Safety Assessment of *Citrus* Peel-Derived Ingredients as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
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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: May 13, 2016
Subject: Draft Tentative Report of the Safety Assessment of *Citrus* Peel-Derived Ingredients

Enclosed is the draft tentative report of the Safety Assessment of *Citrus* Peel-Derived Ingredients as Used in Cosmetics. (It is identified as *cpeels062016rep* in the pdf document.)

At the December 2015 meeting, the Panel issued an Insufficient Data Announcement for the 47 *Citrus* peel-derived ingredients described in the safety assessment. Data needs included:

- Method of manufacturing
- Chemical composition and impurities
- Irritation and sensitization, especially human repeated insult patch tests (HRIPT) on Citrus Aurantium Dulcis (Orange) Peel Extract, Citrus Grandis (Grapefruit) Peel Extract, Citrus Limon (Lemon) Peel Extract, and Citrus Unshiu Peel Extract at maximum use concentrations or greater

Since the December meeting, unpublished data on the method of manufacturing and composition/impurities of Citrus Aurantium Amara (Bitter Orange) Peel Extract, Citrus Reticulata (Tangerine) Peel Extract, and Citrus Unshiu Peel Extract have been received as well as genotoxicity data on Citrus Reticulata (Tangerine) Peel Extract and dermal/ocular irritation and/or dermal sensitization data on Citrus Aurantium Amara (Bitter Orange) Peel Extract, Citrus Grandis (Grapefruit) Peel Extract, Citrus Limon (Lemon) Peel Extract, Citrus Reticulata (Tangerine) Peel Extract, and Citrus Unshiu Peel Extract. In addition, phototoxicity/photosensitization data on Citrus Aurantium Amara (Bitter Orange) Peel Extract and Citrus Reticulata (Tangerine) Peel Extract were received. Composition data of the hexane extract of *Citrus aurantifolia* (lime) peel was found in the published literature. These data have been incorporated into the report and highlighted with |brackets| or highlighted in tables. No other requested data have been received or identified by CIR staff. Comments received from the Council have been considered. The comments and the unpublished data can be found in this report's package (*cpeels062016pcpc and cpeels062016data1-10, respectively).*

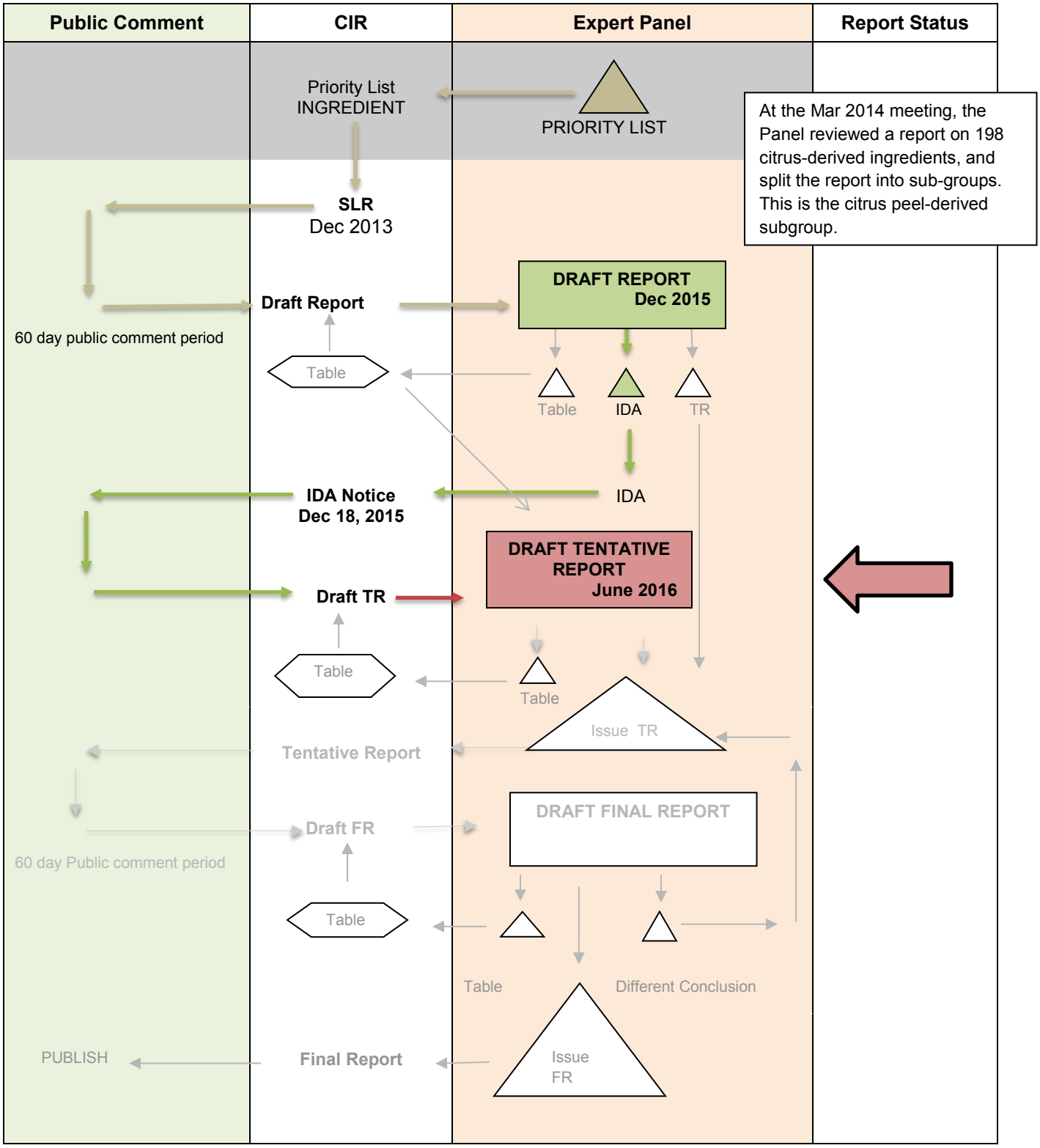
Both the VCRP and the concentration of use data have been updated for these ingredients. Currently, Citrus Limon (Lemon) Peel Extract has the most reported uses of the ingredients in this report in cosmetic products, with a total of 150; more than half of the uses are in rinse-off preparations (e.g. non-coloring hair conditioners, hair shampoos, and skin cleansing preparations). Citrus Paradisi (Grapefruit) Peel Extract has the second greatest number of overall uses reported, with a total of 61; more than half of the uses are in skin care preparations. The results of the concentration of use survey conducted in 2016 by the Council indicate Citrus Aurantium Dulcis (Orange) Peel Powder has the highest reported maximum concentration of use; it is used at up to 2% in skin cleansing preparations. The highest reported maximum concentration of use in a leave-on product is 1.9% in a lipstick for Citrus Aurantium Dulcis (Orange) Peel Wax. Please note that the data requested at the December 2015 meeting were based on the highest uses/concentrations reported at the time and that the ingredients with the highest uses/concentrations may have changed since then. (Citrus Aurantium Amara (Bitter Orange) Peel Powder and Citrus Aurantium Dulcis (Orange) Peel Powder were both previously reported to be used at up to 6% in skin cleansing preparations).

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.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Citrus Peel-Derived Ingredients

MEETING June 2016



Citrus Peel-Derived Ingredients History

December 2013 – Scientific Literature Review announced.

March 2014 - The Panel tabled further discussion of 198 citrus-derived ingredients to allow CIR staff to reorganize the report and to obtain clarification from RIFM on the functions of some of the ingredients. These ingredients were presented in a single safety assessment report addressing ingredients from all of the citrus plant species currently reported to be used in cosmetics in the International Cosmetic Ingredient Dictionary and Handbook. The Panel felt revising this report into smaller subgroups would be a manageable and meaningful alternative approach to assessing the safety of these ingredients. Based on the Panel's recommendation of grouping the ingredients by plant parts according to greatest number of uses, the first assessment reviewed by the Panel was citrus-derived peel oils, followed by citrus fruit-derived ingredients.

September 2015 – The Panel reviewed the report strategy for the remaining citrus ingredients. The Panel agreed that the remaining ingredients could be divided into 3 reports: citrus flower- and leaf-derived ingredients, citrus peel-derived ingredients, and citrus plant- and seed-derived ingredients. These reports can be reviewed concurrently.

December 2015 - The CIR Expert Panel requested additional data to support the safety of the 47 *Citrus* peel-derived ingredients. The additional data needed are:

- Method of manufacturing
- Chemical composition and impurities
- Irritation and sensitization, especially human repeated insult patch tests (HRIPT) on citrus aurantium dulcis (orange) peel extract, citrus grandis (grapefruit) peel extract, citrus limon (lemon) peel extract, and citrus unshiu peel extract at maximum use concentrations or greater.

Citrus Peel-Derived Ingredients Data Profile – June 2016 – Writer, Christina Burnett

	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Genotoxicity	Carcinogenicity	Irritation/Sensitization - Nonhuman	Irritation/Sensitization - Clinical	Ocular/Mucosal	Phototoxicity	Case Studies
Citrus Aurantifolia (Lime) Peel Extract	X			X				X			
Citrus Aurantifolia (Lime) Peel Powder	X										
Citrus Aurantium Amara (Bitter Orange) Peel	X										
Citrus Aurantium Amara (Bitter Orange) Peel Extract	X		X	X			X	X	X	X	
Citrus Aurantium Amara (Bitter Orange) Peel Powder	X										
Citrus Aurantium Amara (Bitter Orange) Peel Wax	X										
Citrus Aurantium Bergamia (Bergamot) Peel Water	X										
Citrus Aurantium Dulcis (Orange) Peel Extract	X										
Citrus Aurantium Dulcis (Orange) Peel Powder	X										
Citrus Aurantium Dulcis (Orange) Peel Wax	X	X	X	X			X	X		X	
Citrus Aurantium Tachibana Peel Extract	X										
Citrus Depressa Peel Extract	X										
Citrus Grandis (Grapefruit) Peel Extract	X							X			
Citrus Jabara Peel Extract	X										
Citrus Junos Peel Extract	X										
Citrus Junos Peel Powder	X										
Citrus Limon (Lemon) Peel	X										
Citrus Limon (Lemon) Peel Extract	X							X	X		
Citrus Limon (Lemon) Peel Powder	X										
Citrus Limon (Lemon) Peel Wax	X										
Citrus Nobilis (Mandarin Orange) Peel Extract	X										
Citrus Paradisi (Grapefruit) Peel Extract	X										
Citrus Reticulata (Tangerine) Peel Extract	X		X	X	X		X	X	X	X	
Citrus Tangerina (Tangerine) Peel Extract	X										
Citrus Unshiu Peel Extract	X		X	X				X			
Citrus Unshiu Peel Powder	X										
Citrus Aurantium Amara (Bitter Orange) Peel Wax (not INCI ingredient)	X										
Citrus Medica Limonum (Lemon) Peel Wax	X										
Citrus Tachibana (Tachibana) Peel Extract	X										
lemon peel juice										X	
orange peel (generic, not INCI ingredient)	X										

NO USES OR DATA WERE AVAILABLE FOR THE REMAINING CITRUS INGREDIENTS LISTED IN TABLE 1.

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

Search Strategy for Citrus Peel-Derived Ingredients

- August 2014 – miscellaneous searches for additional data on constituents
- Scifinder – February 26, 2013
  - Search for INCI citrus ingredients w/ CAS No. – 99 hits, 10 ordered
- PubMed – March 5,2013
  - Search for "citrus cosmetics" – 65 hits, 1 ordered
  - Search for "citrus sensitization" – 36 hits, 8 ordered
  - Search for "citrus dermal" – 12 hits, 0 ordered
  - Search for "citrus phototoxicity" – 24 hits, 10 ordered
- SciFinder – Aug 19 2013
  - toxicity of citrus ingredients – 11 hits; 1 ordered
  - carcinogenicity of citrus – 466 hits; 8 ordered
- SciFinder – Aug 20, 2013
  - Phototoxicity of citrus – 47 hits; 21 ordered
  - Dermal effects of citrus – 51 hits; 1 new ref found
  - Dermal absorption of citrus – 1 hit; not useful
  - Constituents of citrus – 116 hits;
  - Citrus – Belsito, Marks, Bergfeld, Api, RIFM– 2 found

Ordered a few others; printed some directly

Updated searches in November, 2013 – ordered an additional 4 references
Updated searches July 2015 with the term "citrus" – 1 new relevant reference found.
Updated searches October 2015 with the term "citrus AND peel NOT oil"– 0 new relevant references found.
Updated searches February-May 2016 with the term "citrus peel composition NOT oil" – 52 hits, 5 relevant references found (many returns still were on peel oils).

Online Info

- FDA
  - GRAS definitions
- Dr. Duke's Phytochemical and Ethnobotanical Databases
  - Due to volume of data, limited search to Citrus limon (Lemon), Citrus aurantifolia (Lime), Citrus paradisi (Grapefruit), Citrus sinensis (Sweet Orange), and Citrus aurantium (Bitter Orange)
- National Toxicology Program (NTP)
  - Bitter Orange Extract (mixture)
- SCCS/SCCP
  - Opinion on fragrance allergens in cosmetic products
  - Opinion on Furocoumarins in cosmetic products
- Sigma Aldrich
  - Citrus aurantiifolia (lime)
  - Citrus aurantium (bitter orange)
  - Citrus paradisi (grapefruit)
  - Citrus reticulata (tangerine)
- IFRA
  - 7-methoxycoumarin
  - Standard for citrus oils and other furocoumarins containing essential oils. Ingredients include:

Citrus Peel-Derived Ingredients
December 14-15, 2015

Dr. Marks' Team
DR. MARKS: Okay. Moving on to the next, the citrus peel.

This is the first review of these 47 ingredients that include the peel, peel extract, powder, wax juice. Are these ingredients okay, Ron, Ron, and Tom? Are there any ingredients that should be eliminated?

DR. HILL: I'm fine with it.

DR. SHANK: I'm fine with it. So the ingredients are okay. So what needs do we have for the peel-derived ingredients?

DR. SHANK: Irritation and sensitization data.

DR. MARKS: Yep, I agree.

DR. SHANK: On all of the peels at maximum use concentration.

DR. MARKS: Yeah. So what I did with that, Ron, is I took -- I looked at the uses and I picked the three with the highest uses, which was the peel extract, or I should say -- let me see. The orange peel extract, and one at HRIPTs for that at 1.9 percent. That was its use concentration. The grapefruit peel extract, the.5 percent, any unshiu shield peel extract at.94, they were the ones that had the highest uses. Any others, the concentrations by and large were really low, like for the mandarin orange peel extract, there were 19 uses but it was only being used at.03 percent. So I felt those three would give me enough information to be able to feel comfortable with a group.

DR. HILL: Number of uses or greatest concentration use?

DR. MARKS: I took the highest uses and then the concentration corresponded with them. So the orange peel extract at 54 uses at 1.9 percent. The grapefruit peel extract had 48 uses at.5 percent, and the unshiu peel extract had 40 uses at.98, and they were also the highest concentrations of use. So that's why I picked those three and would feel we could read across if they're okay. And I picked several different citrus -- what's unshiu, Christina, do you know?

DR. HILL: I thought there was something on that in the species comparison.

DR. MARKS: So, Ron, does that sound reasonable to you?

DR. SHANK: Well, since lime was of interest before --

MS. BURNETT: It's related to tangerine.

DR. SHANK: You're going on the fact that the concentration of use is low?

DR. MARKS: Yeah,.025 percent. That's why --

DR. SHANK: In a leave-on.

DR. MARKS: Yes.

DR. SHANK: So if that's a leave-on in sunscreen or something --

DR. MARKS: We're probably going to have that 5- MOC in the conclusion anyway.

DR. SHANK: Okay.

DR. MARKS: I would think. I would think that conclusion is going to continue through once we -- we're always going to be putting on their limit the 5-MOC to 15 parts per million.

DR. SHANK: How many uses does the wax have? Not many, right?

DR. MARKS: Four. The orange wax, or which wax?

DR. HILL: Any wax.

DR. SLAGA: Any wax.

DR. MARKS: Four for the orange wax. Orange peel wax. And that was basically --

MS. BURNETT: Five for the bitter orange peel wax.

DR. MARKS: Yeah, so small numbers.

MS. BURNETT: One for lemon --

DR. SLAGA: Because we do have a little data on that. That's the only one.

DR. MARKS: Right. Yeah, actually, I was -- at 100 percent that was okay for the orange peel wax and their irritation and sensitization.

DR. SLAGA: You know, we had a pretty good composition of the waxes, too.

DR. MARKS: Yeah. Do you think you could -- we couldn't extend that over --

DR. SLAGA: I don't know how it could extrapolate it to the other ones --

DR. MARKS: Yeah, exactly.

DR. SLAGA: -- but we do have that.

DR. MARKS: Yeah, I had that one as okay. I guess you could say -- I was thinking we would put an insufficient data announcement and when we came to the conclusion eventually the wax will be safe. I think we can say that right now.

DR. SLAGA: We can say it right now.

DR. HILL: So you said the grapefruit peel extract was one of the ones you wanted to see?

DR. MARKS: Yes.

DR. HILL: Okay.

MS. BURNETT: And lemon?

DR. MARKS: Orange peel, grapefruit peel, and mshiu, if that's how you say it.

DR. SHANK: Tangerine.

DR. MARKS: Oh, tangerine. Okay, thank you.

MS. BURNETT: Lemon has the most uses at 171. PDF page 21.

DR. MARKS: And what's the concentration of use?

MS. BURNETT: .51 is the max. It's a rinse- off.

DR. MARKS: So let's get lemon in here, too.

MS. BURNETT: Let's do all of it.

DR. HILL: I really wanted to see method of manufacture.

DR. MARKS: Yeah, I had that up front in composition. We only had these for the orange peel wax. So the lemon was.5 you said?

MS. BURNETT: .51.

DR. MARKS: Lemon peel extract. Is that the one? 0.5 percent. Thanks, Christina.

So, Tom, Rons, at this point, I like the idea of getting your method of manufacturing composition. Are we going to all the other tox, we're just going to say these are GRAS and we don't need any of them? And we say that in the -- I should say Christina says it in the third paragraph of the introduction, thus, the systemic toxicity potential of citrus peel-derived in the gradiance via oral exposure is not addressed further in this report. The primary focus is the safety on topical exposure. And that GRAS --

So presumably, I'll be seconding a motion with an insufficient data announcement tomorrow and method of manufacture composition of a number of these others, you'd like to see those. Does that seem reasonable?

DR. SLAGA: Yeah.

DR. SHANK: Methods of manufacture, in the report it suggests that orange peel juice of cosmetic grade was not phototoxic but noncosmetic (inaudible) was phototoxic, so is there something in the manufacturer that -- this stems from Table 11, page 26. Now, if we have the Latin name, that means it's cosmetic grade, and if it's just English, that's not --

DR. ANSELL: I'm sorry, what table was it?

DR. SHANK: This is Table 11, page 26.

DR. MARKS: And cosmetic grade is non --

DR. SHANK: Now, my understanding is if the ingredient has a Latin name, that's what's used in cosmetics, and if it doesn't have a Latin name --

DR. ANSELL: No, that's a naming convention for these cosmetics. It goes backwards.

MS. BURNETT: So if the data came through the Council and we were told that it was for that specific entry that has the proper inking name, which is citrus aurantium dulcis orange peel wax. That was data that was collected. If it's a common name that was from the published literature of some university that did research on it and it's not.

DR. SHANK: Not necessarily cosmetic ingredient.

MS. BURNETT: It's not a cosmetic necessarily.

DR. HILL: The second one in that table --

DR. SHANK: But there's a big difference in the response.

DR. HILL: One of them is a peel wax. The other one is not. The one below it is -- it's an extract, alcohol extract. In one case the peel; another other case the mesocarp and a case of fruit. There were three different extracts.

DR. SHANK: And fruit of (inaudible) extract.

MS. BURNETT: It's not written right but there are three different extracts, each of which is alcoholic. It's just not punctuated right is the better way to say it.

DR. SHANK: Well, there are extracts and their direct application.

MS. BURNETT: Okay, let's see. So it was both a peel and a peel extract.

DR. HILL: Pure peel. How do you apply a peel, pure peel? How would you do that?

DR. ANSELL: See, I think we could certainly ask the questions. This is the first time through but I think the reading -- the correct reading from looking at the procedure would be sweet orange peel mesocarp or fruit alcohol extracts. And that they didn't peel the mesocarp or fruit applied directly or as an alcohol extract.

DR. HILL: Okay. Okay, yes. I see it now.

DR. ANSELL: And then they photo (inaudible) radiate it and they examined it one, two, three, and four days. And so a strong (inaudible) 48 hours post-radiation to a peel and peel extract, slight for pure peel extract.

DR. HILL: See, this last one was why I thought there were three different preparations.

DR. MARKS: Okay. So any other comments? So tomorrow presumably we're going to have a motion to -- that there will be an insufficient data announcement from the Belsito team, and we want method of manufacture and composition for as many ingredients as we can get.

DR. SLAGA: Other than wax.

DR. MARKS: Other than wax. We have the wax now. And then we would like to see the HRIPT for a number of these ingredients, the orange peel extract, the grapefruit peel extract, the tangerine peel extract, and lemon peel extract, that their concentrations, the highest concentration of use in leave-ons and we'll go from there. Does that sound reasonable?

DR. SLAGA: Good.

DR. HILL: What I was going to ask about is Table is photosensitization and phototoxicity. Are we just assuming that 5-MOC covers it and there's nothing else that we have to concern ourselves with or how do we -- I mean, maybe we can defer that question until tomorrow, but --

DR. MARKS: Oh, I wouldn't defer it. I think if I understood it correctly, in all these citrus ingredients there's not 7-MOC.

DR. HILL: No, I wasn't 100 percent crystal clear that 5-MOC was the only geraniol coumarin present in any of them at all. I just knew that was a significant one. And actually, I read about this yesterday. I have no recollection what I read last evening about that, or Saturday evening. It all ran together.

DR. MARKS: I think 5-MOC is --

DR. HILL: It's a good enough sentinel to be worried about. Okay.

DR. MARKS: Exactly. Okay. Any other comments?

DR. GILL: Just for clarification, I thought I heard Dr. Shank read someplace in the report where it mentioned a cosmetic grade ingredient, and I just wanted to clarify because I think we had a question from the industry, maybe or someone that says --

DR. HILL: There's no such thing.

DR. GILL: -- there's no such thing as a cosmetic group. It's an ingredient used in cosmetics. So if it's in here, we'll find it and replace that.

DR. ANSELL: Okay. I'll (inaudible).

DR. GILL: Okay.

DR. HILL: Yes, because in that previous report we were talking about the difference between an ingredient name versus the Latin name of the plant that was used.

DR. MARKS: And then, probably one other thing, Christina, to clarify. Let me see. I don't have the page. It's got to be -- I'm sensing it's -- it was a reference to the paper reporting Danish occupational food handlers.

MS. BURNETT: Uh-huh. Under occupational --

DR. HILL: I was going to ask about that, too. That's page 12.

DR. MARKS: Yeah, page 12. As it turn -- when you look at that report, they -- those were positive prick tests. Not patch tests so I would clarify that that you don't get confused that this is delay-type hypersensitivity reaction.

MS. BURNETT: A prick test.

DR. MARKS: They were prick tests and then, the other thing is they related it back to this NDF protein contact dermatitis but they didn't mention any of the workers having respiratory or other symptoms of an anaphylactic type reaction. So I think note it in there but make sure it's reference to prick test and no other mention of systemic effects.

And I don't know how it would be related as a cosmetic ingredient because one, perhaps the concentration but also there aren't reports of contact urticaria to these ingredients. And that's how it would manifest in a topical preparation. Okay.

DR. HILL: So are you suggesting that we'll further mine that reference and make sure that a little --

DR. MARKS: It's clarified.

DR. HILL: -- additional language clarifies what we're dealing with here?
DR. MARKS: Yes.

DR. HILL: All right, great.

DR. MARKS: Yes, it wasn't like the experience in Japan where they having anaphylactic reactions with topical exposure. Okay. And I have that noted in mine here. Okay, any other comments? Okay.

Dr. Belsito's Team

DR. BELSITO: Okay. So then, we move to now, the citrus-peel derived ingredients, and this is the first time we are looking at these. And there was an issue about the actual number of ingredients to be clarified between the INCI dictionary and the VCRP database, and in the meantime though we've included those that aren't in the INCI dictionary, but are in the VCRP database in this report as I recall. Is that correct?

MS. BURNETT: They are at least in the use table.

DR. BELSITO: They are in the use table?

MS. BURNETT: Mm-hmm.

DR. BELSITO: So then how do we deal with that, Bart?

DR. HELDRETH: Until we are given some sort of clarification that the different names overlap and have the same ingredient, and adjust them as -- each as ingredient. I think there are some issues with, you know, one of the suppliers entering information that the VCRP database they may not have the option to enter the INCI name, so they have to pick something else that may not line up, or easily be coordinated with the INCI name.

So, we are left wondering, you know, which ingredient does this specifically apply to? So, until we have some clarification on that, I think it's best to look at these as individual ingredients.

DR. BELSITO: But do we have the ability to add an ingredient as a cosmetic ingredient if it doesn't exist in the dictionary? And which is essentially what we'll be doing, right, if we put this in the use table?

MS. BURNETT: We have several different reports that have the same issue.

DR. BELSITO: Really?

DR. HELDRETH: I mean, we are saying we know that they are in use. If it's recorded in the VCRP database, where we are making the assumption that these ingredients are in use now, but possibly the supplier will use the correct INCI name on their label, and kind of really violated the codification of the INCI names, but at this time we may not have specific information that tells us which VCRP name winds up with which INCI name.

MS. BURNETT: It's not this report but one of the other citrus reports, the whole plant report where we see a huge discrepancy where something was reported in the VCRP was 100-some uses but it's not in the dictionary, and we don't know what it is exactly, but it has the most uses.

DR. BELSITO: I remember it coming up several times in these reports, and so just, I'm trying to clarify, how does this happen? So, if you go into the VCRP, is it just a scroll down, and you have to choose a specific one, and the VCRP has the wrong name, or these people are just typing in the name that they think the product is?

DR. HELDRETH: Maybe a submitter could give us the information because neither one of us have actually done a submission, but I know --

DR. EISENMANN: We've heard from our members when they go to the VCRP, sometimes they don't have the choice of selecting the INCI name. And this is coming up with apple. So, I think FDA has decided at some point that they are going to use their accepted --

DR. LANGE: The agriculture --

DR. EISENMANN: Right. The Agricultural Research Services, except that genus species name for apple is Malus domestica. And so if you want to register a product containing apple, you have to select malus

domestica, but what they are putting on the label, and I get this -- I got some responses, and the last concentration of use survey, they came back and said, Malus domesitica. And I asked, are you putting that on the label? And they said, no, we are using Pyrus Malus, we are using the INCI name on the label.

But FDA has been pushing them for it. So, I'm not sure why that's happening, but that's what our members are reporting, that was a -- it's a botanical issue that FDA is not always accepting the INCI name to register a product. They are rejecting some product registrations when they put it. So, in order to get the product registered they have to go to whatever genus species name FDA is using for that species.

DR. BELSITO: So, it is sort of like a dropdown tab where you --

DR. EISENMANN: That's what I understand, yes.

DR. SNYDER: So, kind of a naïve question. So how often is the dictionary updated, and then what drives updating the dictionary?

DR. LANGE: The INCI or the VCRP?

DR. SNYDER: INCI dictionary.

DR. EISENMANN: They try not to change names on the INCI dictionary, but it's up -- I mean, we do a nightly update, so any little change can get updated.

DR. SNYDER: Okay. So it is.

DR. EISENMANN: So, it's updated frequently.

DR. SNYDER: Frequently. Okay, thank you.

DR. HELDRETH: I think the one thing to remember is the codification is for the INCI name, so even if the VCRP is requiring a supplier under a certain name, the supplier has to use the INCI name. So it's not a matter of the dictionary not getting updated to the correct name, it's a matter of the supplier can't pick the INCI name when they are putting their registration in. So it's really not an update of the dictionary issue. It's this disparity between the nomenclature, between VCRP and INCI.

DR. SNYDER: But there's no mechanism on the survey for them to indicate that the choice they want to use is not found, and they are just allocation or --

DR. HELDRETH: I mean, they could make that known to the industry when they do a survey, but it doesn't show up in the database stuff we get from VCRP each year.

DR. LANGE: My understanding is, in VCRP, if they don't choose one of the given names the application is rejected.

MS. BURNETT: So I suppose if the survey came back, the use survey, if the company knows that it's inputted in the VCRP as this other name, it will be helpful for us, so we would know and not count it as a separate entry in the use table, because that's how it is now, as we don't know how to rectify that, and we just put them in.

DR. EISENMANN: It's unlikely to happen. And likely there's probably different person is doing my survey versus who is doing the VCRP.

MS. BURNETT: Yes. I understand it's not likely -- We try to reflect it where we could figure it out, but in some cases we couldn't figure out what it was.

DR. BELSITO: Okay. So, another layer of confusion for the botanicals, if we don't have enough -- So with these peel-derived ingredients, I thought we were really lacking a lot with manufacturing constituents, impurities, sensitization and irritation of the extract, powder and water. And this is one where I wondered if we had grouped correctly, because we are having waxes and oils, and water and powder from the peels, and it's the peel that's the real issue.

I mean that's where the psoralens are, and I would think that the constituents of a wax and oil are going to be extremely different than the constituents of water. And a powder, I'm presuming is going to be everything that's in the peel so I think this is the report where I really begin thinking, did we lump these correctly, and I'm just throwing that out as a comment, because we don't really know what that means. We have an idea, the overall, what's in a peel, but do we know what's in a peel wax and a peel oil and in a peel powder? And I didn't think so. So, I had problems with this report.

DR. LIEBLER: I think in one of the other reports, we have some flow chart or scheme illustrating the production of the different types of components. Is it -- I can't remember which one it is, I just scrolled down through this one, and I don't see a figure at the end. Do you remember, Christina?

MS. BURNETT: It was fruit water.

DR. LIEBLER: Is it the fruit water?

MS. BURNETT: Mm-hmm.

DR. BELSITO: The only thing that we have a lot of information on in this report is the wax.

DR. LIEBLER: Yes. I mean, the wax is, essentially, are stripped of all of the -- essentially all the low molecular weight. Anything that's the least bit polar, and that includes all of the -- sort of the small organics that are the known constituents of concern.

DR. BELSITO: Right. It says that in the method of manufacture.

DR. LIEBLER: Yes.

DR. BELSITO: Deodorization removes all terpenes and most of the essential oil components.

DR. LIEBLER: Right. And then the juices, is there a peel juice?

MS. BURNETT: That's an extract.

DR. LIEBLER: Peel extract?

MS. BURNETT: I have to look, I'm sort of looking at so many of these I can't tell you.

DR. BELSITO: There is a peel extract.

SPEAKER: A powder.

DR. LIEBLER: Yes. We have peel powder, peel wax, peel extract.

MS. BURNETT: I know the last report we just looked at, there was a peel juice, a tox data, but I think it was peel ingredients --

DR. BELSITO: Peel extract, peel powder, peel water --

MS. BURNETT: No. There's no juice.

DR. BELSITO: There's no peel juice.

DR. LIEBLER: Okay. I don't know why I wrote that, but the -- So it's actually the peel powders and the peel extracts, I think their manufacturer is not very well defined here.

DR. BELSITO: Yes. I mean, they are not -- the only method of manufacture we have. I thought the waxes were okay, that's the only data we have n this whole group, and that's pretty minimal.

DR. LIEBLER: So, we really don't have a very good idea what the peel powders and peel extracts have in them?

DR. BELSITO: Yes -- No --

DR. LIEBLER: So that's I share your concern, Don.

DR. BELSITO: And the highest maximum concentration of use in leave-on 1.9 in lipstick is the peel extract.

DR. LIEBLER: Mm-hmm.

DR. BELSITO: And we have absolutely no data on that.

DR. EISENMANN: No. For all three of these reports, I have sent out a new concentration of use survey, and once that's completed, then I will go and contact all companies for finding the highest use concentration. I just didn't think it was worthwhile to do that with the -- as I was doing the new, to use the old use information.

DR. LIEBLER: Okay.

DR. EISENMANN: So I haven't yet contacted companies that ask for HRIPT data on the high use of concentration practices, because I don't know them yet, because I'm still on -- I still have a new survey underway. And expect the use survey to be done by the end of February, but I'm not convinced I'm going to have the HRIPT data by the March meeting.

DR. BELSITO: Yes. I mean I -- Go ahead, Paul.

DR. SNYDER: Yes. So this was -- I mean this was a report that really drove me to the discussion we had on the last report but -- So, on the summary, the last sentence of the first paragraph we say, "CIR did not review the potential toxicity information on the individual constituents of which the Citrus peel-derived ingredients are comprised." Well, that's not a true statement because we do know that there are constituents of concern, and we did look at the toxicity levels, that's not a true statement. So, we need to modify that.

SPEAKER: Is it deleted?

DR. SNYDER: And then further down, when I read the last sentence of the summary, "No relevant published studies on the toxicokinetics, repeated dose toxicity, reproductive and development toxicity, genotoxicity, carcinogenicity, or dermal, blah-blah-blah --" I was thinking, oh, we are going to have to go insufficient.

DR. BELSITO: We are. I mean, the only sufficiency at all, if you think so, is the wax.

DR. SNYDER: Okay.

DR. BELSITO: Everything else is in -- At least the way I saw it, everything else is insufficient, and I thought it was very surprising that the ingredients that are most used and have the highest concentration of use data, we have no sensitization and irritation, method of manufacture, we have zip on them.

DR. SNYDER: But I thought that this sentence could also be in all of the citrus reports, and so why are we only picking to highlight it on this report, because we didn't have a -- the same -- similar datasets on the one we just reviewed.

DR. BELSITO: I guess the reason we probably did it, is it's the peel where you are concerned about the furocoumarin. The rest of the fruit of the citrus is not an issue.

DR. SNYDER: And we should have left those altogether in one group, and then the peels separate.

DR. BELSITO: You know, I started -- before we even began this discussion, wondering whether we had done this correctly, as particularly with this one, because when we get to the seed, I think we are focusing on, you know, specifics like seed waxes of something, Here, suddenly, you know, we are looking waxes and oils and waters, and to me, those are completely different animals, that are not going to have the same chemical composition. And we don't know anything about their method of manufacture, so this is -- this particular report was the most problematic for me.

DR. SNYDER: Okay. Just as an editorial thing, we can't use things like, comprised of hundreds of constituents, and then the table only has 15, and so if we don't have data to support that there's hundreds of constituents, then the thing is we maybe use numerous, or something, but we can't hundreds.

DR. LIEBLER: Yes. I just said many.

MS. BURNETT: Me, too.

DR. BELSITO: Where was this, Paul?

MS. BURNETT: It's probably in the intro, right?

DR. SNYDER: Under the beginning there. Using it twice -- constituent composition, you use the term I preferred, or complex botanicals made up of numerous constituents, but on the prior one to that, under --

MS. BURNETT: Yes. I see what you are -- It's in the introduction piece.

DR. SNYDER: Under -- Yes, you see, "Botanical ingredients are those derived from citrus, or comprised of hundreds. You do that in all three reports, so we just need to back that off to --

MS. BURNETT: Okay.

DR. SNYDER: Yes. I'll provide you some language.

MS. BURNETT: All right. Thank you.

DR. BELSITO: So, to go back. I mean, my final read on these were that we were okay with the wax, but I thought we were insufficient for manufacturing, constituents impurities, and possibly sensitization and irritation of the extract, the powder and the water, because I have -- we have no data on those.

DR. SNYDER: Right. I agree.

DR. BELSITO: And then, we are going to be talking about the 5-MOP but, again, not the methoxycoumarin for these.

MS. BURNETT: I will make that correction across all of them.

DR. SNYDER: Phototoxicity and photosensitization section, because that is a primary concern. I think we

need a few details in there, because we talk about several rat studies, and then in humans, but yes, there is no details, but I think we should add a little bit about the details, because that appears to be one of the major issues that we are on.

MS. BURNETT: All right. How would the Panel like to carry any relevant data over from the peel oils report? Do you feel that there's any relative -- relevant data that could be incorporated? Or should just reference that report? I guess, maybe, it was -- when the insufficient announcement would go out, and it might help clarify the components.

DR. BELSITO: Right.

MS. BURNETT: But in my mind, when you see an ingredient as a full peel, to me that means it has to have peel oil on it, if it's the full peel.

DR. LIEBLER: I think it takes us back to the need to define what the constituents are in method of manufacture is, because I can -- So, for example, powder seemed to me inconsistent with having significant oil content, otherwise, you are going to get a sludge and not a powder. And then the extracts of course, you know, anybody's guess, as that is defined.

MS. BURNETT: So, we should wait until --

DR. LIEBLER: So I just don't know to what extent we borrow from the oil report at this point.

MS. BURNETT: Okay. So that would be revisited next time. Okay.

DR. BELSITO: And then in the cosmetic -- Let's see where I have this. In the cosmetic use section, these are used in aerosols, and we don't have the aerosol boilerplate there that needs to be added. Okay. So --

MS. BURNETT: Do you mean, if for a discussion that would be needed?

DR. BELSITO: Don't you usually put a little bit of the boilerplate in the cosmetic use section as well?

MS. BURNETT: It's in there.

DR. BELSITO: Oh. Then in the discussion, I guess.

DR. BERGFELD: So, are you going to go insufficient?

DR. BELSITO: Yes. Well, that's what I --

DR. BERGFELD: And you are going safe for the waxes?

DR. BELSITO: Safe as used for the waxes, and insufficient --

DR. BERGFELD: And so this is an announcement?

DR. BELSITO: What?

MS. BURNETT: This is an announcement.

DR. BERGFELD: Announcement?

DR. BELSITO: Yes. Insufficient for manufacturing constituents' impurities and sensitization and irritation for the extracts, powders and water, and wax is okay.

DR. BELSITO: Any other comments?

Full Panel Meeting

DR. BERGFELD: Then moving on to Belsito, the citrus peel.

DR. BELSITO: So citrus peel, so this is the first time we're looking at this report of 47 ingredients. And these ingredients are reported to function primarily as skin conditioning agents, maximum concentration 6 percent in skin cleansing preparations and 1.9 in leave-ons. We looked at the data for the citrus peel-derived ingredients and we thought that overall the data were insufficient for manufacturing, constituents impurities, and possibly sensitization and irritation of the extract, powder, and water. We also raised the issue have we grouped these correctly? Because the water is likely to potentially contain different constituents than the extract, particularly depending upon how it's extracted. The powder we would expect to contain all of the different ingredients that could be extracted in water and in possibly an organic extraction. Would it be better to break this down as waxes, oils, waters, powder, et cetera? So we were having great concern that actually in deciding to look at peel, in fact, we were actually looking at a number of very different cosmetic ingredients, that they really didn't belong to the same class.

As a result, we had a little discussion that perhaps it might be reasonable, as we try to wrap our heads around the botanicals, and as Dan and I know the Fragrance Association is trying to wrap its head around naturals and how to approach this, that perhaps at some point it might be nice to try and hold some type of joint one-day meeting, or however long you feel necessary, with RIFM and perhaps other interested parties to try and discuss how we're all trying to grapple with these. But in terms of this ingredient, insufficient and a question as to whether we grouped it correctly.

DR. BERGFELD: So it's a motion?

DR. BELSITO: That's a motion.

DR. MARKS: Second.

DR. BERGFELD: Any further discussion?

DR. MARKS: Yeah, we had largely the same needs for the insufficient data announcement. I also ask for more HRIPTs in the ingredients that had a large use and the highest concentration, and that's noted in here, like the orange peel extract at 1.9 percent, the grapefruit peel extract at.5 percent, the unshiu peel extract at.94 percent, and the lemon peel extract at 0.1 percent. Some of the others, although they're being used, the concentration was so low I wasn't too concerned about it.

I was looking at water here. Is that one of the ingredients being used, Don? Right off the top, when I looked down here, I don't see water. I know it's one of the ingredients, but I was looking at the ones actually being used. So that can be clarified between now and the next time.

DR. BERGFELD: Ron Hill?

DR. HILL: Did we include method of manufacture? I mean, we've got that for --

DR. MARKS: Yes.

DR. HILL: Okay.

DR. MARKS: Yeah, Don mentioned that.

DR. HILL: Okay.

DR. BERGFELD: Any other requests? There seems to be a consensus of insufficient.

DR. BELSITO: There were no water uses. Most were the extract and the wax. There was one powder, no water.

I guess the only other point to discuss is do we feel we've grouped these right? Do we think that the constituents of the water are going to be the same as the constituents of the powder? Are we going to be looking at multiple different things here?

DR. BERGFELD: Is that something that would be answered after you go the constituents?

DR. BELSITO: I guess.

DR. BERGFELD: Okay.

DR. MARKS: If they're not used, I'm not sure we're going to get the composition constituents, so I think we'd have to use it as we usually do in our conclusions. If used, we would expect it would be in the same concentration and use, whatever, as the others. We may want to also put the caveat --

DR. BELSITO: Except in this case the water may contain a completely different set of chemical constituents than the wax.

DR. MARKS: Yeah, I agree, Don. I think we could cover that in a conclusion by also not only the same use, the same concentration as what we reviewed, but also a similar composition of what we've reviewed.

DR. BELSITO: Or since there are no uses, go insufficient for chemical composition.

DR. MARKS: We could.

DR. BERGFELD: I think that can be determined at the next meeting.

DR. BELSITO: Yes, fine.

DR. MARKS: Yeah, but that'll come up time and time again. I mean, this is only the beginning of -- not the beginning. I actually, as I said earlier, I was half- jokingly about split apart the citrus. Do we put them back together at the end of all this? But any rate, I agree with your motion, we do.

DR. BERGFELD: Paul, are you wanting to say something?

DR. SNYDER: I was just going to (inaudible) Jim he's sitting right next to Christina.

DR. MARKS: Oh, yeah. She heard it yesterday.

DR. BERGFELD: I'm going to call the question then. All those in favor of going insufficient data announcement? Thank you. Unanimous.

DR. LANGE: Can I just make a comment?

DR. BERGFELD: Sure.

DR. LANGE: That Carol has a use survey out and we probably will not have HRIPT data until the June meeting, just as far as timing to set expectations.

DR. BERGFELD: Thank you.

DR. EISENMANN: And this is for all three of these citrus reports, the use survey is now out. And then once that's completed, I'll ask for the high concentrations HRIPT data.

DR. MARKS: Perhaps that would, and the timing you were mentioning earlier, Lillian, perhaps that would be when to bring the citrus back up, when we only have the nine-week window that these ingredients -- we would have the data by then.

DR. GILL: Yeah, we were hoping that this would be a set because we had sent this announcement out and the needs for the information had been out before.

DR. BERGFELD: Ron?

DR. HILL: Yeah, I was just going to comment about the grouping thing. I think at least, at first take, even though I agree with you that a water would be very dissimilar, at least by restricting to the peel we could expect that to some extent one would inform the other and then take into account, so we have done reports where we had subfamilies and we're really careful to make those families be distinct within the body of the report. And I'm not sure how best we do that and we'll talk about formatting, but I think because we've at least restricted to the peel, I'm not sure given the relative dearth of information that further breaking them into separate reports makes sense. But figuring out a way to construct the report, even if it's in a read across table, which doesn't appear in the final publication, still, for me, I'm making use of those and looking what informs that, informs that. And if we have composition tables in relation to that, it's very helpful because then we also have to consider concentrations of use. So if we have something that's only used at.005 percent, then that's very different than we see.2 percent or 5 percent.

DR. BERGFELD: Thank you.

Safety Assessment of *Citrus* Peel-Derived Ingredients as Used in Cosmetics

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DRAFT ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 47 *Citrus* peel-derived ingredients, which are most frequently reported to function in cosmetics as skin 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

Citrus peel-derived ingredients are widely used in cosmetics, and are most frequently reported to function in cosmetics as skin conditioning agents (Table 1).[1] This report assesses the safety of the following 47 ingredients:

Citrus Aurantifolia (Lime) Peel
Citrus Aurantifolia (Lime) Peel Extract
Citrus Aurantifolia (Lime) Peel Powder
Citrus Aurantifolia (Lime) Peel Water
Citrus Aurantium Amara (Bitter Orange) Peel
Citrus Aurantium Amara (Bitter Orange) Peel Extract
Citrus Aurantium Amara (Bitter Orange) Peel Powder
Citrus Aurantium Bergamia (Bergamot) Peel Water
Citrus Aurantium Dulcis (Orange) Peel Extract
Citrus Aurantium Dulcis (Orange) Peel Powder
Citrus Aurantium Dulcis (Orange) Peel wax
Citrus Aurantium Sinensis Peel Extract
Citrus Aurantium Tachibana Peel Extract
Citrus Depressa Peel Extract
Citrus Depressa Peel Powder
Citrus Grandis (Grapefruit) Peel
Citrus Grandis (Grapefruit) Peel Extract
Citrus Grandis (Grapefruit) Peel Powder
Citrus Hassaku/Natsudaidai Peel Powder
Citrus Iyo Peel Extract
Citrus Iyo Peel Water
Citrus Jabara Peel Extract
Citrus Jabara Peel Powder
Citrus Jabara Peel Water
Citrus Junos Peel Extract
Citrus Junos Peel Powder
Citrus Junos Peel Water
Citrus Limon (Lemon) Peel
Citrus Limon (Lemon) Peel Extract
Citrus Limon (Lemon) Peel Powder
Citrus Limon (Lemon) Peel Water
Citrus Limon (Lemon) Peel wax
Citrus Natsudaidai Peel Extract
Citrus Nobilis (Mandarin Orange) Peel Extract
Citrus Nobilis (Mandarin Orange) Peel Powder
Citrus Paradisi (Grapefruit) Peel Extract
Citrus Reticulata (Tangerine) Peel Extract
Citrus Reticulata (Tangerine) Peel Powder
Citrus Shunkokan Peel Extract
Citrus Sunki Peel Extract
Citrus Tachibana/Reticulata Peel Powder
Citrus Tangelo Peel Powder
Citrus Tangerina (Tangerine) Peel
Citrus Tangerina (Tangerine) Peel Extract
Citrus Unshiu Peel Extract
Citrus Unshiu Peel Powder
Citrus Unshiu Peel Water

The Panel has previously reviewed the safety of *Citrus*-derived peel oils and *Citrus* fruit-derived ingredients in separate assessments and concluded that 14 *Citrus*-derived peel oil ingredients and the 80 *Citrus* fruit-derived ingredients are safe for use in both rinse-off and leave-on cosmetic products when formulated to be non-sensitizing and non-irritating, provided that leave-on products do not contain more than 0.0015% (15 ppm) 5-methoxypsoralen (5-MOP).[2,3] The Panel is concurrently reviewing the safety of *Citrus* flower- and leaf-derived ingredients and *Citrus* plant- and seed-derived ingredients in separate reports.

Some of the *Citrus* peels that are used to derive the ingredients described in this safety assessment are consumed as food. The U.S. Food and Drug Administration (FDA) determined that the use of some *Citrus* peels as direct food substances are generally recognized as safe (GRAS). Additionally, essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some *Citrus* peels are GRAS for their intended use in foods for human and animal consumption. Daily consumption of these GRAS foods would result in much larger systemic exposures than what is expected from use in cosmetic products, even if there was 100% absorption. Thus, the systemic toxicity potential of *Citrus* peel-derived ingredients via oral exposure is not addressed further in this report. The primary focus of this safety assessment is the review of safety based on topical exposure.

CIR does not review ingredients that are known to function only as fragrance ingredients because, as fragrances, the safety of these ingredients is evaluated by the Research Institute for Fragrance Materials (RIFM). According to the *Dictionary*, four of the *Citrus* flower- and leaf-derived ingredients in this report are reported to function only as fragrance ingredients (see Table 2).[1] However, personal communications with RIFM in March 2015 did not identify these ingredients as fragrances included on their list of ingredients to be reviewed, thus CIR is reviewing the safety of these ingredients.

Botanical ingredients such as those derived from *Citrus* are complex mixtures of many constituents, some of which have the potential to cause toxic effects; for example, bergapten (aka 5-methoxysporalen or 5-MOP) is a naturally-occurring phototoxic furanocoumarin (psoralen) in some *Citrus* ingredients. In this assessment, CIR is reviewing the potential toxicity

of each *Citrus* peel-derived ingredient as a whole, complex substance. Except for specific constituents of concern that the Panel has identified, CIR is not reviewing the potential toxicity of the individual constituents of the *Citrus* peels from which the ingredients in this report are derived.

Note: In many of the published studies included in this assessment, the information provided is not sufficient to determine how well the substance being tested represents the cosmetic ingredient. In this safety assessment, if a substance tested in a study is not clearly a cosmetic ingredient, because of lack of information on the genus and species from which the substance was derived and/or the method of extraction used, the test substance will be referred to by a common name (e.g. sweet orange peel extract). If the substance is clearly a cosmetic ingredient, the International Nomenclature of Cosmetic Ingredients (INCI) name will be used (e.g. "Citrus Aurantium Dulcis (Orange) Peel Extract"). Additionally, some inconsistencies were noted in both taxonomic and INCI naming conventions. For example, this report includes the sweet orange ingredient described as Citrus Aurantium Dulcis (Orange) in the *International Cosmetic Ingredient Dictionary and Handbook.*[1] In contrast, most of the published literature and FDA Voluntary Cosmetic Registration Program (VCRP) refer to this ingredient as Citrus Sinensis (sweet Orange). Another example of a naming inconsistency is Citrus Grandis (Grapefruit); *Citrus grandis* is generally considered a name for a pummelo, which may also be referred to as *Citrus maxima*. *Citrus paradisi* appears to be the more widely accepted nomenclature for grapefruit. The INCI Committee of the Personal Care Products Council (Council) is working to correct some of these inconsistencies. The genus and species names associated with the ingredient names designated by the INCI Committee are listed in Table 3.[4]

CHEMISTRY

The definitions and functions of the citrus-derived ingredients included in this report are provided in Table 1. The definition indicates what part(s) of the plant from which an ingredient is obtained. In some cases, the definition provides insight on the method(s) of manufacture.

Physical and Chemical Properties

Physical and chemical properties of Citrus Aurantium Dulcis (Orange) Peel Wax are provided in Table 4.

Method of Manufacturing

Citrus Aurantium Amara (Bitter Orange) Peel Extract

A supplier reported that its Citrus Aurantium Amara (Bitter Orange) Peel Extract products are produced by extracting dried raw peels from *Citrus aurantium amara* with an ethanol solution.[5] The resultant materials then undergo various forms of filtration, concentration, sedimentation, and adjustment before packaging. One product (a powdered form) has anhydrous sodium sulfate added as a vehicle prior to packaging.

Another supplier reported that its products are produced by extracting ripe pericarp from *Citrus aurantium* Linne (Rutaceae) with either an ethanol solution or 1,3-butylene glycol solution and then filtering.[6]

Citrus Aurantium Dulcis (Orange) Peel Wax

According to data provided by a supplier, Citrus Aurantium Dulcis (Orange) Peel Wax is a by-product from the manufacturing of orange essential oil and from orange fruit peels following orange juice production.[7] Citrus Aurantium Dulcis (Orange) Peel Wax is obtained from distillation of citrus terpenes and orange essential oil. The crude wax is processed by physical methods only and is further refined with various absorbents and filtration. The deodorization process removes all terpenes and most of the essential oil components.

Citrus Reticulata (Tangerine) Peel Extract

A supplier reported that Citrus Reticulata (Tangerine) Peel Extract is produced through the hydroalcoholic extraction of tangerine peel, which is then concentrated until it contains at least 98% of the flavonoid luteolin.[8] The resultant product is a powder.

Another supplier reported that its products are produced by extracting ripe peels of Citrus reticulate Blanco (Rutaceae) with either an ethanol solution or 1,3-butylene glycol solution and then filtering.[6]

Citrus Unshiu Peel Extract

According to a supplier, Citrus Unshiu Peel Extract is obtained by maceration of fine-cut *Citrus unshiu* peel in water and ethanol.[9] The resultant product is then filtered and dried. Another supplier reports that its Citrus Unshiu Peel Extract products are produced by extracting dried raw peels with either an ethanol solution or a 1,3-butylene glycolic solution.[5] The resultant materials then undergo various forms of filtration, concentration, sedimentation, and adjustment before packaging. One product (a powdered form) has anhydrous sodium sulfate added as a vehicle prior to packaging, while another has squalene added.

Constituents/Composition

The *Citrus* ingredients are complex botanicals made up of numerous constituents. Table 5 lists *Citrus* constituents that are known or recognized contact allergens, according the European Commission's Scientific Committee on Consumer Safety (SCCS).[10]

Citrus Aurantifolia(Lime) Peel Extract

The volatile constituents of the hexane extract of *Citrus aurantifolia* are listed in Table 6.

Citrus Aurantium Amara (Bitter Orange) Peel Extract

A supplier has reported that their Citrus Aurantium Amara (Bitter Orange) Peel Extract products contain flavonoids, sugar, and/or hesperidin.[5]

A supplier of a product containing 1.55% Citrus Aurantium Amara (Bitter Orange) Peel Extract, 25.81% alcohol, and 72.64% water stated the product contained 2.8 ppm 5-MOP.[6] No other analysis was performed on this product. The same supplier has a product containing 2.0% Citrus Aurantium Amara (Bitter Orange) Peel Extract, 29.4% butylene glycol, and 68.6% water: no further composition data were provided.

Citrus Aurantium Dulcis (Orange) Peel Wax

Based on data provided by a supplier, Citrus Aurantium Dulcis (Orange) Peel wax is a water-free substance unlikely to be contaminated by microorganisms (bacteria, yeast, or fungi) because of the high temperature, filtration, and absorbents used during processing.[7]

The provided data indicate that Citrus Aurantium Dulcis (Orange) Peel Wax consists of approximately 60% esters (C42-C60), 18% phytosterols (beta-sitosterol, stigmasterol), 3% sterol esters, 8% free fatty acids, 5% hydrocarbons, and 4% free fatty alcohols.[7] Further, approximately 50% of Citrus Aurantium Dulcis (Orange) Peel Wax consists of unsaturated monoesters of unsaturated fatty acids and long-chain alcohols, with the fatty acids consisting mostly of linoleic, oleic, linolenic, arachidic, and erucic acids.[11] The fatty alcohol portion of the ester is mostly dotriacontanol (C32) and tetratricontanol (C34).

Table 7 and Table 8 present additional chemical composition data on Citrus Aurantium Dulcis (Orange) Peel Wax.

Citrus Reticulata (Tangerine)Peel Extract

A supplier of a product containing 3.06% Citrus Reticulata (Tangerine) Peel Extract, 25.41% alcohol, and 71.53% water reported that its product did not contain furanocoumarins.[6] Another product of this supplier contained 3.0% Citrus Reticulata (Tangerine) Peel Extract, 29.1% water, 67.9% butylene glycol, and no furanocoumarins. No further composition data were provided on these products.

Citrus Unshiu Peel Extract

According to a supplier, Citrus Unshiu Peel Extract is composed of pectin, peptides and amino acids, essential oils, phenolic acids, flavonoids (flavonols, flavones, flavonones), carotenoid pigment, and tocopherol analogues.[9] Another supplier reports that its Citrus Unshiu Peel Extract products contain flavonoids, sugar, and/or hesperidin.[5] One product was reported to contain essential oil component (no further details provided).

Impurities

Citrus Aurantium Amara (Bitter Orange) Peel Extract

A supplier reports that its Citrus Aurantium Amara (Bitter Orange) Peel Extract products contain no more than 20 ppm heavy metals (one product not more than 10 ppm) and no more than 2 ppm arsenic.[5]

Citrus Aurantium Dulcis (Orange) Peel Wax

According to data provided by a supplier of Citrus Aurantium Dulcis (Orange) Peel Wax, 1,4-Dioxane, ethylene oxide, solvents (e.g., benzol), nitrosamines and free amines were not present in the supplier's product.[7] Heavy metals, pesticides, and polycyclic aromatic hydrocarbons were absent or present at very low concentrations (detail not provided). Low concentrations of fragrance allergens were present (detail not provided).

Citrus Unshiu Peel Extract

According to a supplier, a commercial product containing 0.5% Citrus Unshiu Peel Extract (dry) contains < 2.5 ppm (detection limit) allergens, < 1 ppm heavy metals, < 5 ppm (detection limit) formaldehyde, < 0.04 ppm (detection limit) pesticides, and < 10 ppm (detection limit) ethanol.[9] An analysis of just the ingredient Citrus Unshiu Peel Extract found allergens and ethanol to be less than detection limits.

Another supplier reports that its Citrus Unshiu Peel Extract products contain no more than 20 ppm heavy metals (a few products were no more than 10 ppm) and no more than 2 ppm arsenic (one products was no more than 1 ppm).[5]

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 the 2016 VCRP data, Citrus Limon (Lemon) Peel Extract has the most reported uses with a total of 150; more than half are in rinse-off preparations (e.g. non-coloring hair conditioners, hair shampoos, and skin cleansing preparations; Table 9).[12] Citrus Paradisi (Grapefruit) Peel Extract has the second greatest number of overall uses with a total of 61; more than half are in skin care preparations. The results of the concentration of use survey conducted in 2016 by the Council indicate Citrus Aurantium Dulcis (Orange) Peel Powder has the highest reported maximum concentration of use; it is used at up to 2% in skin cleansing preparations.[13] The highest reported maximum concentration of use in a leave-on product is 1.9% in a lipstick for Citrus Aurantium Dulcis (Orange) Peel Wax.

Table 10 lists all *Citrus* peel-derived ingredients not reported to be in use based on the VCRP data or the results of the Council concentration of use survey.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided. For example, Citrus Aurantium Amara (Bitter Orange) Peel Wax is reported to be used in 5 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, Citrus Aurantium Amara (Bitter Orange) Peel was not reported in the VCRP database to be in use, but the industry survey indicated that it is used at concentrations up to 0.2%. It should be presumed that Citrus Aurantium Amara (Bitter Orange) Peel 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, Citrus Aurantium Dulcis (Orange) Peel Wax is used at 1.9% in a lipstick and Citrus Aurantium Amara (Bitter Orange) Peel is used at 0.2% in personal cleanliness products. Additionally, some of these ingredients were reported to be used in fragrance preparations, hair sprays, skin care preparation sprays, and face powders and could possibly be inhaled. For example, Citrus Aurantium Dulcis (Orange) Peel Extract was reported to be used in a moisturizing product at a maximum concentration of 0.15% and Citrus Grandis (Grapefruit) Peel Extract was reported to be used in face powders at up to 0.1%. 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.[14-17] 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.[15,16] 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.[18-20]

The *Citrus* ingredients described in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU); however, furocoumarins are prohibited from use in cosmetics except for normal content in natural essences and in sun protection and bronzing products where the content shall be below 1 mg/kg.[21]

The International Fragrance Association (IFRA) has issued standards for *Citrus* oils and other furocoumarin-containing essential oils.[22] Finished products that are applied to the skin, excluding rinse-off products like bath preparations and soaps, must not contain more than 0.0015% or 15 ppm 5-MOP. This equates to a level of 0.0075% or 75 ppm in a fragrance compound when used at 20% in a consumer product that is applied to the skin. If the level of 5-MOP has not been determined, limits specified for individual oils should be observed, and when such oils are used in combination with other phototoxic constituent containing ingredients, the potential for an additive effect should be considered and use levels should be reduced accordingly.

An IFRA standard also has been issued for 7-methoxycoumarin, which is prohibited for use in fragrance compounds.[23] Based on established maximum levels of this substance from commercially-available natural sources (like essential oils, extracts and absolutes), IFRA has determined that exposure to 7-methoxycoumarin from the use of these oils and extracts is acceptable if the level of 7-methoxycoumarin in the finished product does not exceed 100 ppm.

Non-Cosmetic

The essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from the following *Citrus* plant sources are generally recognized as safe (GRAS) for their intended use in foods for human consumption: *Citrus aurantifolia* (lime); *Citrus aurantium* (bergamot); *Citrus aurantium* (bitter orange; the flowers and peel); *Citrus limon* (lemon); *Citrus paradisi* (grapefruit); *Citrus reticulata* (tangerine); *Citrus reticulata blanco* (mandarin); *Citrus sinensis* (orange; the leaf, flowers, and peel) and citrus peels (species not specified) (21CFR182.20). These essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of these *Citrus* plant sources are GRAS for their intended use in animal drugs, feeds, and related products (21CFR582.20).

Citrus aurantium amara (bitter orange) and extracts of its dried fruit and peel have been used in traditional Western medicines and in Chinese and Japanese herbal medicines.[24]

TOXICOKINETICS

No relevant published toxicokinetics studies on *Citrus* peel-derived ingredients were identified in a literature search for these ingredients and no unpublished data were submitted; these types of data are not expected since these botanical ingredients are mixtures of many constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity

Some of the *Citrus* ingredients in this assessment are foods, and the daily exposure from consumption would result in a much larger systemic dose than that resulting from use in cosmetic products. Also, as noted earlier, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from some *Citrus* peels are GRAS for their intended use in foods for human and animal consumption according to the FDA. Thus, the systemic toxicity potential of *Citrus* peel-derived ingredients via oral exposure is not addressed further in this report. The safety focus of use of these *Citrus* ingredients as cosmetic ingredients is on the potential for irritation and sensitization from topical exposure.

Repeated Dose Toxicity

No relevant published repeated dose toxicity studies on *Citrus* peel-derived ingredients were identified in a literature search and no unpublished data were submitted.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No relevant published reproductive and developmental studies on C*itrus* peel-derived ingredients were identified in a literature search and no unpublished data were submitted.

GENOTOXICITY

Citrus Reticulata (Tangerine) Peel Extract

A formulation containing 3% Citrus Reticulata (Tangerine) Peel Extract was not genotoxic in a reverse mutation assay (no further details provided).[25]

CARCINOGENICITY

No relevant published carcinogenicity studies on *Citrus* peel-derived ingredients were identified in a literature search and no unpublished data were submitted.

IRRITATION AND SENSITIZATION

Dermal Irritation

Dermal irritation studies are summarized in Table 11.[5,7,11,25-30] No irritation potential was observed for Citrus Aurantium Dulcis (Orange) Peel Wax (100%) or Citrus Reticulata (Tangerine) Peel Extract (3.0% in formulation) in in vitro tests. Citrus Aurantium Amara (Bitter Orange) Peel Extract was not irritating when tested up to 100% in rodents. In human subjects, no irritation was observed after topical exposure to Citrus Aurantium Dulcis (Orange) Peel wax (100%), Citrus Limon (Lemon) Peel Extract (0.1% in a moisturizer), and Citrus Unshiu Peel Extract (0.5% in formulation). Any irritation that was observed in tests with Citrus Aurantium Amara (Bitter Orange) Peel Extract (1.55% in formulation; 20% water solution) and Citrus Reticulata (Tangerine) Peel Extract (3.06% in formulation) resolved within 24-h of exposure.

Ocular Irritation

Citrus Aurantium Amara (Bitter Orange) Peel Extract

The ocular irritation potential of an undiluted formulation containing 2.0% Citrus Aurantium Amara (Bitter Orange) Peel Extract was studied in 3 albino rabbits.[28] The test material was instilled into the conjunctival sac of one eye and the other eye served as a control. Eyes were observed for irritation at 0, 1, 24, 48, and 72 h post-instillation. Redness was observed in the conjunctiva immediately after instillation, but not at later time points. No inflammatory signs were observed in the iris or cornea. The test material was considered almost non-irritating.

Citrus Limon (Lemon) Peel Extract

In an Epiocular™ tissue equivalent in vitro assay, a moisturizer containing 0.1% Citrus Limon (Lemon) Peel Extract tested neat at pH 5.5 was not predicted to be an ocular irritant.[31]

Citrus Reticulata (Tangerine) Peel Extract

In an in vitro assay using the neutral red release method on SIRC cell lines, 3.0% Citrus Reticulata (Tangerine) Peel Extract in formulation was classified as having relatively low cytotoxicity.[25]

Sensitization

Dermal sensitization studies are summarized in Table 12.[5,8,25,28,32-37] No sensitization was observed in guinea pigs exposed to Citrus Aurantium Amara (Bitter Orange) Peel Extract (2.0% in formulation). Citrus Aurantifolia (Lime) Peel Extract (2.14% in a face and neck product), Citrus Aurantium Dulcis (Orange) Peel Wax (1.9% in a lipstick), Citrus Grandis (Grapefruit) Peel Extract (up to 0.5% in formulation), Citrus Reticulata (Tangerine) Peel Extract (up to 3.0% in formulation), and Citrus Unshiu Peel Extract (up to 100%) were not dermal irritants or sensitizers in human repeated insult patch tests (HRIPTs).

Phototoxicity and Photosensitization

Phototoxicity and photosensitization studies are presented in Table 13.[25,28,38-42] No photo irritation was observed in an in vitro study of Citrus Reticulata (Tangerine) Peel Extract (3.0% in formulation). Citrus Auratnium Amara (Bitter Orange) Peel Extract (2.0% in formulation) did not induce photo irritation or photosensitization in guinea pigs. Undiluted lemon peel juice produced phototoxic reactions in several rat studies. In humans, Citrus Aurantium Dulcis (Orange) Peel wax (100%) was not phototoxic, but undiluted sweet orange peel produced phototoxic reactions.

Occupational Exposure

In a retrospective study (2001-2010) of professional food handlers in Denmark, 8.5% (16/188) of the patients had positive skin prick test reactions to orange peel and 7.9% (15/191) of the patients had positive skin prick test reactions to lemon peel.[43]

SUMMARY

The 47 *Citrus* peel-derived ingredients described in this report are reported to function in cosmetics primarily as skin conditioning agents. Botanical ingredients such as those derived from the genus *Citrus* are composed of hundreds of constituents, some of which have the potential to cause toxic effects; for example, bergapten (aka 5-methoxypsoralen or 5-MOP) is a naturally-occurring, phototoxic furanocoumarin (psoralen) in *Citrus*. CIR reviewed the information available on the potential toxicity of each *Citrus* peel-derived ingredient as a whole, complex substance. Except for specific constituents of concern that the Panel has identified, CIR is not reviewing the potential toxicity of the individual constituents of the *Citrus* peels from which the ingredients in this report are derived.

Citrus Limon (Lemon) Peel Extract has the most reported uses of the ingredients in this report in cosmetic products, with a total of 150; more than half of the uses are in rinse-off preparations (e.g., non-coloring hair conditioners, hair shampoos, and skin cleansing preparations). Citrus Paradisi (Grapefruit) Peel Extract has the second greatest number of overall uses reported, with a total of 61; more than half of the uses are in skin care preparations. The results of the concentration of use survey conducted in 2016 by the Council indicate Citrus Aurantium Dulcis (Orange) Peel Powder has the highest reported maximum concentration of use; it is used at up to 2% in skin cleansing preparations. The highest reported maximum concentration of use in a leave-on product is 1.9% in a lipstick for Citrus Aurantium Dulcis (Orange) Peel Wax.

Under the rules governing cosmetic products in the European Union, *Citrus*-derived ingredients must have furocoumarin content below 1 mg/kg in sun-protection and bronzing products. IFRA also has issued standards for *Citrus* oils and other furocoumarin-containing essential oils. Finished products that are applied to the skin, excluding rinse-off products like bath preparations and soaps, must not contain more than 0.0015% or 15 ppm 5-MOP. If the level of 5-MOP has not been determined, limits specified for individual oils should be observed, and when these oils are used in combination with other phototoxic ingredients, the potential additive effect should be taken into consideration and use levels in the final formulation should be carefully monitored.

Some of the *Citrus* ingredients in this assessment are found in foods, and the daily exposure from food use would result in a much greater systemic dose than that resulting from exposure to cosmetic products. Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from some citrus fruits are GRAS for their intended use in foods for human and animal consumption according to the FDA.

A formulation containing 3% Citrus Reticulata (Tangerine) Peel Extract was not genotoxic in a reverse mutation assay (no further details provided).

No irritation potential was observed for Citrus Aurantium Dulcis (Orange) Peel Wax (100%) or Citrus Reticulata (Tangerine) Peel Extract (3.0% in formulation) in in vitro tests. Citrus Aurantium Amara (Bitter Orange) Peel Extract was not irritating when tested up to 100% in rodents. In human subjects, no irritation was observed after topical exposure to Citrus Aurantium Dulcis (Orange) Peel wax (100%), Citrus Limon (Lemon) Peel Extract (0.1% in a moisturizer), and Citrus Unshiu Peel Extract (0.5% in formulation). Any irritation that was observed in tests with Citrus Aurantium Amara (Bitter Orange) Peel Extract (1.55% in formulation; 20% water solution) and Citrus Reticulata (Tangerine) Peel Extract (3.06% in formulation) resolved within 24-h of exposure.

In in vitro assays, Citrus Limon (Lemon) Peel Extract (0.1% in a moisturizer) and Citrus Reticulata (Tangerine) Peel Extract (3.0% in formulation) did not predict ocular irritation. An undiluted formulation containing 2.0% Citrus Aurantium Amara (Bitter Orange) Peel Extract was almost non-irritating in 3 albino rabbit's eyes.

No sensitization was observed in guinea pigs exposed to Citrus Aurantium Amara (Bitter Orange) Peel Extract (2.0% in formulation). Citrus Aurantifolia (Lime) Peel Extract (2.14% in a face and neck product), Citrus Aurantium Dulcis (Orange) Peel Wax (1.9% in a lipstick), Citrus Grandis (Grapefruit) Peel Extract (up to 0.5% in formulation), Citrus Reticulata (Tangerine) Peel Extract (up to 3.0% in formulation), and Citrus Unshiu Peel Extract (up to 100%) were not dermal irritants or sensitizers in HRIPTs.

No photo irritation was observed in an in vitro study of Citrus Reticulata (Tangerine) Peel Extract (3.0% in formulation). Citrus Auratnium Amara (Bitter Orange) Peel Extract (2.0% in formulation) did not induce photo irritation or photosensitization in guinea pigs. Undiluted lemon peel juice produced phototoxic reactions in several rat studies. In humans, Citrus Aurantium Dulcis (Orange) Peel wax (100%) was not phototoxic, but undiluted sweet orange peel produced phototoxic reactions.

In a retrospective study of professional food handlers in Denmark, 8.5% (16/188) of the patients had positive skin prick test reactions to orange peel and 7.9% (15/191) of the patients had positive skin prick test reactions to lemon peel.

No relevant published studies on the toxicokinetics, repeated dose toxicity, reproductive and development toxicity, or carcinogenicity of *Citrus* peel-derived ingredients were discovered and no unpublished data were submitted to address these topics.

DISCUSSION

To be determined…

CONCLUSION

To be determined…

TABLES

Table 1. Definitions and functions of *Citrus* peel-derived ingredients.[1]

Ingredient	Definition	Function
Citrus Aurantifolia (Lime) Peel	Citrus Aurantifolia (Lime) Peel is the peel obtained from *Citrus aurantifolia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Peel Extract CAS No. 90063-52-8	Citrus Aurantifolia (Lime) Peel Extract is the extract of the peel of *Citrus aurantifolia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Peel Powder	Citrus Aurantifolia (Lime) Peel Powder is the powder obtained from the dried, ground peel of *Citrus aurantifolia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Peel Water	Citrus Aurantifolia (Lime) Peel Water is the aqueous solution of the steam distillates obtained from the peel of *Citrus aurantifolia.*	Fragrance Ingredients
Citrus Aurantium Amara (Bitter Orange) Peel	Citrus Aurantium Amara (Bitter Orange) Peel is the peel of *Citrus aurantium amara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Peel Extract CAS No. 72968-50-4	Citrus Aurantium Amara (Bitter Orange) Peel Extract is the extract of the peel of *Citrus aurantium amara.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Peel Powder	Citrus Aurantium Amara (Bitter Orange) Peel Powder is the powder obtained from the dried, ground peel of *Citrus aurantium amara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Bergamia (Bergamot) Peel Water	Citrus Aurantium Bergamia (Bergamot) Peel Water is an aqueous solution of the steam distillate obtained from the peel of *Citrus aurantium bergamia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Peel Extract	Citrus Aurantium Dulcis (Orange) Peel Extract is the extract of the peel of *Citrus aurantium dulcis.*	Binders; Emulsion Stabilizers; Skin-Conditioning Agents - Miscellaneous; Viscosity Increasing Agents - Aqueous
Citrus Aurantium Dulcis (Orange) Peel Powder	Citrus Aurantium Dulcis (Orange) Peel Powder is the powder obtained from the dried, ground peel of *Citrus aurantium dulcis.*	Absorbents
Citrus Aurantium Dulcis (Orange) Peel Wax	Citrus Aurantium Dulcis (Orange) Peel Wax is a wax obtained from the peel of the orange, *Citrus aurantium dulcis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Sinensis Peel Extract	Citrus Aurantium Sinensis Peel Extract is the extract of the peel of *Citrus aurantium sinenesis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Tachibana Peel Extract	Citrus Aurantium Tachibana Peel Extract is the extract of the peel of *Citrus aurantium tachibana.*	Skin-Conditioning Agents - Humectant
Citrus Depressa Peel Extract	Citrus Depressa Peel Extract is the extract of the peel of *Citrus depressa.*	Skin-Conditioning Agents - Humectant
Citrus Depressa Peel Powder	Citrus Depressa Peel Powder is the powder obtained from the dried, ground peel of *Citrus depressa.*	Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Peel	Citrus Grandis (Grapefruit) Peel is the peel of *Citrus grandis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Peel Extract	Citrus Grandis (Grapefruit) Peel Extract is the extract of the peel of *Citrus grandis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Peel Powder	Citrus Grandis (Grapefruit) Peel Powder is the powder obtained from the dried, ground peel of *Citrus grandis.*	Absorbents
Citrus Hassaku/Natsudaidai Peel Powder	Citrus Hassaku/Natsudaidai Peel Powder is the powder obtained from the dried, ground peel of a hybrid of *Citrus hassaku* and *Citrus natsudaidai.*	Flavoring Agents
Citrus Iyo Peel Extract	Citrus Iyo Peel Extract is the extract of the peel of *Citrus iyo.*	Skin-Conditioning Agents - Humectant
Citrus Iyo Peel Water	Citrus Iyo Peel Water is an aqueous solution of the steam distillate obtained from the peel of *Citrus iyo.*	Skin-Conditioning Agents - Humectant
Citrus Jabara Peel Extract	Citrus Jabara Peel Extract is the extract of the peel of *Citrus jabara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Jabara Peel Powder	Citrus Jabara Peel Powder is the powder obtained from the dried, ground peels of *Citrus jabara.*	Fragrance Ingredients
Citrus Jabara Peel Water	Citrus Jabara Peel Water is an aqueous solution of the steam distillate obtained from the peel of *Citrus jabara*.	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Junos Peel Extract	Citrus Junos Peel Extract is the extract of the peel of *Citrus junos.*	Skin-Conditioning Agents - Miscellaneous
Citrus Junos Peel Powder	Citrus Junos Peel Powder is the dried, ground powder obtained from the peels of *Citrus junos.*	Fragrance Ingredients
Citrus Junos Peel Water	Citrus Junos Peel Water is an aqueous solution of the steam distillate obtained from the peel of *Citrus junos.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Peel CAS No. 84929-31-7; 85085-28-5; 92346-89-9	Citrus Limon (Lemon) Peel is the peel of *Citrus limon.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Peel Extract CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Peel Extract is the extract of the peel of *Citrus limon.*	Skin Protectants; Skin-Conditioning Agents - Emollient
Citrus Limon (Lemon) Peel Powder CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Peel Powder is the powder obtained from the dried, ground peel of *Citrus limon.*	Absorbents

Table 1. Definitions and functions of *Citrus* peel-derived ingredients.[1]

Ingredient	Definition	Function
Citrus Limon (Lemon) Peel Water CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Peel Water is an aqueous solution of the steam distillate obtained from the peel of *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Peel Wax CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Peel Wax is the wax obtained from the peel of *Citrus limon.*	Skin-Conditioning Agents - Occlusive
Citrus Natsudaidai Peel Extract	Citrus Natsudaidai Peel Extract is the extract of the peel of *Citrus natsudaidai*.	Skin-Conditioning Agents - Humectant
Citrus Nobilis (Mandarin Orange) Peel Extract CAS No. 90063-83-5	Citrus Nobilis (Mandarin Orange) Peel Extract is the extract of the peel of *Citrus nobilis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Nobilis (Mandarin Orange) Peel Powder	Citrus Nobilis (Mandarin Orange) Peel Powder is the powder obtained from the dried, ground peel of *Citrus nobilis.*	Abrasives
Citrus Paradisi (Grapefruit) Peel Extract CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Peel Extract is the extract obtained from the peel of *Citrus paradisi*.	Skin-Conditioning Agents - Miscellaneous
Citrus Reticulata (Tangerine) Peel Extract	Citrus Reticulata (Tangerine) Peel Extract is the extract of the peel of *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Citrus Reticulata (Tangerine) Peel Powder	Citrus Reticulata (Tangerine) Peel Powder is the powder obtained from the dried, ground peel of *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Citrus Shunkokan Peel Extract	Citrus Shunkokan Peel Extract is the extract of the peel of *Citrus shunkokan.*	Antioxidants
Citrus Sunki Peel Extract	Citrus Sunki Peel Extract is the extract of the peel of *Citrus sunki.*	Humectants; Skin Protectants; Skin-Conditioning Agents - Humectant
Citrus Tachibana/Reticulata Peel Powder	Citrus Tachibana/Reticulata Peel Powder is the powder obtained from the finely ground peel of a hybrid of *Citrus tachibana* and *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Citrus Tangelo Peel Powder	Citrus Tangelo Peel Powder is the powder obtained from the dried, ground peel of *Citrus tangelo.*	Flavoring Agents
Citrus Tangerina (Tangerine) Peel	Citrus Tangerina (Tangerine) Peel is the peel of the tangerine, *Citrus tangerina.*	Abrasives
Citrus Tangerina (Tangerine) Peel Extract	Citrus Tangerina (Tangerine) Peel Extract is the extract of the peel of *Citrus tangerina.*	Cosmetic Astringents
Citrus Unshiu Peel Extract	Citrus Unshiu Peel Extract is the extract of the peel of *Citrus unshiu.*	Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu Peel Powder	Citrus Unshiu Peel Powder is the powder of the dried, ground peel of *Citrus unshiu.*	Fragrance Ingredients
Citrus Unshiu Peel Water	Citrus Unshiu Peel Water is the aqueous solution of the steam distillates obtained from the peel of *Citrus unshiu.*	Skin Protectants

Table 2. Citrus-ingredients that potentially function solely as fragrance ingredients.

Citrus Aurantifolia (Lime) Peel Water	Citrus Junos Peel Powder
Citrus Jabara Peel Powder	Citrus Unshiu Peel Powder

Table 3. Review of *Citrus* genus species names.[4]

Genus Species Name Used in INCI Names (common name)	Accepted Genus Species Name
Citrus aurantifolia (lime)	*Citrus x aurantifolia*
Citrus aurantium amara (bitter orange)	*Citrus x aurantium*
Citrus aurantium bergamia (bergamot)	*Citrus x limon*
Citrus aurantium dulcis (orange)	*Citrus x aurantium*
Citrus clementina (clementine)	*Citrus x aurantium*
Citrus depressa	*Citrus reticulata*
Citrus glauca	*Citrus glauca*
Citrus grandis (grapefruit or pomelo)	*Citrus maxima* or *Citrus x aurantium*
Citrus hassaku	*Citrus medica x Citrus x aurantium*
Citrus iyo	*Citrus x aurantium*
Citrus jabara	Not known
Citrus japonica (kumquat)	*Citrus japonica*
Citrus junos	*Citrus x junos*
Citrus limon (lemon)	*Citrus x limon*
Citrus madurensis	*Citrus x microcarpa*
Citrus medica vulgaris	*Citrus reticulata*
Citrus natsudaidai	*Citrus x aurantium*
Citrus nobilis (mandarin orange)	*Citrus reticulata*
Citrus paradisi (grapefruit)	*Citrus x aurantium*
Citrus reticulata (tangerine)	*Citrus reticulata*
Citrus shunkokan	Cultivated hybrid
Citrus sinensis (orange)	*Citrus x aurantium*
Citrus sphaerocarpa	Cultivated hybrid
Citrus sudachi	*Citrus reticulata*
Citrus tachibana	Not listed
Citrus tamurana	Cultivated hybrid
Citrus tangelo (tangelo)	*Citrus x aurantium*
Citrus tangerine (tangerine)	*Citrus reticulata*
Citrus tankan	*Citrus reticulata*
Citrus unshiu	*Citrus reticulata*

Table 4. Physical and chemical properties of Citrus Aurantium Dulcis (Orange) Peel Wax.

Property	Description	Reference
	Citrus Aurantium Dulcis (Orange) Peel Wax	
Color	light reddish-brown to orange	11
Odor	mild to very low characteristic	11
Appearance	semi-solid	11
molecular weight	> 400	7
melting point	45-57 ºC refined; 35-50 ºC deodorized	11
congealing point	45-55 ºC refined; 30-45 ºC deodorized	11
acid value	8-20 refined; 10-20 deodorized	11
saponification value	70-110 refined and deodorized	11
hydroxyl value	20-50 refined; 10-40 deodorized	11
log P	> 3.5	7
UV absorbance	210-240 nm	11

Table 5. Constituents that are known contact allergens in humans, according to the SCCS.

Constituent	**categorized according to number of patients reacting positively and to the number of patients tested (>1000 patients tested, unless indicated as r.t., i.e., rarely tested)** [10]
β-caryophyllene	≤10 (oxidized and non-oxidized)
carvone	≤10 (r.t.)
citral	101 to 1000
citronellol	11-100
coumarin	101 to 1000
farnesol	101 to 1000
geraniol	101 to 1000
linalyl acetate	≤10
α- and β-pinene	11-100
(DL)-limonene	11-100 (non-oxidized); 101 to 1000 (oxidized)
tepineol (mixture of isomers)/α-terpineol	≤10
terpinolene	11-100

Table 6. Volatile constituents from *Citrus aurantifolia* peel extract as analyzed by gas chromatography-mass spectrometry.[44]

Constituent	%
tetrahydro-2-methyl-2*H*-pyran	0.72
4-hexen-3-one	0.51
3-methyl-3-penten-2-one	0.33
3-hexen-2-one	0.48
2,3-dimethyl-2,3-butanediol	1.67
resorcinol	3.65
p-cymene	0.36
1-methoxycyclohexene	8.00
linalool oxide	1.18
crysantenile acetate	0.40
corylone	6.93
terpinen-4-ol	1.66
α-terpineol	5.97
3-nethyl-1,2-cyclopentanedione	8.27
3,7-dimethyl-(*Z*)-2,6-octadienal	1.09
carvone	0.88
geraniol	1.15
citral	2.21
1,8-dimethyl-4-(1-methylethyl)-spiro[4.5]dec-8-en-7-one	0.56
geranyl formate	0.70
oleic acid	0.69
7-methyl-(*Z*)-8-tetradecen-1-ol acetate	2.83
geranyl acetone	1.84
bergamotene	1.00
(*Z*)-8-methyl-9-tetradecenoic acid	1.24
trans-α-bisabolene	1.02
caryophyllene oxide	3.02
spathulenol	1.95
umbelliferone	4.36
(*Z*)-11(13,14-epoxy)tetradecen-1-ol acetate	0.59
trans-phytol	0.22
1-heptatriacontanol	0.42
versalide	0.51
methyl palmitate	0.29
palmitic acid	6.89
5,7-dimethoxycoumarin	15.80
5-methoxypsoralen	1.14
linoleic acid	0.96
tricosane	0.31
5,8-dimethoxypsoralen	6.08
pentacosane	0.46
tetracosanal	0.70
octacosane	0.39
nonacosane	0.50

Table 7. Primary chemical composition of Citrus Aurantium Dulcis (Orange) Peel wax by percent. [11]

unsaturated monoesters, hydroxyl-monoesters, and monoesters	50-65
free fatty acids C12-C26	6-15
hydrocarbons C21- C33	8-15
sterol esters	5-18
free sterols	4-8
free alcohols	2-7
carotenoids	0.5-2
glycolipids	0.5-2
phospholipids	0.5-2
flavonoids	0.2-1
fragrance compounds, natural	0.2-0.8

Table 8. Constituents of Citrus Aurantium Dulcis (Orange) Peel wax with color or aroma characteristics. [11]

color compounds (carotenoids)	**aroma compounds (alcohols, aldehydes, ketones, esters, and hydrocarbons)**
phytoene	octan-1-ol
phytolluene	nonanal
α-carotene	linalool
β-carotene	*p*-mentha-2,8-dien-1-ol
γ-carotene	sabinol
δ-carotene	isopulegol
lycopene	4-methylacetophenone
cryptoxanthin	α-terpineol
hydroxy-α-carotene	ethyl ocatanoate
cyroflevin	decanal
rubiflavin	carveol
rubixanthin	neral
lutein	carvone
canthaxanthin	pipertone
zeaxanthin	geranial
antheraxanthin	perillyl alcohol
violaxanthin	α-cubebene
luteoxanthin	hexyl hexanoate
auroxanthin	β-elemene
β-citraurin	β-famesene
liavoxanthin	caryophyllene
sintaxanthin	γ-selinene
xanthophylls	β-copaene
	δ-cadinene
	bisabolene
	valencene

Table 9. Frequency and concentration of use according to duration and type of exposure for *Citrus* peel-derived ingredients.[12,13]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Citrus Aurantifolia (Lime) Peel Extract		**Citrus Aurantifolia (Lime) Peel Powder**		**Citrus Aurantium Amara (Bitter Orange) Peel**		**Citrus Aurantium Amara (Bitter Orange) Peel Extract[d]**	
Totals[†]	**15**	**0.0000013-1.1**	**3**	**0.06**	**NR**	**0.002-0.2**	**49**	**0.0000016-0.05**
Duration of Use								
Leave-On	13	0.0000013-1.1	2	0.06	NR	0.002-0.16	32	0.00002-0.018
Rinse Off	2	0.0001-0.006	1	NR	NR	0.002-0.2	16	0.0000016-0.05
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	1	0.002
Exposure Type								
Eye Area	NR	0.00005	NR	NR	NR	NR	2	0.00006-0.018
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	0.0002
Incidental Inhalation-Spray	6[a]; 2[b]	0.0005-0.05[a]	NR	NR	NR	NR	1; 13[a]; 10[b]	0.001-0.002; 0.002[a]
Incidental Inhalation-Powder	2[b]	NR	NR	0.06[c]	NR	0.002-0.16[c]	10[b]	0.001; 0.0001-0.005[c]
Dermal Contact	15	0.00005-1.1	3	0.06	NR	0.002-0.2	39	0.0000016-0.05
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.0000013-0.006	NR	NR	NR	0.002	10	0.00001-0.0063
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	0.00002-0.0001
Mucous Membrane	NR	0.0021	NR	NR	NR	0.2	2	0.0000016-0.0032
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Aurantium Amara (Bitter Orange) Peel Powder[d]		**Citrus Aurantium Amara (Bitter Orange) Peel Wax[d]**		**Citrus Aurantium Bergamia (Bergamot) Peel Water**		**Citrus Aurantium Dulcis (Orange) Peel Extract[e]**	
Totals[†]	**2**	**1.6**	**5**	**NR**	**NR**	**0.0001**	**56**	**0.000002-0.25**
Duration of Use								
Leave-On	NR	NR	3	NR	NR	NR	28	0.000002-0.25
Rinse Off	2	1.6	2	NR	NR	0.0001	27	0.0000025-0.14
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	1	0.0025
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	1	0.0005
Incidental Ingestion	NR	NR	3	NR	NR	NR	2	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	14[a]; 4[b]	0.0005-0.15; 0.00001-0.0005[a]
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	4[b]	0.028; 0.000002-0.02[c]
Dermal Contact	2	1.6	1	NR	NR	NR	35	0.000002-0.25
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1	NR	NR	0.0001	19	0.00001-0.03
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	4	NR	NR	NR	15	0.0000025-0.14
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 9. Frequency and concentration of use according to duration and type of exposure for *Citrus* peel-derived ingredients.[12,13]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Citrus Aurantium Dulcis (Orange) Peel Powder		**Citrus Aurantium Dulcis (Orange) Peel Wax[f]**		**Citrus Aurantium Tachibana Peel Extract[g]**		**Citrus Depressa Peel Extract**	
Totals[†]	**11**	**0.4-2**	**9**	**0.5-1.9**	**8**	**0.00016-0.0032**	**NR**	**0.0014**
Duration of Use								
Leave-On	5	NR	9	0.5-1.9	7	0.0016-0.0032	NR	0.0014
Rinse Off	6	0.4-2	NR	NR	1	0.00016-0.0032	NR	0.0014
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	1	0.5-1.9	NR	NR	NR	NR
Incidental Inhalation-Spray	3[b]	NR	4[a]	NR	1[a]; 3[b]	0.0016	NR	NR
Incidental Inhalation-Powder	1; 3[b]	NR	NR	1[c]	3[b]	0.0016-0.0032[c]	NR	0.0014[c]
Dermal Contact	11	0.4-2	5	1	8	0.00016-0.0032	NR	0.0014
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	3	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.4-0.5	1	0.5-1.9	NR	0.00016	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Grandis (Grapefruit) Peel Extract[h]		**Citrus Jabara Peel Extract**		**Citrus Junos Peel Extract[i]**		**Citrus Junos Peel Powder**	
Totals[†]	**49**	**0.0000013-0.5**	**NR**	**0.0037-0.037**	**1**	**0.0012-0.036**	**NR**	**0.002**
Duration of Use								
Leave-On	38	0.0000013-0.5	NR	0.0037-0.037	1	0.036	NR	0.002
Rinse Off	11	0.0001-0.023	NR	NR	NR	0.0012	NR	0.002
Diluted for (Bath) Use	NR	0.0005	NR	NR	NR	0.0012	NR	NR
Exposure Type								
Eye Area	3	0.01-0.5	NR	NR	1	0.036	NR	NR
Incidental Ingestion	1	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	14[a]; 9[b]	0.0095-0.01; 0.0009[b]	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	9[b]	0.1; 0.0009[b]; 0.0009-0.05[c]	NR	0.037; 0.0037[c]	NR	NR	NR	0.002[c]
Dermal Contact	45	0.0002-0.5	NR	0.0037-0.037	1	0.0012-0.036	NR	0.002
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	0.0000013-0.0002	NR	NR	NR	0.0012	NR	0.002
Hair-Coloring	2	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.0005-0.015	NR	NR	NR	0.0012	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 9. Frequency and concentration of use according to duration and type of exposure for *Citrus* peel-derived ingredients.[12,13]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Citrus Limon (Lemon) Peel[j]		**Citrus Limon (Lemon) Peel Extract**		**Citrus Limon (Lemon) Peel Powder**		**Citrus Limon (Lemon) Peel Wax**	
Totals[†]	**4**	**0.4**	**150**	**0.000005-0.14**	**6**	**0.5**	**1**	**NR**
Duration of Use								
Leave-On	3	NR	62	0.000005-0.14	4	NR	NR	NR
Rinse Off	1	0.4	87	0.000008-0.057	2	0.5	1	NR
Diluted for (Bath) Use	NR	NR	1	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	2	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	3	0.000008-0.0025	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]; 1[b]	NR	2; 22[a]; 20[b]	0.000033-0.0005; 0.000008-0.0006 [a]	1[b]	NR	NR	NR
Incidental Inhalation-Powder	1[b]	NR	20[b]	0.0001-0.14[c]	1[b]	NR	NR	NR
Dermal Contact	4	0.4	89	0.000005-0.14	5	0.5	1	NR
Deodorant (underarm)	NR	NR	1[a]	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	55	0.000033-0.0031	NR	NR	NR	NR
Hair-Coloring	NR	NR	2	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	1	NR	NR	NR
Mucous Membrane	NR	0.4	17	0.000008-0.0051	1	0.5	1	NR
Baby Products	NR	NR	1	NR	NR	NR	NR	NR

	Citrus Nobilis (Mandarin Orange) Peel Extract		**Citrus Paradisi (Grapefruit) Peel Extract**		**Citrus Reticulata (Tangerine) Peel Extract[k]**		**Citrus Tangerina (Tangerine) Peel Extract**	
Totals[†]	**19**	**0.0000005-0.05**	**61**	**NR**	**36**	**0.00029-0.01**	**2**	**0.0000048**
Duration of Use								
Leave-On	8	0.0000005-0.025	39	NR	28	0.00048-0.01	1	NR
Rinse Off	11	0.000025-0.05	21	NR	8	0.00029-0.0012	1	0.0000048
Diluted for (Bath) Use	NR	0.0005-0.0025	1	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	1	NR	5	0.002	NR	NR
Incidental Ingestion	NR	NR	3	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	4[a]; 2[b]	0.0001-0.0005	23[a]; 8[b]	NR	17[a]; 4[b]	0.00048[a]	1[a]	NR
Incidental Inhalation-Powder	2[b]	0.0025[c]	8[b]; 2[c]	NR	4[b]	0.0012-0.01[c]	NR	NR
Dermal Contact	16	0.0000005-0.025	51	NR	36	0.00029-0.01	1	NR
Deodorant (underarm)	NR	0.0005	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	3	0.0001-0.05	7	NR	NR	NR	1	0.0000048
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	0.0001-0.0025	12	NR	6	0.00029	NR	NR
Baby Products	NR	NR	3	NR	NR	NR	NR	NR

Table 9. Frequency and concentration of use according to duration and type of exposure for *Citrus* peel-derived ingredients.[12,13]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Citrus Unshiu Peel Extract[l]		**Citrus Unshiu Peel Powder**		**Orange Peel[m]**			
Totals[†]	**46**	**0.000002-0.094**	**NR**	**0.5**	**13**	**NR**		
Duration of Use								
Leave-On	31	0.00005-0.094	NR	NR	5	NR		
Rinse Off	14	0.000002-0.094	NR	NR	5	NR		
Diluted for (Bath) Use	1	0.03	NR	0.5	3	NR		
Exposure Type								
Eye Area	4	0.000002-0.002	NR	NR	NR	NR		
Incidental Ingestion	NR	0.00036	NR	NR	NR	NR		
Incidental Inhalation-Spray	9[a]; 15[b]	0.002	NR	NR	1[b]	NR		
Incidental Inhalation-Powder	15[b]	0.01; 0.0005-0.094[c]	NR	NR	1[b]	NR		
Dermal Contact	40	0.000002-0.094	NR	0.5	13	NR		
Deodorant (underarm)	NR	NR	NR	NR	NR	NR		
Hair - Non-Coloring	6	NR	NR	NR	NR	NR		
Hair-Coloring	NR	NR	NR	NR	NR	NR		
Nail	NR	NR	NR	NR	NR	NR		
Mucous Membrane	2	0.00036-0.03	NR	0.5	6	NR		
Baby Products	NR	NR	NR	NR	NR	NR		

NR = Not reported.

† 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.

[d.] Listed as Citrus Aurantium (Bitter Orange) in the VCRP database.

[e.] Includes uses listed under Citrus Sinensis (Sweet Orange) Peel Extract in the VCRP database.

[f.] Listed as Citrus Sinensis (Sweet Orange) Peel Wax and Orange Peel Wax in the VCRP database.

[g.] Listed as Citrus Tachibana (Tachibana Orange) Peel Extract and Citrus Tachibana Peel Extract in the VCRP database.

[h.] Listed as Citrus Grandis (Pomelo) Peel Extract in the VCRP database.

[i.] Listed as Citrus Junos (Xiaang Cheng) Peel Extract in the VCRP database.

[j.] Listed as Lemon Peel in the VCRP database.

[k] Listed as Citrus Reticulata (Mandarin Orange) Peel Extract in the VCRP database.

[l.] Listed as Citrus Unshiu (Satsuma Orange) Peel Extract in the VCRP database.

[m.] Not in the INCI dictionary. Included because of similarity.

Table 10. Ingredients that are not reported to be in use.

Citrus Aurantifolia (Lime) Peel Water
Citrus Aurantium Sinensis Peel Extract
Citrus Depressa Peel Powder
Citrus Grandis (Grapefruit) Peel
Citrus Grandis (Grapefruit) Peel Powder
Citrus Hassaku/Natsudaidai Peel Powder
Citrus Iyo Peel Extract
Citrus Iyo Peel Water
Citrus Jabara Peel Extract
Citrus Jabara Peel Water
Citrus Junos Peel Water
Citrus Limon (Lemon) Peel Water
Citrus Natsudaidai Peel Extract
Citrus Nobilis (Mandarin Orange) Peel Powder
Citrus Reticulata (Tangerine) Peel Powder
Citrus Shunkokan Peel Extract
Citrus Sunki Peel Extract
Citrus Tachibana/Reticulata Peel Powder
Citrus Tangelo Peel Powder
Citrus Tangerina (Tangerine) Peel
Citrus Unshiu Peel Water

Table 11. Dermal irritation studies for *Citrus* peel-derived ingredients.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
In Vitro					
Citrus Aurantium Dulcis (Orange) Peel Wax	100%	details not provided	MATEX in vitro toxicity testing system; details not provided	no irritation	7,11
Citrus Reticulata (Tangerine) Peel Extract	3.0% in formulation	human reconstructed epidermis	SkinEthic model according to OECD 439; no further details provided	no irritation	25
Animal					
Citrus Aurantium Amara (Bitter Orange) Peel Extract	10% and 100% undiluted solutions	3 rabbits; details not provided	primary skin irritation test; details not provided	no irritation	5
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0% in formulation, undiluted	3 guinea pigs; details not provided	primary skin irritation test on clipped skin; no further details provided	no irritation observed at 24, 48, or 72 h post-dosing	28
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0% in formulation, in 50% water solution	3 guinea pigs; details not provided	cumulative skin irritation test on clipped skin; animals dosed once a day for 2 weeks; animals observed daily	no irritation	28
Human					
Citrus Aurantium Amara (Bitter Orange) Peel Extract	1.55% in formulation, in 20% water solution	30 subjects	48 h patch test; occluded	slight erythema in 1 subject 1 h post-patch removal, no irritation observed 24 h post-patch removal	27
Citrus Aurantium Dulcis (Orange) Peel Wax	100%	details not provided	48 h patch test; details not provided	no irritation	7,11
Citrus Limon (Lemon) Peel Extract	0.1% in a moisturizer	30 subjects	14 day cumulative irritation patch test; 14 applications of ~23 h over 15 days; control materials distilled water and sodium lauryl sulfate; test area was 2 cm^2 and semi-occluded; 0.2 ml test material applied to each patch	no irritation	29
Citrus Reticulata (Tangerine) Peel Extract	3.06% in formulation	30 subjects	48 h patch test; occluded	slight erythema observed in 2 subjects and well-defined erythema observed in 1 subject 1 h post-patch removal; no irritation observed 24 h post-patch removal	26
Citrus Unshiu Peel Extract	0.5% in formulation	10 subjects	24 h single patch test; details not provided	no irritation	30

Table 12. Dermal sensitization studies for *Citrus* peel-derived ingredients.

Test Article	Concentration/Dose	Test Population	Procedure	Results	References
Animal					
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0% in formulation; undiluted	12 guinea pigs; no further details	sensitization study with adjuvant on clipped skin; occluded; no further details	no dermal sensitization	[28]
Human					
Citrus Aurantifolia (Lime) Peel Extract	2.14% in a face and neck product	109 subjects	modified HRIPT; test area was 2 cm^2 and semi-occluded; 150µl test material applied to each patch	no dermal irritation or sensitization	[33]
Citrus Aurantium Dulcis (Orange) Peel Wax	1.9% in a lipstick	33 sensitive skin subjects	4-week use test	no dermal irritation or sensitization	[35]
Citrus Aurantium Dulcis (Orange) Peel Wax	1.9% in a lipstick; undiluted	105 subjects	HRIPT; details not provided	no dermal irritation or sensitization	[36]
Citrus Grandis (Grapefruit) Peel Extract	0.1% in a face and neck product	209 subjects	modified HRIPT; test area was 2 cm^2 and semi-occluded; 200µl test material applied to each patch	no dermal irritation or sensitization	[32]
Citrus Grandis (Grapefruit) Peel Extract	0.5% in an eye product	55 subjects	HRIPT; details not provided	no dermal irritation or sensitization	[34]
Citrus Reticulata (Tangerine) Peel Extract	no provided	54 subjects	HRIPT; details not provided	no dermal irritation or sensitization	[8]
Citrus Reticulata (Tangerine) Peel Extract	3.0% in formulation; undiluted	56 subjects	HRIPT; semi-occluded; no further details	hypoallergenic	[25]
Citurs Unshiu Peel Extract	0.5%	50 subjects	HRIPT (Marzulli and Maibach method); occlusive patch; no further details	no dermal irritation or sensitization	[37]
Citrus Unshiu Peel Extract	10%	49 subjects	HRIPT; details not provided	no dermal irritation or sensitization	[5]
Citrus Unshiu Peel Extract	100% undiluted	54 subjects	HRIPT; details not provided	no dermal irritation or sensitization	[5]

Table 13. Photosensitization and phototoxicity studies.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			In-Vitro		
Citrus Reticulata (Tangerine) Peel Extract	3.0% in formulation	mouse fibroblasts	in vitro 3T3 NRU phototoxicity test according to OECD 432	no photo irritation	25
			Animal		
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0% in formulation; undiluted	5 guinea pigs; no further details	phototoxicity study on clipped skin; no further details	no photo irritation	28
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0% in formulation; undiluted	10 guinea pigs; no further details	photosensitization study with adjuvant on clipped skin; no further details	no photo sensitization	28
lemon fruit juice and lemon peel juice (Tahitian and Sicilian varieties)	undiluted; liberally applied	3 adult rats (strain not specified) per group	-rats were painted with fresh lemon fruit juice or lemon peel juice from 2 lemon varieties on depilated skin on the right back; left side was negative control with only sunlight exposure -rats were placed in plastic tubes with eight orifices to allow natural sunlight through - exposure to sunlight was 2.5, 5 , 7.5, or 10 min -experiment repeated with Tahitian variety lemon peel juice with sun block SPF 45, UVA and UVB -biopsies performed for each time period for histopathological studies and photodocumentation	-phytophotodermatitis observed after 48 h after exposure to both types of peel juice -no reactions observed to peel juice without sun exposure or to sun exposure alone -minimum exposure time of 2.5 min sufficient to induce phototoxic reaction, with longer exposures causes more intense reactions -histopathological studies showed epithelial time-dependent vacuolar degeneration -sunblock diminished reaction intensity, but did not prevent it	38
lemon peel juice (Tahitian variety)	undiluted; liberally applied	4 albino rats	-epilated right half of back of rats was sprayed with peel juice -one quadrant exposed to natural sunlight for 5 min and the other for 8 min; -left back served as control -biopsies taken after 1, 2, 3, 4, 5, 6, 24, 48, and 72 h from both sides	-normal epidermis observed for first 6 time intervals on both sides -after 24 h, treated area showed keratinocyte necrosis, cytoplasmic vacuolization and spongiosis in all rats, independent of exposure time -after 48 h, erythema evident, strong vacuolization observed that progressed to sub- or intraepidermal blisters -erythema persisted after 72 h at a lesser intensity -control side has isolated keratinocyte necrosis with only 8 min of exposure after 24 h, but after 48 h only slight spongiosis was observed which resolved by 72 h	39
lemon peel juice (Tahitian variety)	undiluted	4 adult rats (strain not specified)	-test material was applied to depilated skin on the right side of the animal's back, left side served as a control -animals exposed for 8 min to mid-day sunlight -biopsies performed immediately after induction and after 1 and 2 h and evaluated by transmission electron microscopy -at 24 and 48 h after induction, light microscopy performed on tissues to evaluate changes	-no histological changes observed on control sites -immediately after induction, keratinocyte cytoplasmatic vacuolization and membrane ruptures near vacuolization sties were observed -at 1 h after, desmosomal changes observed in addition to vacuolization, keratin filaments were not attached to demosomal plaques, and free demosomes and membrane ruptures were observed -at 2 h after, similar changes were observed in addition to granular degeneration of keratin	40

Table 13. Photosensitization and phototoxicity studies.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			Human		
Citrus Aurantium Dulcis (Orange) Peel wax	100% undiluted	11 subjects, fair skinned with skin types I-III	- 2 sites treated with 0.2 ml of the test material and 1 site was untreated; patches were occluded and applied to the back - 24 h after dosing, subjects were exposed to sunlight for 5-10 min, a Solar UV Simulator® with a 150 watt xenon arc lamp (UVA and UVB 290-400 nm) with a Schott WG 345 to filter out UVB (290-320 nm) so that only UVA was delivered (320-400 nm). - test sites were examined 15 min, 24 h, and 48 h after irradiation	no phototoxic response was observed	42
sweet orange peel, mesocarp, and fruit; alcohol extractions of all 3	undiluted	3 subjects with type I skin and 1 subject with type II skin	-in duplicate Finn Chambers, peel, mesocarp, or fruit were applied directly to skin or as alcohol extract solutions (0.2 g/0.2 ml) at 20 µl on paper discs -closed patches were 1 h in duration - 48 h after dosing, subjects were exposed to sunlight for 30 min, a Phillips blacklight TL 20W/09 (320-440 nm) that delivered a total dose of 2.5 J/cm^2 - test sites were examined 8, 24, 48, 72, and 96 h after irradiation	-strong erythema (++) observed in 2 subjects with type 1 skin and strong erythema and infiltration (+++) observed in 1 subject with type I skin after48 h after irradiation and exposure to pure peel and peel extract -slight erythema observed in all 3 type I subjects after exposure to pure peel and peel extract with no sun exposure after 48 h -no reactions observed to mesocarp or fruit, either pure or extract -no reactions induced in the type II skin subject	41

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2016 FDA VCRP RAW DATA – Citrus Peel-Derived Ingredients

12A - Cleansing	CITRUS AURANTIFOLIA (LIME) PEEL EXTRACT	2
12D - Body and Hand (exc shave)	CITRUS AURANTIFOLIA (LIME) PEEL EXTRACT	2
12F - Moisturizing	CITRUS AURANTIFOLIA (LIME) PEEL EXTRACT	5
12J - Other Skin Care Preps	CITRUS AURANTIFOLIA (LIME) PEEL EXTRACT	5
13A - Suntan Gels, Creams, and Liquids	CITRUS AURANTIFOLIA (LIME) PEEL EXTRACT	1
12H - Paste Masks (mud packs)	CITRUS AURANTIFOLIA (LIME) PEEL POWDER	1
12J - Other Skin Care Preps	CITRUS AURANTIFOLIA (LIME) PEEL POWDER	2
05F - Shampoos (non-coloring)	CITRUS AURANTIUM (BITTER ORANGE) PEEL WAX	1
07E - Lipstick	CITRUS AURANTIUM (BITTER ORANGE) PEEL WAX	3
10A - Bath Soaps and Detergents	CITRUS AURANTIUM (BITTER ORANGE) PEEL WAX	1
02A - Bath Oils, Tablets, and Salts	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	1
03C - Eye Shadow	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	2
04A - Cologne and Toilet waters	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	1
05A - Hair Conditioner	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	5
05F - Shampoos (non-coloring)	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	5
07I - Other Makeup Preparations	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	1
11E - Shaving Cream	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	1
12A - Cleansing	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	3
12C - Face and Neck (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	7
12D - Body and Hand (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	3
12F - Moisturizing	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	10
12G - Night	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	2
12H - Paste Masks (mud packs)	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	1
12I - Skin Fresheners	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	1
12J - Other Skin Care Preps	CITRUS AURANTIUM (BITTER ORANGE) PEEL EXTRACT	5
10A - Bath Soaps and Detergents	CITRUS AURANTIUM (BITTER ORANGE) PEEL POWDER	1
12A - Cleansing	CITRUS AURANTIUM (BITTER ORANGE) PEEL POWDER	1
02D - Other Bath Preparations	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	1
03D - Eye Lotion	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	1

05A - Hair Conditioner	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	3
05E - Rinses (non-coloring)	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	1
05F - Shampoos (non-coloring)	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	8
05H - Wave Sets	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	2
05I - Other Hair Preparations	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	2
07A - Blushers (all types)	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	1
07C - Foundations	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	3
07I - Other Makeup Preparations	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	1
09A - Dentifrices	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	2
10A - Bath Soaps and Detergents	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	9
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	2
12A - Cleansing	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	3
12C - Face and Neck (exc shave)	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	3
12D - Body and Hand (exc shave)	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	1
12F - Moisturizing	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	4
12G - Night	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	1
12J - Other Skin Care Preps	CITRUS AURANTIUM DULCIS (ORANGE) PEEL EXTRACT	2
07B - Face Powders	CITRUS AURANTIUM DULCIS (ORANGE) PEEL POWDER	1
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM DULCIS (ORANGE) PEEL POWDER	2
12A - Cleansing	CITRUS AURANTIUM DULCIS (ORANGE) PEEL POWDER	2
12D - Body and Hand (exc shave)	CITRUS AURANTIUM DULCIS (ORANGE) PEEL POWDER	3
12H - Paste Masks (mud packs)	CITRUS AURANTIUM DULCIS (ORANGE) PEEL POWDER	2
12J - Other Skin Care Preps	CITRUS AURANTIUM DULCIS (ORANGE) PEEL POWDER	1
03D - Eye Lotion	CITRUS GRANDIS (POMELO) PEEL EXTRACT	2
03G - Other Eye Makeup Preparations	CITRUS GRANDIS (POMELO) PEEL EXTRACT	1
05A - Hair Conditioner	CITRUS GRANDIS (POMELO) PEEL EXTRACT	1
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	CITRUS GRANDIS (POMELO) PEEL EXTRACT	2
07E - Lipstick	CITRUS GRANDIS (POMELO) PEEL EXTRACT	1
07F - Makeup Bases	CITRUS GRANDIS (POMELO) PEEL EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS GRANDIS (POMELO) PEEL EXTRACT	1
12A - Cleansing	CITRUS GRANDIS (POMELO) PEEL EXTRACT	4
12C - Face and Neck (exc	CITRUS GRANDIS (POMELO) PEEL EXTRACT	7

shave)		
12D - Body and Hand (exc shave)	CITRUS GRANDIS (POMELO) PEEL EXTRACT	2
12F - Moisturizing	CITRUS GRANDIS (POMELO) PEEL EXTRACT	6
12G - Night	CITRUS GRANDIS (POMELO) PEEL EXTRACT	5
12H - Paste Masks (mud packs)	CITRUS GRANDIS (POMELO) PEEL EXTRACT	3
12I - Skin Fresheners	CITRUS GRANDIS (POMELO) PEEL EXTRACT	1
12J - Other Skin Care Preps	CITRUS GRANDIS (POMELO) PEEL EXTRACT	10
13A - Suntan Gels, Creams, and Liquids	CITRUS GRANDIS (POMELO) PEEL EXTRACT	2
03D - Eye Lotion	CITRUS JUNOS (XIANG CHENG) PEEL EXTRACT	1
01A - Baby Shampoos	CITRUS LIMON (LEMON) PEEL EXTRACT	1
02A - Bath Oils, Tablets, and Salts	CITRUS LIMON (LEMON) PEEL EXTRACT	1
03D - Eye Lotion	CITRUS LIMON (LEMON) PEEL EXTRACT	1
03G - Other Eye Makeup Preparations	CITRUS LIMON (LEMON) PEEL EXTRACT	1
04B - Perfumes	CITRUS LIMON (LEMON) PEEL EXTRACT	1
04E - Other Fragrance Preparation	CITRUS LIMON (LEMON) PEEL EXTRACT	1
05A - Hair Conditioner	CITRUS LIMON (LEMON) PEEL EXTRACT	21
05F - Shampoos (non-coloring)	CITRUS LIMON (LEMON) PEEL EXTRACT	22
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS LIMON (LEMON) PEEL EXTRACT	2
05I - Other Hair Preparations	CITRUS LIMON (LEMON) PEEL EXTRACT	9
06G - Hair Bleaches	CITRUS LIMON (LEMON) PEEL EXTRACT	1
06H - Other Hair Coloring Preparation	CITRUS LIMON (LEMON) PEEL EXTRACT	1
07E - Lipstick	CITRUS LIMON (LEMON) PEEL EXTRACT	1
08E - Nail Polish and Enamel	CITRUS LIMON (LEMON) PEEL EXTRACT	1
09A - Dentifrices	CITRUS LIMON (LEMON) PEEL EXTRACT	2
10A - Bath Soaps and Detergents	CITRUS LIMON (LEMON) PEEL EXTRACT	8
10B - Deodorants (underarm)	CITRUS LIMON (LEMON) PEEL EXTRACT	1
10E - Other Personal Cleanliness Products	CITRUS LIMON (LEMON) PEEL EXTRACT	5
11E - Shaving Cream	CITRUS LIMON (LEMON) PEEL EXTRACT	1
12A - Cleansing	CITRUS LIMON (LEMON) PEEL EXTRACT	22
12C - Face and Neck (exc shave)	CITRUS LIMON (LEMON) PEEL EXTRACT	14
12D - Body and Hand (exc shave)	CITRUS LIMON (LEMON) PEEL EXTRACT	6
12F - Moisturizing	CITRUS LIMON (LEMON) PEEL EXTRACT	16
12G - Night	CITRUS LIMON (LEMON) PEEL EXTRACT	1
12H - Paste Masks (mud packs)	CITRUS LIMON (LEMON) PEEL EXTRACT	3

12I - Skin Fresheners	CITRUS LIMON (LEMON) PEEL EXTRACT	3
12J - Other Skin Care Preps	CITRUS LIMON (LEMON) PEEL EXTRACT	4
08G - Other Manicuring Preparations	CITRUS LIMON (LEMON) PEEL POWDER	1
10E - Other Personal Cleanliness Products	CITRUS LIMON (LEMON) PEEL POWDER	1
12A - Cleansing	CITRUS LIMON (LEMON) PEEL POWDER	1
12D - Body and Hand (exc shave)	CITRUS LIMON (LEMON) PEEL POWDER	1
12J - Other Skin Care Preps	CITRUS LIMON (LEMON) PEEL POWDER	2
10E - Other Personal Cleanliness Products	CITRUS LIMON (LEMON) PEEL WAX	1
05A - Hair Conditioner	CITRUS NOBILIS (MANDARIN ORANGE) PEEL EXTRACT	1
05F - Shampoos (non-coloring)	CITRUS NOBILIS (MANDARIN ORANGE) PEEL EXTRACT	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS NOBILIS (MANDARIN ORANGE) PEEL EXTRACT	1
07A - Blushers (all types)	CITRUS NOBILIS (MANDARIN ORANGE) PEEL EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS NOBILIS (MANDARIN ORANGE) PEEL EXTRACT	2
10E - Other Personal Cleanliness Products	CITRUS NOBILIS (MANDARIN ORANGE) PEEL EXTRACT	5
12A - Cleansing	CITRUS NOBILIS (MANDARIN ORANGE) PEEL EXTRACT	2
12D - Body and Hand (exc shave)	CITRUS NOBILIS (MANDARIN ORANGE) PEEL EXTRACT	2
12F - Moisturizing	CITRUS NOBILIS (MANDARIN ORANGE) PEEL EXTRACT	3
12J - Other Skin Care Preps	CITRUS NOBILIS (MANDARIN ORANGE) PEEL EXTRACT	1
01A - Baby Shampoos	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	1
01B - Baby Lotions, Oils, Powders, and Creams	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	2
02D - Other Bath Preparations	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	1
03G - Other Eye Makeup Preparations	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	1
05A - Hair Conditioner	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	2
05F - Shampoos (non-coloring)	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	2
07C - Foundations	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	1
07E - Lipstick	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	3
10A - Bath Soaps and Detergents	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	8
12A - Cleansing	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	8
12C - Face and Neck (exc shave)	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	1
12D - Body and Hand (exc	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	7

shave)		
12F - Moisturizing	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	20
12G - Night	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	1
12J - Other Skin Care Preps	CITRUS PARADISI (GRAPEFRUIT) PEEL EXTRACT	1
03D - Eye Lotion	CITRUS RETICULATA (MANDARIN ORANGE) PEEL EXTRACT	3
03G - Other Eye Makeup Preparations	CITRUS RETICULATA (MANDARIN ORANGE) PEEL EXTRACT	2
10A - Bath Soaps and Detergents	CITRUS RETICULATA (MANDARIN ORANGE) PEEL EXTRACT	4
10E - Other Personal Cleanliness Products	CITRUS RETICULATA (MANDARIN ORANGE) PEEL EXTRACT	2
12A - Cleansing	CITRUS RETICULATA (MANDARIN ORANGE) PEEL EXTRACT	2
12C - Face and Neck (exc shave)	CITRUS RETICULATA (MANDARIN ORANGE) PEEL EXTRACT	1
12D - Body and Hand (exc shave)	CITRUS RETICULATA (MANDARIN ORANGE) PEEL EXTRACT	2
12F - Moisturizing	CITRUS RETICULATA (MANDARIN ORANGE) PEEL EXTRACT	14
12G - Night	CITRUS RETICULATA (MANDARIN ORANGE) PEEL EXTRACT	3
12J - Other Skin Care Preps	CITRUS RETICULATA (MANDARIN ORANGE) PEEL EXTRACT	2
12C - Face and Neck (exc shave)	CITRUS RETICULATA (TANGERINE) PEEL EXTRACT	1
10E - Other Personal Cleanliness Products	CITRUS SINENSIS (SWEET ORANGE) PEEL EXTRACT	1
12A - Cleansing	CITRUS SINENSIS (SWEET ORANGE) PEEL EXTRACT	1
12F - Moisturizing	CITRUS SINENSIS (SWEET ORANGE) PEEL EXTRACT	1
07E - Lipstick	CITRUS SINENSIS (SWEET ORANGE) PEEL WAX	1
11A - Aftershave Lotion	CITRUS SINENSIS (SWEET ORANGE) PEEL WAX	4
12A - Cleansing	CITRUS TACHIBANA (TACHIBANA ORANGE) PEEL EXTRACT	1
12F - Moisturizing	CITRUS TACHIBANA (TACHIBANA ORANGE) PEEL EXTRACT	1
12J - Other Skin Care Preps	CITRUS TACHIBANA (TACHIBANA ORANGE) PEEL EXTRACT	3
12C - Face and Neck (exc shave)	CITRUS TACHIBANA PEEL EXTRACT	3
05A - Hair Conditioner	CITRUS TANGERINA (TANGERINE) PEEL EXTRACT	1
12G - Night	CITRUS TANGERINA (TANGERINE) PEEL EXTRACT	1
02A - Bath Oils, Tablets, and Salts	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	1
03D - Eye Lotion	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	3
03E - Eye Makeup Remover	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	1

05A - Hair Conditioner	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	2
05F - Shampoos (non-coloring)	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	4
10A - Bath Soaps and Detergents	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	1
12A - Cleansing	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	5
12C - Face and Neck (exc shave)	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	14
12D - Body and Hand (exc shave)	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	1
12F - Moisturizing	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	7
12H - Paste Masks (mud packs)	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	1
12I - Skin Fresheners	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	2
12J - Other Skin Care Preps	CITRUS UNSHIU (SATSUMA ORANGE) PEEL EXTRACT	4
02A - Bath Oils, Tablets, and Salts	ORANGE PEEL	2
02D - Other Bath Preparations	ORANGE PEEL	1
10A - Bath Soaps and Detergents	ORANGE PEEL	2
10E - Other Personal Cleanliness Products	ORANGE PEEL	1
12A - Cleansing	ORANGE PEEL	2
12D - Body and Hand (exc shave)	ORANGE PEEL	1
12J - Other Skin Care Preps	ORANGE PEEL	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	ORANGE PEEL WAX	3
12F - Moisturizing	ORANGE PEEL WAX	1
12A - Cleansing	LEMON PEEL	1
12D - Body and Hand (exc shave)	LEMON PEEL	1
12G - Night	LEMON PEEL	1
12J - Other Skin Care Preps	LEMON PEEL	1

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: January 8, 2016

SUBJECT: Information on a product containing Citrus Aurantium Dulcis (Orange) Peel Wax

Anonymous. 2011. Summary of an HRIPT of a lipstick containing 1.9% Citrus Aurantium Dulcis (Orange) Peel Wax.

Anonymous. 2012. Summary of a 4-week use test of a lipstick containing 1.9% Citrus Aurantium Dulcis (Orange) Peel Wax.

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Summaries of Studies of Lipstick Containing Citrus Aurantium Dulcis (Orange) Peel Wax

Year Completed:	2011
Study Type:	HRIPT
Product Type:	Lipstick (tested undiluted)
Concentration of Ingredient:	1.9% Citrus Aurantium Dulcis (Orange) Peel Wax
Number of Subjects:	105
Conclusion:	Test material did not induce dermal irritation nor any evidence of induced allergic contact dermatitis in human subjects

Year Completed:	2012
Study Type:	4-week use test
Product Type:	Lipstick
Concentration of Ingredient:	1.9% Citrus Aurantium Dulcis (Orange) Peel Wax
Number of Subjects:	33 sensitive skin subjects
Conclusion:	Test in clinically-demonstrated sensitive skin subjects did not result in clinically significant dermal irritation or hypersensitivity.

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: January 27, 2016

SUBJECT: Summary Information Citrus Reticulata (Tangerine) Peel Extract

Anonymous. 2016. Summary information Citrus Reticulata (Tangerine) Peel Extract.

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January 2016

Summary Information Citrus Reticulata (Tangerine) Peel Extract

Method of Manufacture:	Hydroalcoholic extraction of tangerine peel which is then concentrated until in contains 98% minimum of the flavonoid luteolin
Physical Form:	Powder
Safety Testing:	An HRIPT in 54 subjects was completed on the Citrus Reticulata (Tangerine) Peel Extract as described above. Citrus Reticulata (Tangerine) Peel Extract did not demonstrate a potential for eliciting dermal irritation or sensitization.

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: February 10, 2016

SUBJECT: Citrus Unshiu Peel Extract

Sederma. 2016. Citrus Unshiu Peel Extract - Summary.

Laboratoire Dermscan. 2002. Summary: Evaluation of the acute cutaneous safety of a raw material (0.5% Citrus Unshiu Peel Extract) on 10 adult volunteers using 24-hours single patch test method under dermatological control.

Laboratoire Dermscan. 2002. Summary: Evaluation of the irritating and sensitizing potential of one cosmetic product (0.5% Citrus Unshiu Peel Extract) by repeated 48-hours epicutaneous applications under occlusive patch-test (Marzulli & Maibach method).

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INCI name	Citrus Unshiu Peel Extract
INCI Monograph ID	9931
Trade name of SEDERMA mixture from PcPc website	MELASLOW™
Manufacturing process	Our Citrus Unshiu Peel Extract is obtained by maceration of fine-cut *Citrus unshiu* peel in water and ethanol, filtration, drying.
Composition	The bibliographical study (1) gives the following groups: - Pectin - Peptides and amino acids - Essential oils - Phenolic acids - Flavonoids (Flavonols, Flavones, Flavonones) - Carotenoid pigment - Tocopherol analogues
Impurities	The following analyses have been carried out on **commercial product containing approx. 0,5%** of Citrus Unshiu Peel Extract (as dry): - Allergens < 2,5ppm (quantification limit) (GC-MS) - Heavy metals < 1ppm (ICP-MS) - Formaldehyde < 5ppm (quantification limit) (DNPH/GC/MS) - Pesticides < 0,04ppm (quantification limit) (ME-0112 GC/TSD - GC/ECD) - Ethanol < 10ppm (quantification limit) (GC-MS) The ingredient **Citrus Unshiu Peel Extract has aslo been analyzed**: - Allergens < 2ppm (quantification limit) (GC-MS) - Ethanol < 10ppm (quantification limit) (GC-MS)
Safety data	Please find safety data package for the mixture MELASLOW (product code: OCT 02197) which contains approx. 0,5% of Citrus Unshiu Peel Extract (as dry). - Primary Cutaneous Tolerance - Patch test (Report n° 1020545-1), July 2002: **Non irritant** - Repeated Insult Patch Test - HRIPT (Report n° 1020545-2), December 2002: **Hypoallergenic**
Other safety information	Citrus Unshiu Peel Extract has been used up to 0,5% (as dry) in several Sederma's products and widely supplied since 2002 in The EU, The US, Canada, Korea, Japan, Australia without any complaint concerning their innocuity.

(1)
- Preventive Effects of Citrus unshiu Peel Extracts on Bone and Lipid Metabolism in OVX Rats
Dong Wook Lim, Youngseok Lee and Yun Tai Kim
Molecules 2014, 19, 783-794;
- Citrus flavonoids in fruit and traditional Chinese medicinal food ingredients in China.
Lu Y, Zhang C, Bucheli P, Wei D.
Plant Foods Hum Nutr. 2006 Jun;61(2):57-65. Epub 2006 Jul 1;
- Accumulation of Carotenoids and Expression of Carotenoid Biosynthetic Genes during Maturation in Citrus Fruit
Masaya Kato,* Yoshinori Ikoma, Hikaru Matsumoto, Minoru Sugiura, Hiroshi Hyodo, and Masamichi Yano
Plant Physiol. 2004 Feb; 134(2): 824–837;
- Phenolic compounds and antioxidant activity of extracts from ultrasonic treatment of Satsuma Mandarin (Citrus unshiu Marc.) peels.
Ma YQ, Ye XQ, Fang ZX, Chen JC, Xu GH, Liu DH.
J Agric Food Chem. 2008 Jul 23;56(14):5682-90. doi: 10.1021/jf072474o. Epub 2008 Jun 24;
- Chemical composition, antioxidant and antibacterial activities of essential oil from Korean Citrus unshiu peel
X. N. Yang, S. C. Kang
Journal of Agricultural Chemistry and Environment 2 (2013) 42-49;
- Preliminary Evaluation for Comparative Antioxidant Activity in the Water and Ethanol Extracts of Dried Citrus Fruit (Citrus unshiu) Peel Using Chemical and Biochemical in Vitro Assays
Joo-Shin Kim
Food and Nutrition Sciences, 2013, 4, 177-188.
- Composition of Peel Oil from Citrus Unshiu
Yukie Kita, Yoichi Nakatani, Akio Kobayashi & Tei Yamanishi
Agricultural and Biological Chemistry, 33:11,1559-1565.

LABORATOIRE DERMSCAN®

Evaluation of the acute cutaneous safety of a raw material on 10 adult volunteers using 24-hours single patch test method under dermatological control

Version n° 02/002, July 09, 2002

GROUPE DERMSCAN

SIEGE SOCIAL - LYON
27, bd du 11 Novembre 1918
B.P. 2132
69603 VILLEURBANNE Cedex
FRANCE

Tél. : 33 (0)4 72 82 36 56
Fax : 33 (0)4 78 89 60 48

e-mail : info@dermscan.com
internet : www.dermscan.com

Study : TCP24H/1020545-1

Product : OCT 02197

MELASLOW N 0.5% Citrus Unshiu Peel Extract

Sponsor : **SEDERMA**
29, rue du chemin vert
78610 Le Perray en Yvelines
FRANCE

Saint-Etienne, July 09, 2002

5 - CONCLUSION

Under the study conditions, 30 minutes and 24 hours after removal of the patch, no volunteer presented significant skin irritation due to an intolerance skin reaction.

No secondary effect was observed.

It can be concluded that the product **OCT 02197 Dermscan reference 54362**, tested under dermatological control, applied pure and locally under occlusive patch for 24 hours, to the skin of 10 adult volunteers, is **non irritating**.

Dr Séverine MAITRE
Dermatologist

LABORATOIRE DERMSCAN®

EVALUATION OF THE IRRITATING AND SENSITIZING POTENTIAL OF ONE COSMETIC PRODUCT BY REPEATED 48-HOURS EPICUTANEOUS APPLICATIONS UNDER OCCLUSIVE PATCH-TEST (MARZULLI & MAIBACH METHOD)

GROUPE DERMSCAN

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FRANCE

Tél. : 33 (0)4 72 82 36 56
Fax : 33 (0)4 78 89 60 48

e-mail : info@dermscan.com
internet : www.dermscan.com

Report:	**#1020545-2 (#DN-016)**
Estimate:	**#20020859**
Product:	**OCT 02197** MELASLOW ~ 0.5% Citrus Unshiu Peel Extract
Form:	**Orange lotion**
Application:	**Scapular part of the back**
Sponsor:	**SEDERMA SA** **29, rue du chemin vert** **B.P. 33** **78612 LE PERRAY EN YVELINES** **FRANCE**
Estimate date:	**June 21, 2002**
Test completion date:	**August 23, 2002**
Report date:	**December 20, 2002**

Document: 1/2

6. CONCLUSION

This document is an assessor's report of the above study done in an European laboratory.

The study took place from July 15 to August 23, 2002. It was realized by an European Clinical Laboratory in collaboration with Laboratoire DERMSCAN.

The aim of this study was to determine the hypoallergenicity of the product "OCT 02197" by evaluation of its irritating and sensitizing potential according to the MARZULLI-MAIBACH method.

The study was done in three phases:

- Induction phase: patches were applied to the same site on Monday, Wednesday and Friday for a three-week period. The test material was applied under an occlusive patch to the upper back and allowed to remain in direct skin contact for a period of 48 hours.
- Rest period: no product application during two weeks.
- Challenge phase: the challenge patches were applied to the previously treated sites on the back (homolateral) and to newly defined sites, previously unexposed (controlateral). After 48 hours, the patches were removed and the test sites were evaluated for dermal reactions. The test sites were again evaluated at 96 hours.

The study was done on 52 healthy volunteers, two volunteers have discontinued study. 50 subjects, aged between 18 and 60 (average age: 39±2) completed the study.

Conclusions are:

	Induction phase	Challenge phase	Conclusion
OCT 02197	No clinically significant potential for dermal irritation	No clinically significant potential for dermal sensitization	HYPOALLERGENIC

Based on results obtained during both induction and challenge phases, the product "OCT 02197" can be considered hypoallergenic.

7. CERTIFICATION

Data were obtained using current internal procedures of the European Clinical Research Laboratory and in compliance with the principles of Good Clinical Practice.

Only the hard copy of the report (green bands) transmitted by Laboratoire DERMSCAN can be considered an attestation and official. Digitally-produced or electronic documents transmitted by Laboratoire DERMSCAN are not protected by an electronic signature, according the Law n°2000-230 of March 13, 2000 and its applicable decrees. The contents of digitally-produced or electronic documents in no means engage the responsibility of Laboratoire DERMSCAN.
Any modifications are the sole responsibility of the author of the modification, whether he/she is acting for the sponsor or independently. Any partial or total reproduction of this trial report requires prior written agreement from Laboratoire DERMSCAN.

This study was totally implemented under the responsibility of the European Clinical Research Laboratory and controlled by Laboratoire DERMSCAN.

All documents relating to this test will be archived for fifteen years and a sample of the product will be kept for one year.

After this period the archives for this study will be destroyed unless otherwise stipulated in writing by the sponsor.

Lyon, December 20, 2002.

Clinical Responsible

Dr. Yvette WELTERT
Dermatologist

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: February 10, 2016

SUBJECT: Citrus Aurantium Amara (Bitter Orange) Peel Extract and Citrus Unshiu Peel Extract

Anonymous. 2016. Summary information: Citrus Aurantium Amara (Bitter Orange) Peel Extract and Citrus Unshiu Peel Extract.

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February 2016

Citrus Aurantium Amara (Bitter Orange) Peel Extract, Citrus Unshiu Peel Extract

1.Method of manufacture

2.Chemical composition

3.Impurities

4. Dermal irritation and sensitization data on products containing the highest concentrations of these ingredients, especially human repeated insult patch tests (HRIPT) on Citrus Aurantium Dulcis (Orange) Peel Extract, Citrus Grandis (Grapefruit) Peel Extract, Citrus Limon (Lemon) Peel Extract and Citrus Unshiu Peel Extract

1.Method of manufacture

● Citrus Aurantium Amara (Bitter Orange) Peel Extract

Trade Name	Method of manufacture
Bitter Orange Peel Extract	Dried raw material⇒extract with 90vol% ethanolic solution⇒filtrate ⇒concentration⇒sedimentation⇒filtrate⇒adjustment⇒packaging
Bitter Orange Peel Extract LA	Dried raw material⇒extract with 30vol% ethanolic solution⇒filtrate ⇒sedimentation⇒adjustment⇒packaging
Bitter Orange Peel Extract Powder-S	Dried raw material⇒extract with 30vol% ethanolic solution⇒filtrate ⇒ concentration ⇒ add anhydrous sodium sulfate as vehicle ⇒ packaging

● Citrus Unshiu Peel Extract

Trade Name	Method of manufacture
Citrus Unshiu Extract BG	Dried raw material ⇒ extract with 50vol% 1,3-butylene glycolic solution⇒filtrate⇒sedimentation⇒adjustment⇒packaging
Citrus Unshiu Extract BG100	Dried raw material⇒extract with 30vol% ethanolic solution⇒filtrate ⇒concentration⇒add 1,3-butylene glycol⇒sedimentation⇒filtrate⇒ adjustment⇒packaging
Citrus Unshiu Extract-J	Dried raw material⇒extract with 90vol% ethanolic solution⇒filtrate ⇒concentration⇒sedimentation⇒filtrate⇒adjustment⇒packaging
Citrus Unshiu Extract LA	Dried raw material⇒extract with 30vol% ethanolic solution⇒filtrate ⇒concentration⇒adjustment⇒sedimentation⇒filtrate⇒adjustment ⇒packaging
Citrus Unshiu Extract Powder-S	Dried raw material⇒extract with 30vol% ethanolic solution⇒filtrate ⇒ concentration ⇒ add anhydrous sodium sulfate as vehicle ⇒ packaging
Citrus Unshiu Extract SQ	Dried raw material⇒extract with 30vol% ethanolic solution⇒filtrate ⇒ concentration ⇒ add squalane ⇒ sedimentation ⇒ filtrate ⇒

	adjustment⇒packaging

2.Chemical composition

● Citrus Aurantium Amara (Bitter Orange) Peel Extract

Trade Name	Chemical composition
Bitter Orange Peel Extract	flavonoid, sugar and hesperidin
Bitter Orange Peel Extract LA	flavonoid, sugar and hesperidin
Bitter Orange Peel Extract Powder-S	flavonoid

● Citrus Unshiu Peel Extract

Trade Name	Chemical composition
Citrus Unshiu Extract BG	flavonoid and sugar
Citrus Unshiu Extract BG100	flavonoid, sugar and hesperidin
Citrus Unshiu Extract-J	flavonoid
Citrus Unshiu Extract LA	flavonoid, sugar and hesperidin
Citrus Unshiu Extract Powder-S	flavonoid, sugar and hesperidin
Citrus Unshiu Extract SQ	essential oil component

3.Impurities

● Citrus Aurantium Amara (Bitter Orange) Peel Extract

Trade Name	Impurities
Bitter Orange Peel Extract	Heavy metals : Not more than 20ppm , Arsenic : Not more than 2ppm
Bitter Orange Peel Extract LA	Heavy metals : Not more than 20ppm , Arsenic : Not more than 2ppm
Bitter Orange Peel Extract Powder-S	Heavy metals : Not more than 10ppm , Arsenic : Not more than 2ppm

● Citrus Unshiu Peel Extract

Trade Name	Impurities
Citrus Unshiu Extract BG	Heavy metals : Not more than 20ppm , Arsenic : Not more than 2ppm
Citrus Unshiu Extract BG100	Heavy metals : Not more than 10ppm , Arsenic : Not more than 2ppm
Citrus Unshiu Extract-J	Heavy metals : Not more than 20ppm , Arsenic : Not more than 2ppm
Citrus Unshiu Extract LA	Heavy metals : Not more than 10ppm , Arsenic : Not more than 1ppm
Citrus Unshiu Extract Powder-S	Heavy metals : Not more than 10ppm , Arsenic : Not more than 2ppm
Citrus Unshiu Extract SQ	Heavy metals : Not more than 10ppm , Arsenic : Not more than 2ppm

4. Dermal irritation and sensitization data on products containing the highest concentrations

Citrus Aurantium Amara (Bitter Orange) Peel Extract

Trade Name	Safety data
Bitter Orange Peel Extract	No data
Bitter Orange Peel Extract LA	Primary skin irritation test (negative)(10%, 100%;undiluted solution) (tested in 3 rabbits)
Bitter Orange Peel Extract Powder-S	No data

● Citrus Unshiu Peel Extract

Trade Name	Safety data
Citrus Unshiu Extract BG	HRIPT (10%) (negative) n=49
Citrus Unshiu Extract BG100	No data
Citrus Unshiu Extract-J	No data
Citrus Unshiu Extract LA	No data
Citrus Unshiu Extract Powder-S	No data
Citrus Unshiu Extract SQ	HRIPT (100%;undiluted solution) (negative) n=54

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: February 10, 2016

SUBJECT: Citrus Aurantium Amara (Bitter) Orange Peel Extract and Citrus Reticulata (Tangerine) Peel Extract

Ichimaru Pharcos Co., Ltd. 2016. Citrus peel-derived ingredients as used in cosmetics (method of manufacture and impurities).

Ichimaru Pharcos Co., Ltd. 2016. Toxicity & safety TOUHI Liquid (mixture containing Citrus Aurantium Amara (Bitter Orange) Peel Extract).

Ichimaru Pharcos Co., Ltd. 2016. Toxicity & safety TOUHI Liquid B (mixture containing Citrus Aurantium Amara (Bitter Orange) Peel Extract).

Ichimaru Pharcos Co., Ltd. 2014. Toxicity & safety CHINPI Liquid (mixture containing Citrus Reticulata (Tangerine) Peel Extract).

Ichimaru Pharcos Co., Ltd. 2014. Toxicity & safety MandarinClear (mixture containing Citrus Reticulata (Tangerine) Peel Extract).

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Ichimaru Pharcos Co., Ltd

Feb. 2016

Citrus peel-derived ingredients as Used in Cosmetics

We will provide a following information to you.

	Product Name	Method of manufacture	Chemical composition and impurities	Safety data
Citrus Aurantium Amara (Bitter Orange) Peel Extract	1.55 % Peel Extract 25.81 % Alcohol TOUHI Liquid 72.64 % Water	Add ethanol solution to the ripe pericarp of Citrus aurantium Linne (Rutaceae), extract, and filter. Allow the filtrate to stand in a dark, cold place for a while, and filter to obtain the product.	We do not analyze this product. So, we cannot describe chemical composition and impurities. 2.8 ppm as 5-Methoxy psoralen was contained in this product.	Please, refer to the Toxicity & Safety.
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0 % Peel Extract 29.4 % Butylene Glycol TOUHI Liquid B 68.6 % Water	Add 1,3-butylene glycol solution to the ripe pericarp of Citrus aurantium Linne (Rutaceae), extract, and filter to obtain the product.	We do not analyze this product. So, we cannot describe chemical composition and impurities.	Please, refer to the Toxicity & Safety.
Citrus Reticulata (Tangerine) Peel Extract	3.06 % Peel Extract 25.41 % Alcohol CHINPI Liquid 71.53 % Water	Add ethanol solution to the the ripe peel of Citrus reticulata Blanco (Rutaceae), extract, and filter. Keep the filtrate in a dark, cold place, and filter to obtain the product.	We do not analyze this product. So, we cannot describe chemical composition and impurities. Furanocoumarins was not contained in this product.	Please, refer to the Toxicity & Safety.
Citrus Reticulata (Tangerine) Peel Extract	3.0 % Peel Extract 29.1 % Water MandarinClear 67.9 % Butylene Glycol	Add 1,3-butylene glycol solution to the ripe peel of Citrus reticulata Blanco (Rutaceae), extract, and filter. Keep the filtrate in a dark, cold place, and filter to obtain the product.	We do not analyze this product. So, we cannot describe chemical composition and impurities. Furanocoumarins was not contained in this product.	Please, refer to the Toxicity & Safety.

Furanocoumarins: Psoralen, Bergaptol (5-Hydroxy psoralen), Bergapten (5-Methoxy psoralen), Isoimperatorin, Bergamottin, 6', 7'-Dihydroxy Bergamottin, Xanthotoxol (8-Hydroxy psoralen), Xanthotoxin (8-Methoxy psoralen), Imperatorin, Xanthotoxol Geranyl Ether, Isopimpinellin (5,8-Dimethoxy psoralen), Angelicin, Isobergapten, Trioxsalen (Trioxysalen)

Published on February 3 2016

TOXICITY & SAFETY

TRADE Name	:	TOUHI Liquid
Completion Data	:	January 25 1990
INCI Name	:	Water, Alcohol, Citrus Aurantium Amara (Bitter Orange) Peel Extract

* Important information

These toxicological safety tests were performed in accordance with Japanese Pharmaceutical Affairs Law or our company policy based on its law. It does not provide any guarantee about the cosmetic preparations or formulations used these test data.

ICHIMARU PHARCOS Co.,Ltd.

Published on February 3 2016

TRADE NAME	TOUHI Liquid

Ⅰ. Animal Test or Non-animal Test

Test Categories	Result			Test species
Acute Oral Toxicity ALD : Approximate lethal dose	・ALD : ・Mortality	Male : /		
		Female : /		
	Result	Dosing concentration	Test species	Number of subjects
Primary Skin Irritation	Not Performed			
Cumulative Skin Irritation	Not Performed			
Skin Sensitization	Not Performed			
Photo Toxicity	Not Performed			
Photosensitization	Not Performed			
Ocular Irritation	Not Performed			
Remark				

Ⅱ. Human Patch Test

Dosing concentration	20% water solution					
	−	±	+	++	+++	++++
48 hours	29	1	0	0	0	0
72 hours	30	0	0	0	0	0

《Remark》
− : No reaction
± : Slight erythema
+ : Well defined erythema
++ : Erythema + Papule or Edema
+++ : Erythema + Papule, Edema + Vesicle
++++ : Large blister

Published on February 3 2016

TRADE NAME	TOUHI Liquid

Ⅲ. Mutagenicity Test

Test Categories	Result
Mutagenicity (Reverse mutation)	Not Performed
Mutagenicity (Chromosomal aberration)	Not Performed

Published on February 3 2016

TRADE NAME : TOUHI Liquid

Acute Oral Toxicity Test

Not Performed

Primary Skin Irritation

Not Performed

Cumulative Skin Irritation

Not Performed

Skin Sensitization

Not Performed

Photo Toxicity

Not Performed

Photosensitization

Not Performed

Ocular Irritation

Not Performed

Human Patch Test

Occlusive patch with the diluted sample for 20% water solution was applied on the brachium to 30 healthy adults for 48 hours.
The subjects were examined for signs of erythema and edema etc. at 1 and 24 hours after removal of patches.

29 persons were observed no irritating responses at 1 hour after removal of patches, however 1 person was observed slight erythema (±).
No erythema and no edema were observed at 24 hours after removal of patches.

Mutagenicity (Reverse mutation)

Not Performed

Mutagenicity (Chromosomal aberration)

Not Performed

Published on February 3 2016

TOXICITY & SAFETY

TRADE Name	:	TOUHI Liquid B
Completion Data	:	June 19 2003
INCI Name	:	Water, Butylene Glycol, Citrus Aurantium Amara (Bitter Orange) Peel Extract

* Important information

These toxicological safety tests were performed in accordance with Japanese Pharmaceutical Affairs Law or our company policy based on its law. It does not provide any guarantee about the cosmetic preparations or formulations used these test data.

ICHIMARU PHARCOS Co.,Ltd.

Published on February 3 2016

TRADE NAME	TOUHI Liquid B

Ⅰ. Animal Test or Non-animal Test

Test Categories	Result			Test species
Acute Oral Toxicity ALD : Approximate lethal dose	・ALD : Not less than 15mL/kg ・Mortality Male : 0 / 5 Female : 0 / 5			Mice
	Result	Dosing concentration	Test species	Number of subjects
Primary Skin Irritation	No Irritation	Undiluted	Guinea pigs	3
Cumulative Skin Irritation	No Irritation	Diluted	Guinea pigs	3
Skin Sensitization (+Adjuvant)	No Sensitization	Undiluted	Guinea pigs	12
Photo Toxicity	No Irritation	Undiluted	Guinea pigs	5
Photosensitization (+Adjuvant)	No Sensitization	Undiluted	Guinea pigs	10
Ocular Irritation	Almost no Irritaiton	Undiluted	Rabbits	3

Remark

Ocular Irritation : three animals showed redness (Score:1) at 0 hours after instillation in conjunctiva.

Dosing concentration:
The test sample was used 50vol% water solution in Cumulative Skin Irritation,

Ⅱ. Human Patch Test

Dosing concentration						
	−	±	+	++	+++	++++
24 hours						
48 hours						

《Remark》
− : No reaction
± : Slight erythema
+ : Well defined erythema
++ : Infiltration or Erythema with edema
+++ : Erythema + Infiltration + Papule − Vesicle
++++ : Large blister

Published on February 3 2016

TRADE NAME	TOUHI Liquid B

Ⅲ. Mutagenicity Test

Test Categories	Result
Mutagenicity (Reverse mutation)	Not Performed
Mutagenicity (Chromosomal aberration)	Not Performed

ICHIMARU PHARCOS Co.,Ltd.

Published on February 3 2016

TRADE NAME : TOUHI Liquid B

Acute Oral Toxicity Test

15mL/kg dose of the sample was orally administered through gavage to 2 groups (5×2 mice). The animals were dosed once and were observed for mortality and signs of toxicity for 14 days following dosing.

No major signs of toxicity were observed after dosing in any of the animals of the 15mL/kg group. The body weight of the animals gradually increased in the male group throughout the 14-day observation period.
No marked changes in body weight were observed in the female group throughout the 14-day observation period.
ALD : Not less than 15mL/kg.

Primary Skin Irritation

The sample was applied topically on the clipped skin of guinea pigs. The animals were examined for signs of erythema and edema at 24, 48 and 72 hours after dosing.

No erythema and no edema were observed on the skin of guinea pigs at 24, 48 and 72 hours after dosing.

Cumulative Skin Irritation

The diluted sample for 50vol% water solution was applied topically on the clipped skin of guinea pigs once a day for 2 weeks (five times a week). The animals were examined for signs of erythema and edema before dosing every day and at 24 hours after final dosing.

No erythema and no edema were observed on the clipped skin of guinea pigs for 2 weeks.

Skin Sensitization (+Adjuvant)

An emulsion of FCA with water (E-FCA), the sample, and an emulsion of FCA with the sample were injected intradermally into clipped dorsal skin area. Then occlusive patch with the sample was applied on the same sites. (Induction)
Occlusive patches with the sample were applied on the clipped flank skin of guinea pigs in the test sample group (5 guinea pigs) and the negative control group (5 guinea pigs). (Challenge)
The animals were examined for signs of erythema and edema at 24 and 48 hours after removal of the challenge patch.

No erythema and no edema were observed on the skin of guinea pigs in the test sample group and negative control group at 24 and 48 hours after challenge.

Photo Toxicity

The sample was applied topically to two sites on the clipped dorsal skin area of guinea pigs, and one side was irradiated by UV, and the other side was protected with a cover. The animals were examined for signs of erythema and edema in the first, second and third day after application.

No erythema and no edema were observed on the skin of guinea pigs in the first, second and third day after application.

Photosensitization (+Adjuvant)

An emulsion of FCA with water was injected intradermally into a clipped nuchal area. The injection site was stripped with cellophane tape, and the sample was applied topically on the site followed by UV irradiation. (Photoinduction)
The sample was applied topically on the clipped dorsal skin area of guinea pigs in the test sample group (5 guinea pigs) and negative control group (5 guinea pigs), and one side was irradiated by UV, and the other side was protected with a cover. (Photochallenge)
The animals were examined for signs of erythema and edema at 24 and 48 hours after photochallenge.

No erythema and no edema were observed on the skin of guinea pigs in the test sample group and negative control group at 24 and 48 hours after photochallenge.

Ocular Irritation

The sample was instilled into the conjunctivae sac of one of the eyes of albino rabbits, and the other eye serves as the control. The animals were examined for signs of inflammation in conjunctiva, iris and cornea at 0, 1, 24, 48 and 72 hours after instillation.

No inflammatory signs were observed in iris and cornea at 0, 1, 24, 48 and 72 hours after instillation. In conjunctiva, no inflammatory signs were observed except that three animals showed redness (Score:1) at 0 hours after instillation.

Human Patch Test

Not Performed

Mutagenicity (Reverse mutation)

Not Performed

Mutagenicity (Chromosomal aberration)

Not Performed

Published on June 20 2014

TOXICITY & SAFETY

TRADE Name : CHINPI Liquid

Completion Data : June 22 1989

INCI Name : Water, Alcohol, Citrus Reticulata (Tangerine) Peel Extract

* Important information

These toxicological safety tests were performed in accordance with Japanese Pharmaceutical Affairs Law or our company policy based on its law. It does not provide any guarantee about the cosmetic preparations or formulations used these test data.

ICHIMARU PHARCOS Co.,Ltd.

Published on June 20 2014

TRADE NAME	CHINPI Liquid

Ⅰ. Animal Test or Non-animal Test

Test Categories	Result			Test species
Acute Oral Toxicity ALD : Approximate lethal dose	・ALD : ・Mortality	Male : / Female : /		
	Result	Dosing concentration	Test species	Number of subjects
Primary Skin Irritation	Not Performed			
Cumulative Skin Irritation	Not Performed			
Skin Sensitization	Not Performed			
Photo Toxicity	Not Performed			
Photosensitization	Not Performed			
Ocular Irritation	Not Performed			
Remark				

Ⅱ. Human Patch Test

Dosing concentration	Undiluted					
	−	±	+	++	+++	++++
48 hours	27	2	1	0	0	0
72 hours	30	0	0	0	0	0

《Remark》
− : No reaction
± : Slight erythema
+ : Well defined erythema
++ : Erythema + Papule or Edema
+++ : Erythema + Papule, Edema + Vesicle
++++ : Large blister

Published on June 20 2014

TRADE NAME	CHINPI Liquid

Ⅲ. Mutagenicity Test

Test Categories	Result
Mutagenicity (Reverse mutation)	Not Performed
Mutagenicity (Chromosomal aberration)	Not Performed

Published on June 20 2014

TRADE NAME : CHINPI Liquid

Acute Oral Toxicity Test

Not Performed

Primary Skin Irritation

Not Performed

Cumulative Skin Irritation

Not Performed

Skin Sensitization

Not Performed

Photo Toxicity

Not Performed

Photosensitization

Not Performed

Ocular Irritation

Not Performed

Human Patch Test

Occlusive patch with the sample was applied on the branchium to 30 healthy adults for 48 hours. The subjects were examined for signs of erythema and edema etc. at 1 and 24 hours after removal of patches.

27 persons were observed no irritating responses at 1 hour after removal of patches, however 2 persons were observed slight erythema (±), 1 person was observed well defined erythema (+). No erythema and no edema were observed at 24 hours after removal of patches.

Mutagenicity (Reverse mutation)

Not Performed

Mutagenicity (Chromosomal aberration)

Not Performed

Published on May 9 2013

TOXICITY & SAFETY

TRADE Name	:	MandarinClear
Completion Data	:	April 5 2013
INCI Name	:	Butylene Glycol, Water, Citrus Reticulata (Tangerine) Peel Extract

* Important information

These toxicological safety tests were performed in accordance with Japanese Pharmaceutical Affairs Law or our company policy based on its law. It does not provide any guarantee about the cosmetic preparations or formulations used these test data.

ICHIMARU PHARCOS Co.,Ltd.

Published on May 9 2013

TRADE NAME	MandarinClear

Ⅰ. Animal Test or Non-animal Test

Test Categories	Result			Test species
Acute Oral Toxicity ALD : Approximate lethal dose	・ALD : ・Mortality	Male : / Female : /		
	Result	Dosing concentration	Test species	Number of subjects
Primary Skin Irritation	Non Irritant	–	–	
Cumulative Skin Irritation	Not Performed			
Skin Sensitization	Hypoallergenic	Undiluted	Human	56
Photo Toxicity	Non phototoxic	–	–	
Photosensitization	Not Performed			
Ocular Irritation	Relatively low cytotoxicity	–	–	

Remark

The studies were conducted according to the following method.
Primary Skin Irritation(In Vitro Skin Irritation): Human reconstructed epidermis (SkinEthic model) (OECD 439)
Skin Sensitization: 9 Repeated Insult (semi-occlusive) Patch Test (9-RIPT)
Photo Toxicity: In Vitro 3T3 NRU Phototoxcity Test (OECD 432)
Ocular Irritation: Neutral red release method on SIRC cell line

Ⅱ. Human Patch Test

Dosing concentration						
	−	±	+	++	+++	++++
24 hours						
48 hours						

《Remark》
− : No reaction
± : Slight erythema
+ : Well defined erythema
++ : Infiltration or Erythema with edema
+++ : Erythema + Infiltration + Papule - Vesicle
++++ : Large blister

Published on May 9 2013

TRADE NAME	MandarinClear

Ⅲ. Mutagenicity Test

Test Categories	Result
Mutagenicity (Reverse mutation)	Reverse mutation was negative.
Mutagenicity (Chromosomal aberration)	Not Performed

Published on May 9 2013

TRADE NAME : MandarinClear

Acute Oral Toxicity Test

Not Performed

Primary Skin Irritation

Performed the test under the OECD guideline 439.

The sample was non irritant.

Cumulative Skin Irritation

Not Performed

Skin Sensitization

Performed the test under the 9 Repeated Insult (semi-occlusive) Patch Test (9-RIPT).

The sample did not induce clinically significant skin irritation nor show any evidence of induced allergic contact dermatitis.

Photo Toxicity

Performed the test under the OECD guideline 432.

The sample can be assigend as non phototoxic.

Photosensitization

Not Performed

Ocular Irritation

Performed the test under neutral red release method on SIRC cell line.

The sample may be classified as relatively low cytotoxicity.

Human Patch Test

Not Performed

Mutagenicity (Reverse mutation)

Performed the test under the OECD guideline 471.

Reverse mutation was negative.

Mutagenicity (Chromosomal aberration)

Not Performed

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: February 11, 2016

SUBJECT: Concentration of Use by FDA Product Category: Citrus Peel-Derived Ingredients

Concentration of Use by FDA Product Category – Citrus Peel-Derived Ingredients*

Citrus Aurantifolia (Lime) Peel Extract
Citrus Aurantifolia (Lime) Peel Powder
Citrus Aurantifolia (Lime) Peel Water
Citrus Aurantifolia (Lime) Peel
Citrus Aurantium Amara (Bitter Orange) Peel
Citrus Aurantium Amara (Bitter Orange) Peel Extract
Citrus Aurantium Amara (Bitter Orange) Peel Powder
Citrus Aurantium Amara (Bitter Orange) Peel Wax
Citrus Aurantium Bergamia (Bergamot) Peel Water
Citrus Aurantium Dulcis (Orange) Peel Extract
Citrus Aurantium Dulcis (Orange) Peel Powder
Citrus Aurantium Dulcis (Orange) Peel Wax
Citrus Aurantium Sinensis Peel Extract
Citrus Aurantium Tachibana Peel Extract
Citrus Depressa Peel Extract
Citrus Depressa Peel Powder
Citrus Grandis (Grapefruit) Peel Extract
Citrus Grandis (Grapefruit) Peel Powder
Citrus Grandis (Grapefruit) Peel
Citrus Hassaku/Natsudaidai Peel Powder
Citrus Iyo Peel Extract
Citrus Iyo Peel Water
Citrus Jabara Peel Extract
Citrus Jabara Peel Water
Citrus Junos Peel Powder
Citrus Junos Peel Extract
Citrus Junos Peel Water
Citrus Limon (Lemon) Peel
Citrus Limon (Lemon) Peel Extract
Citrus Limon (Lemon) Peel Powder
Citrus Limon (Lemon) Peel Water
Citrus Limon (Lemon) Peel Wax
Citrus Natsudaidai Peel Extract
Citrus Nobilis (Mandarin Orange) Peel Extract
Citrus Nobilis (Mandarin Orange) Peel Powder
Citrus Paradisi (Grapefruit) Peel Extract
Citrus Reticulata (Tangerine) Peel Powder
Citrus Reticulata (Tangerine) Peel Extract
Citrus Shunkokan Peel Extract
Citrus Sunki Peel Extract
Citrus Tachibana/Reticulata Peel Powder
Citrus Tangelo Peel Powder
Citrus Tangerina (Tangerine) Peel Extract
Citrus Tangerina (Tangerine) Peel
Citrus Unshiu Peel Extract
Citrus Unshiu Peel Powder
Citrus Unshiu Peel Water

Ingredient	**Product Category**	**Maximum Concentration of Use**
Citrus Aurantifolia (Lime) Peel Extract	Eye lotions	0.00005%
Citrus Aurantifolia (Lime) Peel Extract	Shampoos (noncoloring)	0.0003-0.006%
Citrus Aurantifolia (Lime) Peel Extract	Tonics, dressings and other hair grooming aids Not spray	0.0000013%
Citrus Aurantifolia (Lime) Peel Extract	Foundations	0.05%
Citrus Aurantifolia (Lime) Peel Extract	Bath soaps and detergents	0.0021%
Citrus Aurantifolia (Lime) Peel Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0001-0.005%
Citrus Aurantifolia (Lime) Peel Extract	Face and neck products Not spray or powder	0.00035-1.1%
Citrus Aurantifolia (Lime) Peel Extract	Body and hand products	

	Not spray or powder	0.0088%
Citrus Aurantifolia (Lime) Peel Extract	Moisturizing products Not spray	0.0005%
Citrus Aurantifolia (Lime) Peel Extract	Other skin care preparations	0.005%
Citrus Aurantifolia (Lime) Peel Extract	Suntan products Not spray	0.0005%
Citrus Aurantifolia (Lime) Peel Extract	Indoor tanning preparations	0.0005%
Citrus Aurantifolia (Lime) Peel Extract	Other suntan preparations	0.05%
Citrus Aurantifolia (Lime) Peel Powder	Body and hand products Not spray	0.06%
Citrus Aurantium Amara (Bitter Orange) Peel	Hair conditioners	0.002%
Citrus Aurantium Amara (Bitter Orange) Peel	Shampoos (noncoloring)	0.002%
Citrus Aurantium Amara (Bitter Orange) Peel	Other personal cleanliness products	0.2%
Citrus Aurantium Amara (Bitter Orange) Peel	Face and neck products Not spray	0.002%
Citrus Aurantium Amara (Bitter Orange) Peel	Body and hand products Not spray	0.002-0.16%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Bath oils, tablets and salts	0.002%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Eye shadows	0.018%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Eye lotions	0.00006-0.005%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Hair conditioners	0.00001-0.0063%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Hair sprays Pump spray	0.001%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Shampoos (noncoloring)	0.00001-0.0063%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Tonics, dressings and other hair grooming aids	0.002%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Blushers	0.0002-0.001%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Face powders	0.001%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Foundations	0.0002-0.002%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Lipstick	0.0002%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Basecoats and undercoats (manicuring preparations)	0.00002%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Nail polish and enamel	0.0001%
Citrus Aurantium Amara (Bitter Orange)	Bath soaps and detergents	0.0000016-0.0032%

Peel Extract		
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0032%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Face and neck products Not spray Spray	 0.002-0.005% 0.002%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Body and hand products Not spray	 0.0001-0.002%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Moisturizing products Not spray	 0.00015%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Night products Not spray	 0.001%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Paste masks and mud packs	0.0006-0.05%
Citrus Aurantium Amara (Bitter Orange) Peel Extract	Suntan products Not spray	 0.001%
Citrus Aurantium Amara (Bitter Orange) Peel Powder	Paste masks and mud packs	1.6%
Citrus Aurantium Bergamia (Bergamot) Peel Water	Hair conditioners	0.0001%
Citrus Aurantium Bergamia (Bergamot) Peel Water	Shampoos (noncoloring)	0.0001%
Citrus Aurantium Dulcis (Orange) Peel Extract	Bubble baths	0.0025%
Citrus Aurantium Dulcis (Orange) Peel Extract	Other bath preparations	0.0025%
Citrus Aurantium Dulcis (Orange) Peel Extract	Other eye makeup preparations	0.0005%
Citrus Aurantium Dulcis (Orange) Peel Extract	Colognes and toilet waters	0.0005%
Citrus Aurantium Dulcis (Orange) Peel Extract	Powders (dusting and talcum)	0.028%
Citrus Aurantium Dulcis (Orange) Peel Extract	Hair conditioners	0.0016-0.03%
Citrus Aurantium Dulcis (Orange) Peel Extract	Rinses (noncoloring)	0.0005%
Citrus Aurantium Dulcis (Orange) Peel Extract	Shampoos (noncoloring)	0.0007-0.014%
Citrus Aurantium Dulcis (Orange) Peel Extract	Tonics, dressings and other hair grooming aids	0.00001%
Citrus Aurantium Dulcis (Orange) Peel Extract	Foundations	0.0005%
Citrus Aurantium Dulcis (Orange) Peel Extract	Makeup bases	0.1%
Citrus Aurantium Dulcis (Orange) Peel Extract	Bath soaps and detergents	0.0005-0.14%
Citrus Aurantium Dulcis (Orange) Peel	Other personal cleanliness	0.0001%

Extract	products Foot soak	 0.0000025%
Citrus Aurantium Dulcis (Orange) Peel Extract	Shaving cream	0.028%
Citrus Aurantium Dulcis (Orange) Peel Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0005-0.1%
Citrus Aurantium Dulcis (Orange) Peel Extract	Face and neck products Not spay	 0.0025-0.02%
Citrus Aurantium Dulcis (Orange) Peel Extract	Body and hand products Not spray	 0.000002-0.0005%
Citrus Aurantium Dulcis (Orange) Peel Extract	Moisturizing products Not spray Spray	 0.0005-0.03% 0.15%
Citrus Aurantium Dulcis (Orange) Peel Extract	Skin fresheners	0.0005%
Citrus Aurantium Dulcis (Orange) Peel Extract	Other skin care preparations	0.25%
Citrus Aurantium Dulcis (Orange) Peel Powder	Bath soaps and detergents	0.4-0.5%
Citrus Aurantium Dulcis (Orange) Peel Powder	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	2%
Citrus Aurantium Dulcis (Orange) Peel Wax	Lipstick	0.5-1.9%
Citrus Aurantium Dulcis (Orange) Peel Wax	Face and neck products Not spray	 1%
Citrus Aurantium Tachibana Peel Extract	Bath soaps and detergents	0.00016%
Citrus Aurantium Tachibana Peel Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0008-0.0032%
Citrus Aurantium Tachibana Peel Extract	Face and neck products Not spray Spray	 0.0032% 0.0016%
Citrus Aurantium Tachibana Peel Extract	Body and hand products Not spray	 0.0016%
Citrus Depressa Peel Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0014%
Citrus Depressa Peel Extract	Face and neck products Not spray	 0.0014%
Citrus Depressa Peel Extract	Body and hand products Not spray	 0.0014%
Citrus Grandis (Grapefruit) Peel Extract	Bath oils, tablets and salts	0.0005%
Citrus Grandis (Grapefruit) Peel Extract	Eyeliners	0.064%
Citrus Grandis (Grapefruit) Peel Extract	Eye lotions	0.1-0.5%
Citrus Grandis (Grapefruit) Peel Extract	Eye makeup removers	0.01%
Citrus Grandis (Grapefruit) Peel Extract	Colognes and toilet waters	0.01%
Citrus Grandis (Grapefruit) Peel Extract	Shampoos (noncoloring)	0.0001%
Citrus Grandis (Grapefruit) Peel Extract	Tonics, dressings and other hair	

	grooming aids Not spray	 0.0000013-0.0002%
Citrus Grandis (Grapefruit) Peel Extract	Face powders	0.1%
Citrus Grandis (Grapefruit) Peel Extract	Foundations	0.1%
Citrus Grandis (Grapefruit) Peel Extract	Bath soaps and detergents	0.0015-0.015%
Citrus Grandis (Grapefruit) Peel Extract	Other personal cleanliness products	0.0095%
Citrus Grandis (Grapefruit) Peel Extract	Aftershave lotions	0.2%
Citrus Grandis (Grapefruit) Peel Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0002-0.023%
Citrus Grandis (Grapefruit) Peel Extract	Face and neck products Not spray	 0.0009-0.05%
Citrus Grandis (Grapefruit) Peel Extract	Body and hand products Not spray Spray	 0.0095-0.05% 0.0095-0.01%
Citrus Grandis (Grapefruit) Peel Extract	Foot products	0.0009%
Citrus Grandis (Grapefruit) Peel Extract	Moisturizing products Not spray	 0.009%
Citrus Grandis (Grapefruit) Peel Extract	Paste masks and mud packs	0.003%
Citrus Grandis (Grapefruit) Peel Extract	Other skin care preparations	0.0094-0.03%
Citrus Grandis (Grapefruit) Peel Extract	Suntan products Not spray	 0.03%
Citrus Jabara Peel Extract	Face powders	0.037%
Citrus Jabara Peel Extract	Foundations	0.037%
Citrus Jabara Peel Extract	Face and neck products Not spray	 0.0037%
Citrus Junos Peel Powder	Hair conditioners	0.002%
Citrus Junos Peel Powder	Shampoos (noncoloring)	0.002%
Citrus Junos Peel Powder	Face and neck products Not spray	 0.002%
Citrus Junos Peel Powder	Body and hand products Not spray	 0.002%
Citrus Junos Peel Extract	Bath oils, tablets and salts	0.0012%
Citrus Junos Peel Extract	Eye lotions	0.036%
Citrus Junos Peel Extract	Hair conditioners	0.0012%
Citrus Limon (Lemon) Peel	Bath soaps and detergents	0.4%
Citrus Limon (Lemon) Peel Extract	Colognes and toilet waters	0.0005%
Citrus Limon (Lemon) Peel Extract	Hair conditioners	0.00005-0.002%
Citrus Limon (Lemon) Peel Extract	Hair sprays Pump spray	 0.000033%
Citrus Limon (Lemon) Peel Extract	Shampoos (noncoloring)	0.00005-0.0031%
Citrus Limon (Lemon) Peel Extract	Tonics, dressings and other hair grooming aids	0.0006%
Citrus Limon (Lemon) Peel Extract	Blushers	0.000005%
Citrus Limon (Lemon) Peel Extract	Foundations	0.016%
Citrus Limon (Lemon) Peel Extract	Lipstick	0.0012-0.0025%

Citrus Limon (Lemon) Peel Extract	Mouth washes and breath fresheners	0.000008%
Citrus Limon (Lemon) Peel Extract	Bath soaps and detergents	0.0005-0.0051%
Citrus Limon (Lemon) Peel Extract	Aftershave lotions	0.1%
Citrus Limon (Lemon) Peel Extract	Skin cleansing (cold creams, cleansing lotions, liquid and pads)	0.000048-0.057%
Citrus Limon (Lemon) Peel Extract	Face and neck products Not spray	0.0001-0.12%
Citrus Limon (Lemon) Peel Extract	Body and hand products Not spray	0.0005-0.14%
Citrus Limon (Lemon) Peel Extract	Moisturizing products Not spray	0.012%
Citrus Limon (Lemon) Peel Extract	Paste masks and mud packs	0.004-0.015%
Citrus Limon (Lemon) Peel Powder	Bath soaps and detergents	0.5%
Citrus Nobilis (Mandarin Orange) Peel Extract	Bubble baths	0.0025%
Citrus Nobilis (Mandarin Orange) Peel Extract	Other bath preparations	0.0005%
Citrus Nobilis (Mandarin Orange) Peel Extract	Colognes and toilet waters	0.0005%
Citrus Nobilis (Mandarin Orange) Peel Extract	Other fragrance preparations	0.0001%
Citrus Nobilis (Mandarin Orange) Peel Extract	Hair conditioners	0.0003-0.005%
Citrus Nobilis (Mandarin Orange) Peel Extract	Shampoos (noncoloring)	0.0003-0.05%
Citrus Nobilis (Mandarin Orange) Peel Extract	Tonics, dressings and other hair grooming aids Not spray	0.0001%
Citrus Nobilis (Mandarin Orange) Peel Extract	Blushers	0.025%
Citrus Nobilis (Mandarin Orange) Peel Extract	Bath soaps and detergents	0.0001%
Citrus Nobilis (Mandarin Orange) Peel Extract	Deodorants Not spray	0.0005%
Citrus Nobilis (Mandarin Orange) Peel Extract	Other personal cleanliness products	0.0001%
Citrus Nobilis (Mandarin Orange) Peel Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.000025-0.023%
Citrus Nobilis (Mandarin Orange) Peel Extract	Body and hand products Not spray	0.0025%
Citrus Nobilis (Mandarin Orange) Peel Extract	Moisturizing products Not spray	0.000005-0.009%
Citrus Nobilis (Mandarin Orange) Peel Extract	Paste masks and mud packs	0.003%
Citrus Nobilis (Mandarin Orange) Peel Extract	Other skin care preparations	0.0000005%

Citrus Reticulata (Tangerine) Peel Extract	Eye lotion	0.002%
Citrus Reticulata (Tangerine) Peel Extract	Foundations	0.01%
Citrus Reticulata (Tangerine) Peel Extract	Bath soaps and detergents	0.00029%
Citrus Reticulata (Tangerine) Peel Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0012%
Citrus Reticulata (Tangerine) Peel Extract	Face and neck products Not spray	 0.01%
Citrus Reticulata (Tangerine) Peel Extract	Body and hand products Not spray	 0.0012%
Citrus Reticulata (Tangerine) Peel Extract	Suntan products Not spray	 0.00048%
Citrus Reticulata (Tangerine) Peel Extract	Indoor tanning preparations	0.00048%
Citrus Tangerina (Tangerine) Peel Extract	Shampoos (noncoloring)	0.0000048%
Citrus Unshiu Peel Extract	Bath oils, tablets and salts	0.03%
Citrus Unshiu Peel Extract	Eye lotions	0.00036-0.002%
Citrus Unshiu Peel Extract	Eye makeup removers	0.000002%
Citrus Unshiu Peel Extract	Face powders	0.01%
Citrus Unshiu Peel Extract	Foundations	0.00005-0.0002%
Citrus Unshiu Peel Extract	Lipstick	0.00036%
Citrus Unshiu Peel Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0005-0.094%
Citrus Unshiu Peel Extract	Face and neck products Not spray Spray	 0.0005-0.094% 0.002%
Citrus Unshiu Peel Extract	Body and hand products Not spray	 0.002-0.0095%
Citrus Unshiu Peel Extract	Moisturizing products Not spray	 0.00094-0.002%
Citrus Unshiu Peel Extract	Other skin care preparations	0.0005%
Citrus Unshiu Peel Powder	Bath oils, tablets and salts	0.5%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported

Information collected in 2015-2016
Table prepared February 9, 2016

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: February 16, 2016

SUBJECT: Citrus Grandis (Grapefruit) Peel Extract

Anonymous. 2013. Summary HRIPT of an eye area product containing 0.5% Citrus Grandis (Grapefruit) Peel Extract.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Summary - HRIPT of an Eye Area Product Containing 0.5% Citrus Grandis (Grapefruit) Peel Extract

Study completed in 2013

Eye are product containing 0.5% Citrus Grandis (Grapefruit) Peel Extract was tested undiluted 55 subjects completed the HRIPT

Conclusion: The test material did not induce dermal irritation or clinically significant irritant contact dermatitis in human subjects

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: February 16, 2016

SUBJECT: Citrus Limon (Lemon) Peel Extract

Institute for In Vitro Sciences, Inc. 2012. Tissue equivalent assay with EpiOcular™ cultures (moisturizer containing 0.1% Citrums Limon (Lemon) Peel Extract).

Alba Science Ltd. 2011. A 14 day human cumulative irritation patch test (moisturizer with 0.1% Citrus Limon (Lemon) Peel Extract).

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

FINAL REPORT

Study Title

TISSUE EQUIVALENT ASSAY WITH EPIOCULAR™ CULTURES

Test Articles

[redacted]

Test article of interest is a moisturizer with 0.1% Citrus Limon (Lemon) Peel Extract.

Greg Mun, B.A.
Nicole Barnes, B.S.

Study Completion Date

15 March 2012

Performing Laboratory

Institute for In Vitro Sciences, Inc.
30 West Watkins Mill Road, Suite 100
Gaithersburg, MD 20878

Study Number

[redacted]

[redacted]

Laboratory Project Number

[redacted]

TISSUE EQUIVALENT ASSAY WITH EPIOCULAR™ CULTURES

SUMMARY

IIVS Test Article Number	Sponsor's Designation	Conc.	t_{50} (hours)		pH
			Preliminary (24 Aug 2011)	Trial 1 (31 Aug 2011)	
[redacted]					
moisturizer w/ 0.1% lemon peel ext		Neat	4.6	4.3	5.5
[redacted]					
Positive Control	0.3% Triton-X-100®	NA	37.2 minutes	26.7 minutes	NA

NA - Not Applicable

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The Tissue Equivalent Assay With EpiOcular™ Cultures of the test articles, [redacted] was conducted in compliance with the U.S. FDA Good Laboratory Practice Regulations as published in 21 CFR 58 and the principles presented in the OECD series on Good Laboratory Practice in all material aspects with the following exceptions:

> The identity, strength, purity and composition or other characteristics to define the test articles have not been determined by the testing facility. The certificates of analysis were not provided by the Sponsor.
>
> The stability of the test articles under the storage conditions at the testing facility and under the actual test conditions has not been determined by the testing facility and is not included in the final report.

Greg Mun, B.A.
Study Director

15 March 2012
Date

QUALITY ASSURANCE STATEMENT

Study Title: Tissue Equivalent Assay with EpiOcular Cultures

Study Number: [redacted]

Study Director: Greg Mun, B.A.

This study was divided into a series of in-process phases. Using a random sampling approach, Quality Assurance monitored each of these phases over a series of studies. Procedures, documentation, equipment records, etc., were examined in order to assure that the study was performed in accordance with the U.S. FDA Good Laboratory Practice Regulations (21 CFR 58), and the OECD Principles of Good Laboratory Practice and to assure that the study was conducted according to the protocol and relevant Standard Operating Procedures.

The following are the inspection dates, phases inspected and report dates of QA inspections of this study:

Phase Inspected	Audit Date(s)	Reported to Study Director	Reported to Management
Protocol and Initial Paperwork	23-Aug-11	23-Aug-11	20-Oct-11
Definitive Assay – Rinsing of Tissues / Addition of MTT – 4 hour time point	31-Aug-11	31-Aug-11	01-Sep-11
Draft Report and Data	21&24-Oct-11	25-Oct-11	25-Oct-11
Final Report	13-Mar-12	13-Mar-12	14-Mar-12

This report describes the methods and procedures used in the study and the reported results accurately reflect the raw data of the study.

Amanda K. Ulrey, RQAP-GLP
Quality Assurance

15-March-2012
Date

SIGNATURE PAGE

TISSUE EQUIVALENT ASSAY WITH EPIOCULAR™ CULTURES

Initiation Date: 19 August 2011

Completion Date: 15 March 2012

Sponsor: [redacted]

Sponsor's Representative: [redacted]

Testing Facility and Study Director Address: Institute for In Vitro Sciences, Inc.
30 West Watkins Mill Road, Suite 100
Gaithersburg, MD 20878

Archive Location: [redacted]

Study Director: _____ 15 March 2012
Greg Mun, B.A. Date

Laboratory Manager: Nathan R. Wilt, B.S.

Laboratory Supervisor: Allison Hilberer, M.S.

TEST ARTICLE RECEIPT

IIVS Test Article Number	Sponsor's Designation	Physical Description	Receipt Date	Storage Conditions*
[redacted]				
[redacted]		cloudy off-white cream	12 August 2011	room temperature
[redacted]				

* - Protected from exposure to light

INTRODUCTION

The EpiOcular™ Human Cell Construct (MatTek Corporation) was used to assess the potential ocular irritancy of the test article. The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) conversion assay, which measures the NAD(P)H-dependent microsomal enzyme reduction of MTT (and to a lesser extent, the succinate dehydrogenase reduction of MTT) to a blue formazan precipitate, was used to assess cellular metabolism after exposure to a test article for various exposure times[1]. The duration of exposure resulting in a 50% decrease in MTT conversion in test article-treated EpiOcular™ human cell constructs, relative to control cultures, was determined (t_{50}).

The purpose of this study was to evaluate the potential toxicity of the test articles, supplied by [redacted] as measured by the conversion of MTT by EpiOcular™ human cell constructs after exposure to a test article for various exposure times. The laboratory phase of the study was conducted from 23 August 2011 to 1 September 2011 at the Institute for In Vitro Sciences, Inc. After a time range finding assay, the test articles were tested in a valid definitive assay to determine the time of exposure to a test article, which resulted in the t_{50} endpoint.

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1 Berridge, M.V., Tan, A.S., McCoy, K.D., Wang, R. (1996) The Biochemical and Cellular Basis of Cell Proliferation Assays That Use Tetrazolium Salts. Biochemica 4:14-19.

MATERIALS AND METHODS

Receipt of the EpiOcular™ Human Cell Construct Model

Upon receipt of the EpiOcular™ Human Cell Construct Kit (MatTek Corporation), the solutions were stored as indicated by the manufacturer. The EpiOcular™ human cell constructs were stored at 2-8°C until used. On the day of dosing an appropriate volume of EpiOcular™ human cell construct assay medium was removed and warmed to approximately 37°C. Nine hundred µL of assay medium were aliquoted into the wells of 6-well plates. The six-well plates were labeled to indicate test article and exposure time. The samples were inspected for air bubbles between the agarose gel and Millicell® insert prior to opening the sealed package. Cultures with air bubbles covering greater than 50% of the Millicell® area were not used. The 24-well shipping containers were removed from the plastic bag and their surfaces were disinfected with 70% ethanol. The EpiOcular™ human cell constructs were transferred aseptically into the 6-well plates. The EpiOcular™ human cell constructs were then incubated at 37±1°C in a humidified atmosphere of 5±1% CO_2 in air for at least one hour. The medium was then aspirated and 0.9 mL of fresh medium were added to each assay well below the EpiOcular™ human cell construct. The plates were returned to the incubator until treatment was initiated. Upon opening the shipping bag, any remaining unused tissues were briefly gassed with an atmosphere of 5% CO_2/95% air and placed back at 2-8°C for later use.

Test Article Preparation

As instructed by the Sponsor, each test article was administered to the test system without dilution.

Assessment of Direct Test Article Reduction of MTT

Each test article was added to a 1.0 mg/mL MTT (Sigma) solution in warm Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 2 mM L-glutamine (MTT Addition Medium) to assess its ability to directly reduce MTT. Approximately 100 µL of each test article were added to 1 mL of the MTT solution and the mixtures were incubated in the dark at 37°C for approximately one hour. If the MTT solution color turned blue/purple, the test article was presumed to have reduced the MTT.

The test articles were not observed to reduce MTT in the absence of viable cells.

pH Determination

The pH of each neat liquid test article was measured using pH paper (EMD Chemicals Inc.). Initially, the test articles were added to pH paper with 0-14 pH range in 1.0 pH unit increments to approximate a narrow pH range. Next, the test articles were added to pH paper with a narrower range of 0-6 and/or 5-10 pH units with 0.5 pH unit increments, to obtain a more accurate pH value. The pH values obtained from the narrower range pH paper are presented in Table 1.

Time Range Finding Assay

A time range finding assay was performed to establish an appropriate exposure time range to be used in the definitive assay for each test article. Four exposure times of 1, 4, 8, and 16 hours were tested in the time range finding assay. One culture was treated per exposure time with 100 µL of the appropriate test article or control. The negative control, 100 µL of sterile, deionized water (Quality Biological), was exposed for 16 hours. The positive control, 100 µL of 0.3% Triton®-X-100 (Fisher), was exposed for 15 and 45 minutes (one culture per exposure time). The exposed cultures were then incubated for the appropriate amount of time at 37±1°C in a humidified atmosphere of 5±1% CO_2 in air.

After the appropriate exposure time, the EpiOcular™ cultures were extensively rinsed with Calcium and Magnesium-Free Dulbecco's Phosphate Buffered Saline ($Ca^{++}Mg^{++}$-Free DPBS) and the wash medium was decanted. After rinsing, the tissue was transferred to 5 mL of Assay Medium for a 10 to 20 minute soak at room temperature to remove any test article absorbed into the tissue. A 1.0 mg/mL solution of MTT in warm MTT Addition Medium was prepared no more than 2 hours before use. Three hundred µL of MTT solution were added to designated wells in a prelabeled 24-well plate. The EpiOcular™ constructs were transferred to the appropriate wells after rinsing with $Ca^{++}Mg^{++}$-Free DPBS. The trays were incubated at 37±1°C for approximately three hours in a humidified atmosphere of 5±1% CO_2 in air.

After the incubation period with MTT solution, the EpiOcular™ cultures were blotted on absorbent paper, cleared of excess liquid, and transferred to a prelabeled 24-well plate containing 2.0 mL of isopropanol in each designated well. The plates were sealed with parafilm and stored in the refrigerator (2-8°C) until the last exposure time was harvested. The plates were then shaken for at least two hours at room temperature.

At the end of the extraction period, the liquid within the Millicell® inserts was decanted into the well from which the Millicell® insert was taken. The extract solution was mixed and 200 µL were transferred to the appropriate wells of a 96-well plate. Two hundred µL of isopropanol were added to the two wells designated as the blanks. The absorbance at 550 nm (OD_{550}) of each well was measured with a Molecular Devices Vmax plate reader.

Definitive Assay

Based on the results of the time range finding assay, four to five exposure times were chosen for the definitive assay. The exposure times for the test articles, [redacted] and [redacted] were 0.33, 1, 2, 4, and 8 hours. The exposure times for the test article, [redacted] were 4, 8, 16, and 24 hours. The exposure times for the test articles, [redacted] were 1, 4, 8, and 16 hours. The exposure times for the test article, of interest were 1, 2, 4, and 8 hours. The exposure times were chosen such that generally two exposure times were expected to result in survivals lower than 50% and two exposure times were expected to result in survivals greater than 50%. In general, the negative control exposure times were selected to fit the range of the test article or positive control exposure times. The negative control (100 µL of sterile, deionized water) was exposed for 0.25, 4, 8, and 24 hours. The positive control (100 µL of 0.3% Triton®-X-100) was exposed for 15 and 45 minutes. The procedures used to conduct the definitive assay were essentially the same as for the time range finding assay with the exception that at least duplicate cultures were dosed per exposure time.

Presentation of Data

The raw absorbance values were captured. The mean OD_{550} value of the blank wells was calculated. The corrected mean OD_{550} value of the negative controls was determined by subtracting the mean OD_{550} value of the blank wells from their mean OD_{550} values. The corrected OD_{550} value of the individual test article exposure times and the positive control exposure times was determined by subtracting the mean OD_{550} value of the blank control from their OD_{550} values. The individual % of Control values were averaged to get the mean % of Control value. All calculations were performed using an Excel spreadsheet. The following percent of control calculations were made:

$$\% \text{ of Control} = \frac{\text{corrected } OD_{550} \text{ of Test Article or Positive Control Exposure Time}}{\text{appropriate corrected mean } OD_{550} \text{ of Negative Control}} \times 100$$

Exposure time response curves were plotted with the % of Control on the ordinate and the test article or positive control exposure time on the abscissa. The t_{50} value was interpolated from each plot. To determine the t_{50}, the two consecutive points were selected, where one exposure time resulted in a relative survival greater than 50%, and one exposure time resulted in less than 50% survival. Two select points were used to determine the slope and the y-intercept for the equation $y=m(x) + b$. Finally, to determine the t_{50}, the equation was solved for $y=50$.

Criteria for a Valid Test

The assay results were accepted when the positive control, 0.3% Triton®-X-100, caused a t_{50} value within two standard deviations of the historical mean. The corrected mean OD_{550} value for the minimum negative control exposure time should be within 20% of the corrected mean OD_{550} value for the maximum negative control exposure time (up to 4 hours).

RESULTS AND DISCUSSION

Time Range Finding Assay

A time range finding assay was performed, consisting of four exposure times of 1, 4, 8, and 16 hours for the test articles supplied by [redacted] The exposure time response curves are included in Appendix B. Based upon the results of the time range finding assay, four to five exposure times were selected for each test article for the definitive assay (see Materials and Methods). The t_{50} results for the time range finding assay are reported in Table 1, under "Preliminary".

The test articles were not observed to reduce MTT directly in the absence of viable tissue.

The test article, [redacted] could not be completely removed from all the exposed tissues following the rinsing and soaking process after the 8 hour exposure time in the time range finding assay. Following a consultation with the Sponsor, the rinsing of the tissues was performed in the same manner in the definitive assay using the Calcium and Magnesium-Free Dulbecco's Phosphate Buffered Saline ($Ca^{++}Mg^{++}$-Free DPBS) at the room temperature and the soaking of the tissues was performed in the Assay Medium at the room temperature for all test articles in the definitive assay.

Definitive Assay

Four to Five exposure times were treated in duplicate for each test article. The exposure times for the test articles, [redacted] were 0.33, 1, 2, 4, and 8 hours. The exposure times for the test article, [redacted] were 4, 8, 16, and 24 hours. The exposure times for the test articles [redacted] were 1, 4, 8, and 16 hours. The exposure times for the test article, of interest were 1, 2, 4, and 8 hours. The negative control was also exposed in duplicate for 0.25, 4, 8, and 24 hours. Table 1 summarizes the t_{50} results of the definitive Tissue Equivalent Assay With EpiOcular™ Cultures for the test articles and the positive control, 0.3% Triton®-X-100, under "Trial 1". The exposure time response curves are included in Appendix B. Since the positive control fell within two standard deviations of the historical mean (15.8 – 38.9 minutes), and the corrected mean OD_{550} value for the minimum negative control exposure time (1.225) was within 20% of the corrected mean OD_{550} value for the maximum negative control exposure time (up to 4 hours) (1.140), the assay results were accepted.

Table 1

IIVS Test Article Number	Sponsor's Designation	Conc.	t_{50} (hours)		pH
			Preliminary (24 Aug 2011)	Trial 1 (31 Aug 2011)	
[redacted]					
[redacted] moisturizer w/ 0.1% lemon peel ext.		Neat	4.6	4.3	5.5
[redacted]					
Positive Control	0.3% Triton-X-100®	NA	37.2 minutes	26.7 minutes	NA

NA - Not Applicable

STUDY DETAILS

STUDY NO	[redacted]
SPONSOR STUDY NO	[redacted]
STUDY TITLE	A 14 Day Human Cumulative Irritation Patch Test
STUDY DATES	16 Aug 2011 - 30 Aug 2011
TEST MATERIALS	[redacted] moisturizer with 0.1% Citrus limon (lemon) peel extract
CONTROL MATERIALS	Distilled Water Sodium Lauryl Sulfate
CRO NAME	Alba Science Ltd.
PROJECT MANAGER	Marie Reynolds BSc (Hons), SCS Dip.
CRO ADDRESS	Alba Science Ltd. 24 Broughton Street Edinburgh EH1 3RH United Kingdom
DERMATOLOGY CONSULTANT	Dr Terrina Dickson MBChB MRGCP DRCOG DPD
SPONSOR NAME	[redacted]
SPONSOR CO-ORDINATOR	[redacted]
SPONSOR ADDRESS	[redacted]

STUDY SUMMARY

STUDY NO	[redacted]
SPONSOR STUDY NO	[redacted]
STUDY TITLE	A 14 Day Human Cumulative Irritation Patch Test
REGULATORY STATUS	Cosmetic
STUDY DATES	16 Aug 2011 - 30 Aug 2011
STUDY OBJECTIVES	To assess the potential of test substances to elicit human skin irritation by repetitive topical application.
STUDY DESIGN	Single-centre, within-subject comparison, double blind, randomised
STUDY POPULATION	30 subjects
TEST MATERIALS	[redacted] moisturizer with 0.1% lemon peel extract
CONTROL MATERIALS	Distilled Water Sodium Lauryl Sulfate
ADMINISTRATION ROUTE	Topical.
FREQUENCY & DURATION	14 applications (approximately 23h) over 15 Days
EVALUATION CRITERIA	Skin Assessment - Visual assessment of erythema, dryness and other signs.
ADVERSE EVENTS	Recorded throughout study period
STATISTICAL ANALYSIS	Statistical Analysis of Irritation.

SIGNATURES	
STUDY NO	[redacted]
SPONSOR STUDY NO	[redacted]
STUDY TITLE	A 14 Day Human Cumulative Irritation Patch Test
PROJECT MANAGER	Marie Reynolds BSc (Hons), SCS Dip.
SIGNED	Marie Reynolds DATE 25 Oct 2011

DOCUMENT INFORMATION

VERSION	1.3
ISSUED DATE	21 Oct 2011
AUTHOR	Lilian Fotheringham
STATUS	Final

REVISION HISTORY

VERSION	ISSUE DATE	REASON FOR ISSUE
1.3	21 Oct 2011	QA Audited. Authorisation by Sponsor to finalise.
1.2	17 Oct 2011	Reviewed by Sponsor.
1.1	05 Oct 2011	Reviewed by Sponsor.
1.0	10 Sep 2011	Issued for review/comment

1 INTRODUCTION

This study was conducted on behalf of [redacted] A 14 Day Cumulative Human Irritation Patch test was carried out with 6 products and 2 controls applied under fully occlusive patch conditions. The test materials were compared with the standard positive (0.1% SLS) and negative (Sterile water) controls. The study was completed in 30 healthy subjects.

2 STUDY OBJECTIVE

The purpose of this study was to assess the potential of test substances to elicit human skin irritation by repetitive topical application.

3 STUDY METHOD

Study Protocol

The study was performed in accordance with Alba Science Ltd. Study Protoco[redacted]

A copy of the Study Protocol is included in Appendix D.

Design Description

A double-blind, within-subject comparison study was performed. There was 1 group of 35 subjects, each testing all of the test materials on each day of the study.

Primary Endpoints

The primary endpoint of the study was skin irritation (average skin grades and cumulative irritation index).

Secondary Endpoints

There was no secondary endpoint.

4 TEST MATERIALS

Supply of Test Materials

The following test materials were supplied for inclusion on the study by the Sponsor and were received by Alba Science on 09 Aug 2011.

Test Materials			
No.	Code	Name	Test Concentration
1	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	Moisturiser	100%

The following control materials were supplied for inclusion on the study by Alba Science.

Control Materials			
No.	Code	Name	Test Concentration
8	Negative Control	Sterile Water	100%
9	Positive Control	Sodium Lauryl Sulfate	0.1% w/v in Sterile Water

Test Material Receipt Procedure

Numbers were assigned to each of the test materials to facilitate the randomisation of the products during their application.

All containers were individually checked for integrity and to ensure that product / code numbers were correct as expected for the study. All containers were weighed and all details were entered into a controlled sample inventory and management computer system.

Test Material Safety

The test materials were formulated and tested to comply with current European regulations.

A safety assessment was conducted by an appropriately qualified individual on behalf of the Sponsor and the test materials were considered safe by that individual under reasonably foreseeable conditions of use associated with the study. The test materials were stable for the duration of the study.

Labelling

The test materials supplied were labelled with an Alba Science Test Material label, containing the Study Number and the assigned Test Material Number.

Storage

The test materials were stored in the dark at ambient temperature.

Preparation

The test materials were diluted to the concentrations described above prior to each daily application. They were applied directly to the Webril pads in 0.2 ml amounts no more than 15 min prior to the patch being applied to the skin.

5 LOCATION

The study was conducted at the premises of Alba Science Ltd., 24 Broughton Street, Edinburgh, EH1 3RH, United Kingdom.

6 TIMING

The study was performed from 16 Aug 2011 until 30 Aug 2011.

7 STUDY SUMMARY

Application and Exposure

Each subject was exposed to the test materials on one outer upper arm for 14 consecutive periods of approximately 23 hours. Prior to the first patch application the skin on the upper arms was wiped with isopropyl alcohol to remove excess oil.

The Test Materials coded 1 to 6 were applied to the skin by means of 2cm x 2cm squares of Webril backed with semi-occlusive Hypafix adhesive tape (5cm wide low allergy dressing retention sheet, BSN Medical GmbH, Hamburg, Germany). Control Materials coded 8 and 9 were applied to the skin by means of 2cm x 2cm squares of Webril backed with occlusive Blenderm adhesive tape. All test materials were applied in 0.2 ml amounts. Test materials were applied to the patch no longer than 15 min prior to skin application. Skin markers were used to mark the skin at either end of the patch strips to allow exact relocation to the test areas at subsequent applications.

Approximately 23 hours (± 1 h) after application of the first patch scheme, the subjects returned to the test centre for patch removal. The test sites were wiped with water and patted dry to remove any residual test material. The test sites were assessed approximately 20 - 40 min later by a trained assessor following the scoring system detailed in section 13 of this document.

After assessment of reactions, an identical patch scheme was reapplied to the same area for a further period of approximately 23 hours. The test materials were reapplied to the same site as before following assessment. Any test material which elicited erythema or dryness with a score of 2 or more was not reapplied.

If a score of 2 or more was observed for any test material and consequently no longer applied, then a score of 2 will have been used for the remainder of the study for that site unless the score increased, in which case the higher score will have been recorded. The residual score will also have been recorded but not used for the calculations or statistical analysis.

Treatment was over 15 consecutive days commencing on Day 1 when the test materials were applied as described. The test materials were applied on Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14. Skin reactions were assessed on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15. A Dermatologist also examined skin reactions on Day 15.

Application Areas

The application area for the test materials was the upper, outer arm.

Treatment Period

The total study duration from screening to study completion was 15 days. The total treatment period for each subject was 14 days

8 SUBJECT PARTICIPATION

Participation Summary

49 subjects were recruited for the study, of which 36 were screened. Of these, 35 subjects participated in this study. 30 subjects completed the study. 5 subjects were withdrawn from the study.

Information and Consent

Subjects were provided with a Volunteer Information document and were asked to provide signed consent to take part in the study. This was done by signing two copies of a Subject Consent Form. One copy is stored in the Project File and the other was retained by the subject.

Screening

Screening was based on the completion of a Medical and Dermatological History Questionnaire for each subject. Subjects were assessed for eligibility onto the main phase of the study based on the defined inclusion/exclusion criteria detailed in the Study Protocol.

9 RANDOMISATION

Test Materials were referred to throughout the study only by their test material number, as allocated during the test material receipt process outlined above.

A Randomised Product Application Schedule was generated by a computer system for each subject in order to randomly allocate each product to an application site. The Randomised Product Application Schedules were allocated to each subject prior to the application of any test materials. These are retained in the project file.

10 MEASURING EQUIPMENT

No special measuring equipment was used to aid skin assessments for this study.

11 ENVIRONMENTAL CONDITIONS

Standard Northlight lighting conditions were used throughout the study.

12 DATA COLLECTION AND PROCESSING

Recorded Data

The following data was recorded during the study.

- Skin Irritation Scores

Recording Methods

Data was recorded onto a 'Subject Assessment Sheet' at each visit to the test centre.

Data Checking

All data was 100% checked for accuracy and completeness by Alba Science personnel.

Data Storage

All data was entered into a computer system where it was subject to a further 100% check against source data.

Data Processing

For data processing, a computer system checked and prepared the raw study data to produce the processed data for the study. Where appropriate, this processing used any Randomised Product Application Schedules involved in the study. A Data Analysis Report was generated containing both raw and processed data, together with other information gathered throughout the study.

Data Analysis

The Data Analysis Report was made available for the purposes of formal independent Statistical Analysis and Quality Control inspection.

13 SCORING SYSTEM

The following P&G Uniform Laboratory Patch Test Grading Scale was used during the study.

[redacted] Patch Test Grading Scale	
Grade	**Description**
0	No apparent cutaneous involvement.
0.5	Greater than 0, less than 1.
1	Faint but definite erythema, no eruptions or broken skin or no erythema but definite dryness; may have epidermal fissuring.
1.5	Greater than 1, less than 2.
2	Moderate erythema, may have a few papules or deep fissures, moderate-to-severe erythema in the cracks. Cut-off Grade - Patches are not reapplied
2.5	Greater than 2, less than 3.
3	Severe erythema (beet redness), may have generalized papules or moderate-to-severe erythema with slight oedema (edges well defined by raising).
3.5	Greater than 3, less than 4.
4	Generalized vesicles or eschar formations or moderate-to-severe erythema and/or oedema extending beyond the area of the patch.

NOTE: The degree of reaction expressed by such descriptive terms as "moderate" and "severe" is, in itself, subjective. Such terminology can be accurately understood only through experience.

Typical Examples of Half-Grade Scores	
Grade	Description
0.5	Faint, barely perceptible erythema or slight dryness (glazed appearance).
1.5	Well-defined erythema or faint erythema with definite dryness, may have epidermal fissuring.
2.5	Moderate erythema with barely perceptible oedema or severe erythema not involving a significant portion of the patch (halo effect around the edges), may have a few papules or moderate-to-severe erythema.
3.5	Moderate-to-severe erythema with moderate oedema (confined to patch area) or moderate-to-severe erythema with isolated eschar formations or vesicles.

14 ADVERSE REACTIONS / ADVERSE EVENTS

Details of the adverse events reported during the study are provided below.

Adverse Events Summary					
Subject	Details	Severity	Relationship	Status	Medication
112401	Cold Symptoms Started : 21 Aug 11 Resolved : 23 Aug 11	Mild	Unrelated	Resolved	None
111191	Cold Symptoms Started : 25 Aug 11 Resolved : 27 Aug 11	Mild	Unrelated	Resolved	None
115527	Cold Symptoms Started : 27 Aug 11 Resolved : 29 Aug 11	Mild	Unrelated	Resolved	None
112207	Cold Symptoms Started : 17 Aug 11 Resolved : 19 Aug 11	Mild	Unrelated	Resolved	Benylin PRN
112207	Dizziness Started : 27 Aug 11 Resolved : 27 Aug 11	Mild	Unrelated	Resolved	None

15 DISCUSSION AND CONCLUSION

All test materials were well tolerated under the conditions of the 14 Day Cumulative Human Skin Irritation Patch Test with less irritation than the positive control.

16 QUALITY ASSURANCE

The draft report was reviewed by our Quality Assurance personnel and audited prior to this Final Report being issued.

All data was 100% checked for accuracy.

17 GOOD CLINICAL PRACTICE

No formal claim of GCP compliance has been made for this study, however the practices and procedures adopted during the conduct of this study have been consistent with the Principles of Good Clinical Practice (CPMP/ICH/135/95).

18 ETHICS COMMITTEE AND REGULATORY APPROVAL

As this was a cosmetic study, Ethics Committee and Regulatory approval for the study was not required. As the study involved human subjects, it was conducted in consideration of the requirements of the 1996 Declaration of Helsinki.

19 ARCHIVING

The Sponsor's study protocol states that appropriate documentation to permit complete reconstruction of the study will be retained by the Investigator (Alba Science Ltd).

However, the sponsor's representative requires the Trial Master File to be returned to [redacted] upon the issue of the Final Report. Alba Science Ltd. will, therefore, not retain any study documentation pertaining to this study.

20 REFERENCES

None.

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: March 2, 2016

SUBJECT: Citrus Aurantifolia (Lime) Peel Extract and Citrus Grandis (Grapefruit) Peel Extract

Product Investigations, Inc. 2006. Determination of the irritating and sensitizing propensities of a face and neck product containing 2.14% Citrus Aurantifolia (Lime) Peel Extract.

Product Investigations, Inc. 2012. Determination of the irritating and sensitizing propensities of a face and neck product containing 0.1% Citrus Grandis (Grapefruit) Peel Extract.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Citrus Aurantifolia (Lime) Peel Extract @ 2.14% in a face/neck product [MT#2238737]

PRODUCT INVESTIGATIONS, INC.

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

REPORT: PII Nº 21381

DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF MT# 2238737 ON HUMAN SKIN

PREPARED FOR

[redacted]

29 November 2006

[redacted]

[redacted]

TABLE OF CONTENTS

DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF MT# 2238737 ON HUMAN SKIN

1.00 OBJECTIVES:

.01 To identify and characterize the skin-damaging propensities that MT# 2238737 can be induced to exercise under the conditions of this modified patch test procedure.

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

2.00 DESIGN:

.01 A modified version of the Repeated Insult Patch Test (cf. Protocol MSM-205.E.L.) was conducted under double blind conditions on a panel composed of more than one hundred subjects at the outset.

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

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

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

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

3.00 SPONSOR:

Project Director:

Authorization:

4.00 STUDY PRODUCT:

Type of Product:	Facial Cream
Sponsor Identification:	MT# 2238737
Date received:	10/9/06
Quantity rec'd:	> 600 g. gross wt.
Form used in study:	as supplied
PI №	21381

5.00 SITE OF STUDY:

Product Investigations, Inc.
151 East Tenth Avenue
Conshohocken, PA 19428

Study Personnel:

Medical Director:	Morris V. Shelanski, MDCM
Dir. Derm. Services:	Joseph E. Nicholson III
Technicians:	Kay Walk, Margaret Reilly
Quality Assurance:	Samuel J. Charles III

6.00 DATES OF STUDY:

Started:	16 October 2006
Completed:	15 November 2006

7.00 SELECTION OF SUBJECTS:

.01 RECRUITING:

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

.02 INFORMED CONSENT:

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

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

.03 DETERMINATION OF ELIGIBILITY:

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

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

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

.04 PANEL INFORMATION:

a. **Panel Nº:** 06239

b. **Demographics:**

SEX	Number	Age Range
Female	82	18 - 70
Male	27	20 - 66

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8.00 SITE INFORMATION:

.01 LOCATION:

MT# 2238737 was assigned Band #4 on the left side of the back of each subject.

.02 IDENTIFICATION OF A CONTACT SITE:

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

9.00 PATCHING DEVICES:

.01 TYPE OF DEVICE:

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

.02 PREPARATION OF A PATCHING DEVICE:

a. The webril pad of a patching device was infused with 150µl of the test material.

.03 POSITIONING AND REMOVING A PATCHING DEVICE:

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

10.00 DATA ACQUISITION:

.01 GRADING PROCEDURE:

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

.02 CRITERIA FOR GRADING RESPONSE INTENSITY:

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

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

.04 SITE CHANGES:

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

11.00 OVERVIEW OF STUDY REGIMEN:

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week #1	Apply	Remove	Rem/Gr/Apply	Remove	Rem/Gr/Apply	(Removed)	--
Week #2	Grade/Apply	Remove	Rem/Gr/Apply	Remove	Rem/Gr/Apply	(Removed)	--
Week #3	Grade/Apply	Remove	Rem/Gr/Apply	Remove	Rem/Gr/Apply	(Removed)	--
Week #4	Grade	—	—	--	--	--	--
Week #6	Apply	Remove/Grade	Grade	Grade*	Grade*	--	--

*If necessary

12.00 STUDY REGIMEN:

.01 INITIAL/INDUCTION PHASE-

Week #1:

Monday:

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

Tuesday:

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

Wednesday:

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

Thursday:

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

Friday:

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

Week #2 / Week #3:

Monday:

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

Tuesday, Wednesday, Thursday, Friday:

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

Week #4:

Monday:

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii a) If the subject had undergone all nine induction applications, she/he was dismissed after being instructed as follows:
   i) to report back to the clinic on the second Monday following to receive the challenge applications, and
   ii) to notify the investigator without delay should any significant changes occur in the skin of the contact site before Monday of the challenge week.
   b) If the subject had not received the required number of induction applications and was deficient without valid reason, applications were continued. As many as two missed applications could be made up during this week. When the subject had undergone the required number of make up applications, she/he was dismissed after being instructed as in sections ii(a), above.

.02 **HIATUS/MAKE UP PHASE-**

Week # 4:

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

.03 **CHALLENGE PHASE-**

Week #5:

Monday:

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

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

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

Wednesday:

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

.04 **FOLLOW-UP PHASE:**

Week No. 6 and Week No. 7:

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

13.00 PROCEDURE DEVIATIONS:

None were necessary.

14.00 COMPLIANCE:

PHASE	No. Of AEC's Required	EXCUSED	COMPLIANT	
			YES	NO
Induction	8	0	109	0
Challenge	1/1	0	109	0

109 of the 109 Subjects were in compliance with the number of required application/examination cycles during induction.
109 of the 109 Subjects were in compliance with the number of required application/examination cycles during challenge.

15.00 INCIDENCE OF RESPONSES:

			Challenge Phase	
Grade	Type of Response	Induction Phase	Original Contact Site	Naive Contact Site
0	No visible change	109 subjects	109 subjects	109 subjects
1	Faint redness, undefined border	0 "	0 "	0 "
2	Intense redness, defined border	0 "	0 "	0 "
3	Redness + definite edema	0 "	0 "	0 "
4	Redness + papules, or vesicles, etc.	0 "	0 "	0 "
	No. of Responders	0 subjects	0 subjects	0 subjects
	No Data Acquired	0 subjects	0 subjects	0 subjects

16.00 SIGNIFICANCE OF THE RESPONSES:

.01 Initial/Induction Phase:

No responses were noted on any of the 109 subjects who underwent at least one post-application examination. The absence of responses characterize the product as one which is devoid of clinically significant skin-irritating propensities.

.02 Challenge Phase:

a. **Original Contact Sites:**
No responses were noted on any of the 109 subjects who participated in this phase of the study. The absence of responses characterize the product as one which is devoid of clinically significant skin sensitizing propensities.

b. **Naive Contact Sites:**
No responses were noted on any of the 109 subjects who participated in this phase of the study. The absence of responses characterize the product as one which is devoid of clinically significant skin sensitizing propensities.

17.00 CONCLUSIONS:

.01 MT# 2238737 was found to be neither a clinically significant skin irritant nor a skin sensitizer under the conditions of this study.

.02 MT# 2238737 is not contraindicated for usages entailing repeated applications on human skin under conditions appropriate for such products.

PRODUCT INVESTIGATIONS, INC.

11/29/06
Date

Joseph E. Nicholson III
Director, Clinical Studies

18.00 COMPLIANCE WITH GOOD QUALITY ASSURANCE STANDARDS:

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

Samuel Charles
Director, Quality Assurance

PANEL 06239

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Sponsor Code:	MT#2238737	PI No: 21381	Site: L4

Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE WEEK					
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5					
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M
001	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
002	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
003	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
004	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
005	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
006	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
007	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
008	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
009	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
010	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
011	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
012	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
013	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
014	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
015	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
016	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
017	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
018	B/0		0		0	0		0		A	0		0		0	0					B/0	0/0	0/0			
019	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
020	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
021	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
022	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
023	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
024	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
025	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
026	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
027	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
028	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
029	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
030	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			

PANEL 06239

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Subj #	Sponsor Code:					MT#2238737										PI No: 21381					Site: L4					
	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE WEEK					
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5					
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M
031	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
032	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
033	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
034	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
035	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
036	B/0		0		0	A		0		0	0		A		0	0					B/0	0/0	0/0			
037	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
038	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
039	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
040	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
041	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
042	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
043	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
044	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
045	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
046	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
047	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
048	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
049	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
050	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	A -			
051	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
052	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
053	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
054	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
055	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
056	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
057	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
058	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
059	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
060	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			

PANEL 06239

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Sponsor Code:	MT#2238737	PI No: 21381	Site: L4

Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE WEEK					
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5					
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M
061	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
062	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
063	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
064	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
065	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	A			
066	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
067	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
068	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
069	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
070	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
071	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
072	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
073	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
074	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
075	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
076	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
077	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
078	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
079	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
080	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
081	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
082	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
083	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
084	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
085	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
086	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
087	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
088	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
089	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
090	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			

PANEL 06239

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	Sponsor Code:					MT#2238737										PI No: 21381					Site: L4					
Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE WEEK					
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5					
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M
091	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
092	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
093	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
094	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
095	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
096	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
097	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
098	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
099	B/0		0		0	0		0		A	0		0		0	0					B/0	0/0	0/0			
100	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
101	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
102	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
103	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
104	B/0		0		0	0		0		0	A		0		0	0					B/0	0/0	0/0			
105	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
106	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
107	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
108	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			
109	B/0		0		0	0		0		0	0		0		0	0					B/0	0/0	0/0			

LEGEND

A = Absent
D = Dropped

Monday week 6: Only if any reactions on the last Friday week 5 (challenge week)

Citrus Grandis (Grapefruit) Peel Extract @ 0.1% in an eye lotion [MT#22518941]

PRODUCT INVESTIGATIONS, INC

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

REPORT: PII Nº 30899

DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF MT#2518941 ON HUMAN SKIN

PREPARED FOR

[redacted]

[redacted] MT#2518941

28 November 2012

[redacted]

TABLE OF CONTENTS

DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF MT#2518941 ON HUMAN SKIN

1.00 OBJECTIVES:

.01 To identify and characterize the skin-damaging propensities that MT#2518941 can be induced to exercise under the conditions of this modified patch test procedure.

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

2.00 DESIGN:

.01 A modified version of the Repeated Insult Patch Test (cf. Protocol MSM-205 F.1.) was conducted on two panels whose combined total was greater than two hundred subjects at the outset.

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

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

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

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

[redacted]

4.00 STUDY PRODUCT: [redacted]

Sponsor Identification:	MT#2518941 (MH)
Date received:	9/12/12
Quantity rec'd:	>665 g. gross wt.
Form used in study:	Volatilized
PI N°	30899

5.00 SITE OF STUDY:

Product Investigations, Inc.
1010 Carver Road
Modesto, CA 95350

Study Personnel:

Medical Director:	Morris V. Shelanski, MD/CM
CA Physician:	Clinton E. Prescott Jr., MD
Dir. Derm. Services:	Joseph F. Nicholson III
Technicians:	Lisa A. Cortez, Henry Cortez
Quality Assurance:	Samuel J. Charles III

6.00 DATES OF STUDY:

Started:	24 September 2012
Completed:	2 November 2012

7.00 SELECTION OF SUBJECTS:

.01 RECRUITING:

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

.02 INFORMED CONSENT:

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

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

.03 DETERMINATION OF ELIGIBILITY:

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

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

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

.04 PANEL INFORMATION:

a. Panel N^{os}: 12403 and 12417

b. Demographics:

SEX	Number	Age Range
Female	133	18 - 86
Male	87	18 - 71

[redacted]

8.00 SITE INFORMATION:

.01 LOCATION:

MT#2518941 was assigned Band #4 on the left side of the back of each subject

.02 IDENTIFICATION OF A CONTACT SITE:

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

9.00 PATCHING DEVICES:

.01 TYPE OF DEVICE:

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

.02 PREPARATION OF A PATCHING DEVICE:

The wetted pad of a patching device was infused with 200 µL of the test material and allowed to volatilize for at least 30 minutes prior to application.

.03 POSITIONING AND REMOVING A PATCHING DEVICE:

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

10.00 DATA ACQUISITION:

.01 GRADING PROCEDURE:

a. Examinations of the contact sites to grade the effects elicited by the product were conducted on Mondays, Wednesday and Fridays. When a subject came in on a scheduled examination day, the technician examined the skin of the contact site.
   i. If no adverse effect was detected, a "0" was recorded in the subject's Case Report Form.
   ii. If an adverse effect was detected, the technician entered a grade indicating her assessment of the response's intensity.
b. The subject was then sent into the patching room where the site was examined again by a second technician to ascertain independently whether or not the site should be used again. If she disagreed with the first technician's assessment, the application was held in abeyance until the issue could be resolved with the help of the supervisor and/or the investigator.
c. The supervisor or the investigator was called in not only when a disagreement had to be resolved, but also to validate substantial sudden changes, e.g. when a response is deemed to merit a grade 2-3 or when a response has been judged to have decreased by two or more points from the previous day's status.

.02 CRITERIA FOR GRADING RESPONSE INTENSITY:

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

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

.04 SITE CHANGES:

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

11.00 **OVERVIEW OF STUDY REGIMEN: Please note deviations in schedule**

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

*If necessary

12.00 **STUDY REGIMEN:**

.01 **INITIAL/INDUCTION PHASE:**

Week #1:

Monday:

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

Tuesday:

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

Wednesday:

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

Thursday:

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

Friday:

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

Week #2:

Monday:

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

Tuesday:

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

Wednesday:

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

Thursday:

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

Friday:

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

Week #3:

Monday:

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

Tuesday:

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

Wednesday:

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

Thursday:

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

Friday:

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

Week #4:

Monday:

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. The site-identifying marks were reinforced and the subject was instructed to:
   (i) report back to the clinic on the following Monday to receive the challenge applications, and
   (ii) to notify the investigator without delay should any significant changes occur in the skin of the contact site before Monday of the challenge week.

HIATUS PHASE: Week 4, Tuesday through Friday

.03 **CHALLENGE PHASE:-**

Week #5:

Monday:

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

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

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

Wednesday:

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

.04 **FOLLOW-UP PHASE:**

Week No. 6 and Week No. 7:

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

13.00 PROCEDURE DEVIATIONS:

None were necessary.

14.00 COMPLIANCE

PHASE	No. OF ALLOWED Repeated	EXCUSED	COMPLIANT YES	NO
Induction	8	6	210	10
Challenge	11	0	209	11

[illegible]

15.00 INCIDENCE OF RESPONSES:

GRADE	EFFECT OF RESPONSE	INDUCTION PHASE	CHALLENGE PHASE: ORIGINAL CONTACT SITE	NAIVE CONTACT SITE
0	NO VISIBLE CHANGE.	216 SUBJECTS	209 SUBJECTS	209 SUBJECTS
1	FAINT REDNESS, UNDEFINED BORDER	0 "	0 "	0 "
2	INTENSE REDNESS, DEFINED BORDER	0 "	0 "	0 "
3	REDNESS + DEFINED, EDEMA	0 "	0 "	0 "
4	REDNESS + PAPULES, OR VESICLES, ETC.	0 "	0 "	0 "
	NO. OF RESPONDERS	0 SUBJECTS	0 SUBJECTS	0 SUBJECTS
	NO DATA ACQUIRED	4 SUBJECTS	11 SUBJECTS	11 SUBJECTS

16.00 SIGNIFICANCE OF THE RESPONSES:

.01 **INITIAL/INDUCTION PHASE:**

No responses were noted on any of the 216 subjects who underwent at least one post-application examination. The absence of responses characterizes the product as one which is devoid of clinically significant skin-irritating propensities.

.02 **CHALLENGE PHASE:**

a. **Original Contact Sites:**
No responses were noted on any of the 209 subjects who participated in this phase of the study. The absence of responses characterizes the product as one which is devoid of clinically significant skin sensitizing propensities.

b. **Naive Contact Sites:**
No responses were noted on any of the 209 subjects who participated in this phase of the study. The absence of responses characterizes the product as one which is devoid of clinically significant skin sensitizing propensities.

17.00 CONCLUSIONS:

.01 MT#2518941 was found to be neither a clinically significant skin irritant nor a skin sensitizer under the conditions of this study.

.02 MT#2518941 is not contraindicated for usages entailing repeated applications on human skin under conditions appropriate for such products.

PRODUCT INVESTIGATIONS, INC.

Date: 12/21/97

Joseph E. Nicholson III
Director, Dermatological Studies

18.00 COMPLIANCE WITH GOOD QUALITY ASSURANCE STANDARDS:

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

Samuel Charles
Director, Quality Assurance

[redacted]

Panel: 12403																												
Sample No. 2518941 (MH)																												
PI No: 30899																												
Site: L4																												
Subj #	INDUCTION PHASE																HIATUS/MAKEUPS					CHALLENGE PHASE						
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5						
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F		
1	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
2	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
3	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
4	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
5	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
6	B		A		Dropped																						
7	B		0		0	0		A		Dropped																	
8	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
9	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
10	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
11	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
12	B		0		0	A		0		C	0		0		0	0		0			B	0/0	0/0				
13	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
14	B		0		0	A		A		Dropped																	
15	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
16	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
17	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
18	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
19	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
20	B		0		0	0		0		C	0		0		0	0					B	0/0	0/0				
21	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
22	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
23	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
24	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
25	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
26	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
27	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
28	B		0		0	A		A		Dropped																	
29	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
30	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				

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

[redacted]

	Panel: 12403										Sample No. 2518941 (MH)									PI No: 30899					Site: L4				
Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE PHASE								
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5							
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F				
31	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
32	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
33	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
34	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
35	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
36	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
37	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
38	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
39	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
40	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
41	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
42	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
43	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
44	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
45	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
46	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
47	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
48	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
49	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
50	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
51	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
52	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
53	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
54	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
55	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
56	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
57	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
58	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
59	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						
60	B		C		0	C		0		0	0		0		0	C					B	0/0	0/0						

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

[redacted]

	Panel: 12403										Sample No. 2518941 (MH)										PI No: 30899					Site: L4				
Su j #	INDUCTION PHASE																HIATUS/MAKEUPS					CHALLENGE PHASE								
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5								
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F					
61	B		0		0	C		0		0	0		0		C	0					B	0/C	0/0							
62	B		0		0	C		0		0	0		0		C	0					B	0/C	0/0							
63	B		0		0	C		0		0	0		0		C	0					B	0/C	0/0							
64	B		0		0	C		0		0	0		0		C	0					B	0/C	0/0							
65	B		0		0	C		0		0	0		0		C	0					B	0/C	0/0							
66	B		0		C	C		C		0	0		0		C	0					B	0/C	0/0							
67	B		0		C	0		C		0	0		0		C	0					B	0/C	0/0							
68	B		0		C	0		C		0	0		0		C	0					B	0/C	0/0							
69	B		0		C	0		C		0	0		0		C	0					B	0/C	0/0							
70	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
71	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
72	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
73	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
74	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
75	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
76	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
77	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
78	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
79	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
80	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
81	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
82	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
83	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
84	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
85	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
86	B		0		C	0		C		0	0		0		C	0					B	0/C	0/0							
87	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
88	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							
89	B		0		C	0		C		0	0		0		C	0					B	0/C	0/0							
90	B		0		C	0		C		0	C		0		C	0					B	0/C	0/0							

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

[redacted]

Panel: 12403																											
Sample No. 2518941 (MH)																											
PI No: 30899																											
Site: L4																											
Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE PHASE						
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5						
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F		
91	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
92	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
93	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
94	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
95	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
96	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
97	B		A		Dropped																						
98	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
99	B		0		0	0		0		0	A		A		Dropped												
100	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
101	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
102	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
103	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
104	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
105	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
106	B		A		Dropped																						
107	B		A		Dropped																						
108	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
109	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				
110	B		0		0	0		0		0	0		0		0	0					B	0/0	0/0				

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

[redacted]

Subj #	Panel: 12417										Sample No. 2518941 (MH)										PI No: 30899					Site: L4				
	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE PHASE									
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5								
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F					
1	B		D		C	D		C		D	C		D		D	D					B	D/D	C/D						
2	B		D		C	D		C		D	C		D		D	D					B	D/D	C/D						
3	B		D		C	A		A		Dropped																			
4	B		D		C	D		C		D	C		D		D	D					B	D/D	C/D						
5	B		D		C	D		C		D	C		D		D	D					B	D/D	C/D						
6	B		D		C	D		C		D	C		D		D	D					B	D/D	C/D						
7	B		D		C	D		C		D	C		D		D	D					B	D/D	C/D						
8	B		D		C	D		C		D	C		D		D	D					B	D/D	C/D						
9	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
10	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
11	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
12	B		D		C	A		A		Dropped																			
13	B		D		C	D		C		D	D		D		C	D					B	D/D	C/D						
14	B		D		C	D		C		D	D		D		C	D					B	D/D	C/D						
15	B		D		C	D		C		D	D		D		C	D					B	D/D	C/D						
16	B		D		C	D		C		D	D		D		C	D					B	D/D	C/D						
17	B		D		C	D		C		D	D		D		C	D					B	D/D	C/D						
18	B		D		C	D		C		D	D		D		C	D					B	D/D	C/D						
19	B		D		C	D		C		D	D		D		C	D					B	D/D	C/D						
20	B		D		C	D		C		D	D		D		C	D					B	D/D	C/D						
21	B		D		C	D		C		D	D		D		C	D					B	D/D	C/D						
22	B		D		C	D		C		D	D		D		C	C					B	D/D	C/D						
23	B		D		C	D		C		D	D		D		C	C					B	D/D	C/D						
24	B		D		C	D		C		D	D		D		C	C					B	D/D	C/D						
25	B		D		C	D		C		D	D		D		C	C					B	D/D	C/D						
26	B		D		C	D		C		D	D		D		C	C					B	D/D	C/D						
27	B		D		C	D		C		D	D		D		C	C					B	D/D	C/D						
28	B		D		C	D		C		D	D		D		C	C					B	D/D	C/D						
29	B		D		C	D		C		D	D		D		C	C					B	D/D	C/D						
30	B		D		C	D		C		D	D		D		C	C					B	D/D	C/D						

(Grade) / (Grade) = Original Site / Na ve Site

[redacted]

	Panel: 12417										Sample No. 2518941 (MH)									PI No: 30899					Site: L4				
Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE PHASE								
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5							
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F				
31	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
32	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
33	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
34	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
35	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
36	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
37	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
38	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
39	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
40	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
41	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
42	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
43	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
44	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
45	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
46	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
47	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
48	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
49	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
50	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
51	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
52	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
53	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
54	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
55	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
56	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
57	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
58	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
59	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						
60	B		D		C	D		C		D	C		D		C	D					B	D/D	C/D						

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

[redacted]

Panel: 12417																Sample No. 2518941 (MH)					PI No: 30899					Site: L4		
Subj #	INDUCTION PHASE															HIATUS/MAKEUPS					CHALLENGE PHASE							
	WEEK 1					WEEK 2					WEEK 3					WEEK 4					WEEK 5						
	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F		
61	B		D		D	D		D		D	D		D		C	D					B	D/D	C/D				
62	B		D		D	D		D		D	D		D		C	D					B	D/D	C/D				
63	B		D		C	D		D		D	D		D		C	D					B	D/D	C/D				
64	B		D		C	D		D		D	D		D		C	D					B	D/D	C/D				
65	B		D		D	D		D		D	D		D		C	D					B	D/D	C/D				
66	B		D		C	D		D		D	D		D		C	D					B	D/D	C/D				
67	B		D		D	D		D		D	D		D		C	D					B	D/D	C/D				
68	B		D		C	D		D		D	D		D		C	D					B	D/D	C/D				
69	B		D		C	D		D		D	D		D		C	D					B	D/D	C/D				
70	B		D		C	D		D		D	D		D		C	D					B	D/D	C/D				
71	B		D		C	D		D		D	D		D		C	D					B	D/D	C/D				
72	B		D		C	D		D		D	D		D		C	D					B	D/D	C/D				
73	B		D		C	D		D		D	D		D		C	D					B	D/D	C/D				
74	B		D		C	D		D		D	D		D		C	D					B	D/D	C/D				
75	B		D		C	D		D		D	D		D		Dropped												
76	B		D		C	D		D		D	D		D		C	D					B	D/C	C/D				
77	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
78	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
79	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
80	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
81	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
82	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
83	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
84	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
85	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
86	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
87	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
88	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
89	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				
90	B		D		C	D		D		D	D		D		C	C					B	D/C	C/D				

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

[redacted]

Panel: 12417	Sample No. 2518941 (MH)	PI No: 30899	Site: L4

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

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

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: December 9, 2015

SUBJECT: Comments on the Draft Report: Safety Assessment of *Citrus* Peel-Derived Ingredients as Used in Cosmetics (draft prepared for the December 2015 CIR Expert Panel meeting)

Chemistry - It would be helpful if the Chemistry section stated how the Dictionary describes how a "water" ingredient is made.

Constituents/Composition - Published information about the composition of citrus peels still need to be added to this report.

Cosmetic Use, Summary - The European limit for furocoumarin is not presented correctly. It is now a regulation and should be cited to Annex II of the cosmetic regulations not to the 2005 SCCP opinion (reference 13). The listing in Annex II (entry 358) is for furocoumarins, it is not specifically about citrus-derived ingredients. Annex II entry 358 prohibits the use of "Furocoumarines (e.g. trioxysalen (INN), 8-methoxypsoralen, 5-methoxypsoralen) except for normal content in natural essences used. In sun protection and in bronzing products, furocoumarines shall be below 1 mg/kg."

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