined in the standard protocol. The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table. No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Body Lotion
does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	TVT	51	M	B
02	MTD	55	F	A
03	DMB	42	F	C
04	DVD	59	F	B
05	A-V	20	F	C
06	C-F	43	M	C
07	NPC	29	F	C
08	MMF	31	F	C
09	LTB	42	F	B
10	KLB	36	F	B
11	KDC	48	F	C
12	J-M	39	F	C
13	RFM	42	F	C
14	NMB	30	F	C
15	LJM	40	F	C
16	MSG	65	M	C
17	SCG	61	F	C
18	JMD	53	F	C
19	CES	38	F	C
20	MMD	47	F	C
21	JAD	45	M	C
22	RWD	40	M	C
23	DAR	51	F	C
24	L-M	50	F	C
25	BAM	55	F	C
26	JAV	37	F	C
27	W-L	64	F	B
28	CLL	65	F	B

B = Black
A = Asian
C = Caucasian

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Body Lotion

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	Dropped from the study	
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	Dropped from the study	
23	0	0
24	0	0
25	0	0
26	0	0
27	0	0
28	0	0

Challenge Readings:

48-Hour Reading – December 16, 2009
72-Hour Reading – December 17, 2009

KGL INC

FINAL REPORT dated April 1, 2009

KGL Protocol: #6736

Sample: Body Lotion Contains 2% Butyrospermum Parkii (Shea) Butter Extract

www.kgl-inc.com or www.ivylabs.com

Ivy Laboratories (KGL, INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)

Telephone: [215] 387-8400
FAX: [215] 387-1046

E-mail address: ivystudies@verizon.net

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

Sponsor:

Commitment Letter dated: February 18, 2009

Principal Investigator: Kays Kaidbey, M.D. (Board Certified Dermatologist)

Testing Facility: Ivy Laboratories (KGL, INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)
(Phone: 215-387-8400)
(FAX: 215-387-1046)

Final Report Date: April 1, 2009

Kays Kaidbey, M.D.
Principal Investigator

April 1, 2009
Date

STUDY TITLE:

An assessment of the contact-sensitizing potential of a coded topically-applied test agent using a Human Maximization Assay.

KGL PROTOCOL:

Ivy Laboratories - KGL Protocol #6736

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) (21 CFR 50, 56, 312) ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register) and in accordance with KGL's Standard Operating Procedures (SOP's).

STUDY OBJECTIVE:

The objective of this study was to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

DESIGN RATIONALE:

A repeat insult patch test wherein the test product was applied under an occlusive dressing to an SLS (sodium lauryl sulfate) pre-treated site on the upper outer arm repeatedly to the same designated area for five 48-hour induction periods followed 7-10 days later by a single challenge to a naïve skin site on the opposite outer arm.

STUDY SPONSOR:

SPONSOR STUDY:

Commitment Letter dated February 18, 2009

TESTING FACILITY:

Ivy Laboratories (KGL INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)
Telephone: Philadelphia - (215-387-8400) – Broomall (610-544-1715)
E-mail: Ivystudies@verizon.net

PRINCIPAL INVESTIGATOR:

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KGL ADMINISTRATIVE STRUCTURE:

Marie Windle (Panel Recruitment/Initial Screening)
Jane Chitwood (Technician /Patch Applications/Removals/Recognize/Report AE's)
John B. Chicchi (Evaluator)
Mary J. Massing (Quality Assurance)

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study. Each interviewed panelist who qualified was then asked to read and sign the consent form prior to enrollment. Copies of all consent forms are on file at KGL, Inc.

CONDUCTION DATES:

This study was conducted between February 23, 2009 and March 27, 2009

TEST MATERIAL:

The test product labeled Body Lotion was supplied by the sponsor and tested as supplied viz. neat.

TEST PRODUCT ACCOUNTABILITY:

The test sample was received in good condition by our Quality Assurance Department. The test material was checked for (1) amount (2) product number or code (3) material container etc. The material was individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). The test sample was stored under ambient conditions in an inaccessible location under the supervision of the investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test material(s) will be disposed of in accordance with applicable governmental regulations following submission of the final written report or returned to the Sponsor via a traceable method, if requested.

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. Panelists had no blemishes, excess hair or other marks on their upper outer arms that would obscure grading of the test site. Both male and female panelists were eligible. None of the subjects had a medical or dermatological illness and none were sensitive to sunscreens or to topical preparations and/or cosmetics. A completed subject was a subject who satisfied the admission criteria and who completed the scheduled study procedures.

Inclusion Criteria:

1. Healthy adult male and female volunteers between the ages of 18 and 65 years.
2. All subjects who were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. Subjects with any significant internal diseases e.g., cardiac, pulmonary, renal, hepatic, etc.
2. History of allergy or hypersensitivity to cosmetics, toiletries or other dermatological products
3. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticaria
4. Pregnancy or mothers who are breastfeeding or planning a pregnancy
5. Scars, moles or other blemishes over the upper arm(s) or back which can interfere with the study
6. Subjects receiving systemic or topical drugs or medications which can interfere with delayed immunologic responses e.g., corticosteroids, non-steroidal anti-inflammatories, retinoids, immunosuppressants
7. Other conditions considered by the investigator as sound reasons for disqualification from enrollment into the study

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each subject accepted into the study were recorded sequentially as they were enrolled.

RECORDING OF DATA:

The case report forms (CRF's) for this study were provided by the Investigator. All case report forms were completed in actual time, during each subject's visit. Copies of the CRF's will be retained by the investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS:

All study related documents, case report forms (CRF's), original informed subject consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

STUDY PROCEDURES:

Method and Procedures[1,2]

Patches were applied to the upper outer arm of each subject. The entire test was composed of three distinct phases: (1) an Induction phase and (2) a Rest Phase and (3) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material was applied to the same site before the site was again covered with occlusive tape (Induction patch). The Induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh Induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the Induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Rest Period**:

No exposure to the test material was made during this rest period, which lasted for 10 days after the last Induction patch.

(3) **Challenge Phase**:

After a ten day rest period, the subjects were challenged with a single application of the test material to a new skin site on the opposite upper outer arm in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and 0.05ml of the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded 15-30 minutes later and again 24 hours later for any reaction.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	GRADES:	CLASSIFICATION:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

ADVERSE EXPERIENCES:

No adverse experiences or unanticipated reactions were encountered or reported by any of the panelists.

RESULTS:

A total of twenty-six (26) healthy, adult, volunteers who satisfied the inclusion criteria were enrolled into this study. There were 14 females and 12 males. Their ages ranged from 18 to 65 years. One subject #15 (initials B.M., a male) failed to return to the testing facility for the scheduled visits and was lost to follow-up. He was subsequently dropped from the study. The remaining 25 volunteers completed this investigation, as outlined in the standard protocol. The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Body Lotion does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	W-K	48	M	C
02	R-G	63	M	C
03	S-B	49	F	B
04	E-D	23	F	C
05	M-K	46	F	C
06	M-D	46	F	C
07	S-B	61	M	C
08	J-D	55	M	C
09	N-R	29	F	C
10	C-K	65	M	C
11	K-W	38	F	B
12	G-C	63	M	C
13	R-M	36	F	C
14	R-B	58	F	C
15	B-M	21	M	C
16	R-S	51	F	C
17	D-S	19	M	B
18	K-T	59	F	C
19	S-T	48	F	C
20	M-M	23	F	C
21	K-S	45	F	C
22	P-S	19	M	C
23	R-M	18	M	C
24	D-F	38	M	C
25	J-K	28	M	C
26	S-R	45	F	C

C = Caucasian
B = Black

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Body Lotion

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	Dropped from the study	
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0
26	0	0

Challenge Readings:

48-Hour Reading – March 26, 2009
72-Hour Reading – March 27, 2009

FINAL REPORT

STUDY TITLE:

An assessment of the contact-sensitizing potential of a coded topically-applied test agent using a Human Maximization Assay.

KGL PROTOCOL:

Ivy Laboratories - KGL Protocol #6759

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) (21 CFR 50, 56, 312) ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register) and in accordance with KGL's Standard Operating Procedures (SOP's).

STUDY OBJECTIVE:

The objective of this study was to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

DESIGN RATIONALE:

A repeat insult patch test wherein the test product was applied under an occlusive dressing to an SLS (sodium lauryl sulfate) pre-treated site on the upper outer arm repeatedly to the same designated area for five 48-hour induction periods followed 7-10 days later by a single challenge to a naïve skin site on the opposite outer arm.

STUDY SPONSOR:

SPONSOR STUDY:

Commitment Letter dated March 18, 2009

TESTING FACILITY:

Ivy Laboratories (KGL INC.)
505 Parkway
Broomall, PA 19008-4204 (USA)
Telephone: Philadelphia - (215-387-8400) – Broomall (610-544-1715)
E-mail: ivystudies@verizon.net

PRINCIPAL INVESTIGATOR:

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Medical Director, KGL, INC.
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FAX: (215) 387-1046
E-mail address: ivystudies@verizon.net

KGL ADMINISTRATIVE STRUCTURE:

Diane Kozubal (Panel Recruitment/Initial Screening)
Carolyn Lindsay (Technician /Patch Applications/Removals/Recognize/Report AE's)
John B. Chicchi and Kays Kaidbey, M.D. (Evaluators)
Mary J. Massing (Quality Assurance)

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study. Each interviewed panelist who qualified was then asked to read and sign the consent form prior to enrollment. Copies of all consent forms are on file at KGL, Inc.

CONDUCTION DATES:

This study was conducted between March 23, 2009 through April 24, 2009

TEST MATERIAL:

The test product labeled Face Cream was supplied by the sponsor (1 jar) and tested as supplied viz. neat.

TEST PRODUCT ACCOUNTABILITY:

The test sample was received in good condition by our Quality Assurance Department. The test material was checked for (1) amount (2) product number or code (3) material container etc. The material was individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). The test sample was stored under ambient conditions in an inaccessible location under the supervision of the investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test material(s) will be disposed of in accordance with applicable governmental regulations following submission of the final written report or returned to the Sponsor via a traceable method, if requested.

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. Panelists had no blemishes, excess hair or other marks on their upper outer arms that would obscure grading of the test site. Both male and female panelists were eligible. None of the subjects had a medical or dermatological illness and none were sensitive to sunscreens or to topical preparations and/or cosmetics. A completed subject was a subject who satisfied the admission criteria and who completed the scheduled study procedures.

Inclusion Criteria:

1. Healthy adult male and female volunteers between the ages of 18 and 65 years.
2. All subjects who were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. Subjects with any significant internal diseases e.g., cardiac, pulmonary, renal, hepatic, etc.
2. History of allergy or hypersensitivity to cosmetics, toiletries or other dermatological products
3. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticaria
4. Pregnancy or mothers who are breastfeeding or planning a pregnancy
5. Scars, moles or other blemishes over the upper arm(s) or back which can interfere with the study
6. Subjects receiving systemic or topical drugs or medications which can interfere with delayed immunologic responses e.g., corticosteroids, non-steroidal anti-inflammatories, retinoids, immunosuppressants
7. Other conditions considered by the investigator as sound reasons for disqualification from enrollment into the study

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each subject accepted into the study were recorded sequentially as they were enrolled.

RECORDING OF DATA:

The case report forms (CRF's) for this study were provided by the Investigator. All case report forms were completed in actual time, during each subject's visit. Copies of the CRF's will be retained by the investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS:

All study related documents, case report forms (CRF's), original informed subject consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

STUDY PROCEDURES:

Method and Procedures[1,2]

Patches were applied to the upper outer arm of each subject. The entire test was composed of three distinct phases: (1) an Induction phase and (2) a Rest Phase and (3) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material was applied to the same site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Rest Period**:

No exposure to the test material was made during this rest period, which lasted for 10 days after the last induction patch.

(3) **Challenge Phase**:

After a ten day rest period, the subjects were challenged with a single application of the test material to a new skin site on the opposite upper outer arm in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and 0.05ml of the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded 15-30 minutes later and again 24 hours later for any reaction.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	GRADES:	CLASSIFICATION:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

ADVERSE EXPERIENCES:

No adverse experiences or unanticipated reactions were encountered or reported by any of the panelists.

RESULTS:

A total of twenty-five (25) healthy, adult, volunteers who satisfied the inclusion criteria were enrolled into this study. There were 20 females and 5 males. Their ages ranged from 20 to 62 years. All 25 volunteers completed this investigation, as outlined in the standard protocol. The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Face Cream does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	S-M	51	F	C
02	A-R	51	F	C
03	LMS	51	F	C
04	K-R	20	F	C
05	P-D	60	M	C
06	K-B	43	F	C
07	CMB	38	F	C
08	D-C	59	M	C
09	V-B	25	F	C
10	N-W	50	F	C
11	M-G	44	F	C
12	D-K	43	F	C
13	J-C	62	F	C
14	N-M	29	M	C
15	GCD	44	F	C
16	E-C	44	F	C
17	JMS	53	F	C
18	N-D	43	F	C
19	V-N	22	M	C
20	AAP	20	F	C
21	V-B	21	F	C
22	K-H	36	F	C
23	T-K	40	M	C
24	J-S	56	F	C
25	A-C	47	F	C

C = Caucasian

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Face Cream

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0

Challenge Readings:

48-Hour Reading – April 23, 2009
72-Hour Reading – April 24, 2009

STUDY REF.# TC203909

SUMMARY

containing 5% Butyrospermum Parkii (Shea) Butter Extract

Moisturizer # was tested via a four-week Dermatologist-supervised Clinical Use study. The study was a single-blind, baseline controlled monadic design with Dr. , a Board Certified Dermatologist, as the principal investigator. Subjects were instructed to apply the Facial Cream twice daily.

The Dermatologist did not observe any **visible clinical irritation** related to use of , Moisturizer.

None of the subjects using the Facial Cream reported a perceived discomfort/irritation response during the study period.

A claim of "suitable for sensitive skin" is supported by the results of this study.

Reported By: _____

Senior Clinical Technician

Approved By: _____

Manager

_____ M.D.

Consulting Dermatologist

STUDY REF. # TC203909

TO:

FROM:

DATE: September 18, 2009

SUBJECT: Clinical Use Test Results of Moisturizer

SUMMARY

Moisturizer was tested via a four-week Dermatologist-supervised Clinical Use study. The study was a single-blind, baseline controlled monadic design with Dr. , a Board Certified Dermatologist, as the principal investigator. Subjects were instructed to apply the Facial Cream twice daily.

The Dermatologist did not observe any **visible clinical irritation** related to use of Calming Anti-Redness Moisturizer.

None of the subjects using the Facial Cream reported a perceived discomfort/irritation response during the study period.

A claim of "suitable for sensitive skin" is supported by the results of this study.

STUDY OBJECTIVES

* To determine the potential of Moisturizer to evoke clinical irritation and/or subject-perceived discomfort/irritation when used under consumer use conditions.

* To provide support for a claim of "suitable for sensitive skin" for Moisturizer.

TEST DESIGN

A total of forty-six (46) individuals completed this four-week, Dermatologist-supervised Clinical Use Test. In order to support the claim of "suitable for sensitive skin" thirty-four of these individuals (74%) had Testing Center-assessed sensitive skin while the remaining twelve were considered to be "non-sensitive". Facial exams were conducted at the baseline, two-week interim and final visits. Actual test design and Criteria for Testing Center Assessed Skin Sensitivity are presented in Appendix I. Product identification and product use instructions are presented in Appendix II. Subject demographics are listed in the study file.

STUDY DATES

April 13, 2009 - May 11, 2009

RESULTS: DERMATOLOGIST-ASSESSED VISIBLE IRRITATION

The Dermatologist did not observe any product related irritation. A tabulation of clinical changes may be found in Appendix III.

The Dermatologist observed clinical changes in the categories of scaling and conditions of acne, including papules and pustules. The level of positive changes, in both scaling and acne conditions, was slightly higher than the level of negative changes in these same conditions. The Dermatologist found all observed changes to be within the parameters for normally and/or seasonally occurring fluctuations in skin conditions in the general population.

PERCEIVED IRRITATION

None of the subjects reported experiencing subjective discomfort and/or irritation during the study period.

CONCLUSION

The results of this study will provide support for a claim of "suitable for sensitive skin" for [redacted] Moisturizer

Prepared By: [redacted]

Senior Clinical Technician

Approved By: [redacted]

Manager
Clinical Evaluation

cc: [redacted]

APPENDIX I

TEST DESIGN

Forty-six (46) subjects completed a four-week, Dermatologist-supervised clinical use test. The panel was conducted as single-blind, baseline controlled monadic design evaluation.
The test product was supplied to all of the subjects for the 4-week evaluation period.
Test products were packaged in appropriate packaging and labeled with product type, i.e. Facial Cream. Products were supplied to subjects with use instructions. Dermatologist-assessed facial exams were conducted initially, at the two-week interim visit and upon completion of the study. Questionnaires seeking subject perceived problems were completed by the subjects at the end of each two-week use period.

CRITERIA FOR DETERMINING TESTING CENTER-ASSESSED SENSITIVITY

A SENSITIVES: Must have at least 3 characteristics from List #1
B SENSITIVES: Must have 2 characteristics from List #1 and at least 2 characteristics from List #2.
C SENSITIVES: Must have 2 characteristics from List #1 and at least 1 characteristic from List #2.

(NOTE: Alt data for parameters designated as self-assessed or self-acknowledged is obtained from questionnaires completed by subjects. Testing Center Assessed data was obtained via facial screening exams conducted by Testing Center personnel.)

LIST #1

Self-Assessed Very Sensitive / Sensitive Skin	
Self-Assessed Sun Sensitivity	- (i.e. Fitzpatrick Types I, II)
Allergies	- (self-acknowledged - including but not limited to pollen, dust, drugs, foods – ranging from one to multiple)
Flusher/Blusher	- (self-acknowledged)
Eczema History	- (self-acknowledged)
Testing Center-Assessed Rosacea	- (based upon evaluation screening by Testing Center personnel)
Testing Center-Assessed Seborrheic Dermatitis	- (based upon evaluation screening by Testing Center personnel)

LIST #2

Self-Assessed Skin Type of Normal to Dry or Dry	
Blonde/Red Hair Color	- (self-acknowledged)
Non-Soap User	- (self-acknowledged user of facial cleanser)
Testing Center-Assessed Telangiectasia	- (based upon evaluation screening by Testing Center Personnel)
Testing Center-Assessed Very Fair/Fair Complexion	- (based upon evaluation screening by Testing Center Personnel)
Testing Center-Assessed Freckling	- (based upon evaluation screening by Testing Center Personnel)

USE INSTRUCTIONS
TC-2039-09
FACIAL CREAM

USE THIS PRODUCT TWICE A DAY, MORNING AND EVENING !!

USE IN PLACE OF YOUR REGULAR FACIAL MOISTURIZER !

TO USE:
1. Apply this product twice daily, morning and evening.
2. Cleanse face as usual.
3. Dab small amounts of the product to the forehead, upper / lower cheeks, crowsfeet area, chin and neck.
4. With your fingertips, smooth evenly over face using **gentle** upward and outward strokes. AVOID CONTACT WITH EYES.
5. Use this product in place of your regular facial moisturizer.

NOTE: For external use only. Keep out of reach of children.
Avoid contact with eyes. If product comes in contact with the eyes, rinse thoroughly with water.

REMEMBER:
1. Bring your product with you on the exam dates (April 27th and May 11th).
2. This product is for your use only. Do not let other members of your family use it
3. Should any problems arise while using the product, please call the Testing Center & ask for

APPENDIX III

Total Tabulation of Clinical Changes
Dermatologist-Supervised
N=46

	Test	
	#	%
# of subjects that exhibited a change*	25	54
# of subjects that exhibited no change	21	46

Scaling	Test
increased	0
decreased	4
Acne	
increased	11
decreased	18
Papules	
increased	5
decreased	13
Pustules	
increased	3
decreased	3
Macules	
increased	2
decreased	4
Acne Vulgaris	
increased	1
decreased	0
Rosacea	
increased	1
decreased	0

* - Subjects may have exhibited more than one change.

CLINICAL EVALUATION REPORT: HUMAN PATCH TEST

This test follows the procedure described in SOP, HPT.1 **TO:**

PRODUCT PROFILE NO: 1013907 DATE: April 10, 2009 LAB REF.: TC-2034-09

1. TEST MATERIAL: % Moisturizer contains 5% Butyrospermum Parkii (Shea) Butter Extract

2. CONTROL MATERIAL: Night Cream

3. TEST PROCEDURE:

Single-Insult (24hr.) X Occlusive (Blenderm) Patch X Semi-Occlusive Patch_____.

4. CONCENTRATION:

Full-Strength X Aqueous _____ Solution _____ Dispersion_____ Aqueous Paste_____.
Other:_____.

_____Volatiles were allowed to evaporate prior to occlusion on the patch.
_____Patch was hydrated just prior to application to skin.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
		0	±	1	1+	2	2+	3	3+	4	PII
Moisturizer	18	18	0	0	0	0	0	0	0	0	0.00
Night Cream	18	18	0	0	0	0	0	0	0	0	0.00

___ Skin staining noted. Erythematous response was read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). X

B. _____

Study Conducted By: _____ Approved By: _____

* SCORE
0 = No evidence of any effect.
± (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by choosing the higher of the two Irritation Scores per panelist, adding them all together and dividing by the total number of test subjects.

CC:

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: August 22, 2016

SUBJECT: Concentration of Use by FDA Product Category: Butyrospermum Parkii (Shea) Oil

Concentration of Use by FDA Product Category – Butyrospermum Parkii (Shea) Oil

Product Category	Maximum Concentration of Use
Eyeliners	2%
Eye shadows	0.5%
Eye lotions	4.2-8%
Other eye makeup preparations	0.5%
Other fragrance preparations	1%
Rinses (non-coloring)	0.25%
Shampoos (non-coloring)	0.001-0.0015%
Tonics, dressings and other hair grooming aids Not spray	0.2% 0.01-0.4%
Other hair preparations (noncoloring)	0.01-0.4%
Foundations	0.1%
Lipstick	4-11%
Cuticle softeners	0.1-2%
Other oral hygiene products	0.5%
Bath soaps and detergents	0.005-0.05%
Shaving cream	0.02%
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.5-2.5%
Depilatories	0.01-0.49%
Face and neck products Not spray	 0.95-5%
Body and hand products Not spray or powder Not spray	 0.01-0.4% 3-8%
Paste masks and mud packs	1%

Information collected in 2016

Table prepared August 23, 2016

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: June 1, 2016

SUBJECT: Comments on the Draft Safety Assessment of *Butyrospermum parkii* (Shea)-Derived Ingredients as Used in Cosmetics (prepared for the June 6-7, 2016 meeting)

Key Issue

A concentration of use survey still needs to be completed on Butyrospermum Parkii (Shea) Oil if it is added to the report (the survey on Butyrospermum Parkii (Shea) Butter is complete). In addition, if Butyrospermum Parkii (Shea) Oil is added to the report, more details from the sheanut oil controls in the reproductive and developmental toxicity study and 2 year dietary study should be added to the report.

Additional Considerations

ADME, Oral, Shea Oleine - The Summary states that the oral absorption of shea oleine in rats was 27-52%. This should also be stated in the ADME section.

Chronic - If the toxicology studies are presented by duration, there should also be a Chronic subsection where the 2-year rat study of shea oleine and sheanut oil is mentioned.

Irritation - The following sentence does not make sense. "The erythema was resolved with 3 or 4 days of patching." It is more likely that the erythema resolved 3-4 days after patching.

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