
Safety Assessment of *Citrus* Flower- and Leaf-Derived Ingredients as Used in Cosmetics

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

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* Flower- and Leaf-Derived Ingredients

Enclosed is the draft tentative report of the Safety Assessment of *Citrus* Flower- and Leaf-Derived Ingredients as Used in Cosmetics. (It is identified as *cleaf062016rep* in the pdf document.)

At the December 2015 meeting, the Panel issued an Insufficient Data Announcement for the 32 *Citrus* flower- and leaf-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 Amara (Bitter Orange) Flower Extract and Citrus Aurantium Amara (Bitter Orange) Flower Water at maximum use concentrations or greater

Since the December meeting, unpublished data on the method of manufacturing and composition of Citrus Hystrix Leaf Extract, Citrus Aurantium Dulcis (Orange) Flower Extract, and Citrus Natsudaïdai Flower Oil have been received as well as irritation and/or sensitization data on Citrus Hystrix Leaf Extract, Citrus Aurantium Amara (Bitter Orange) Flower Oil, Citrus Natsudaïdai Flower Oil, Citrus Aurantium Dulcis (Orange) Flower Oil, and Citrus Aurantium Amara (Bitter Orange) Flower Extract. Composition data of leaves and flowers of several *Citrus* species were 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 (*cleaf062016pcpc* and *cleaf062016data1-9*, respectively).

After review of the available composition data on *Citrus* flowers and leaves, it appears that these ingredients do not contain furocoumarins. Language that had referred to restrictions imposed from the European Union and IFRA have thus been removed from this report.

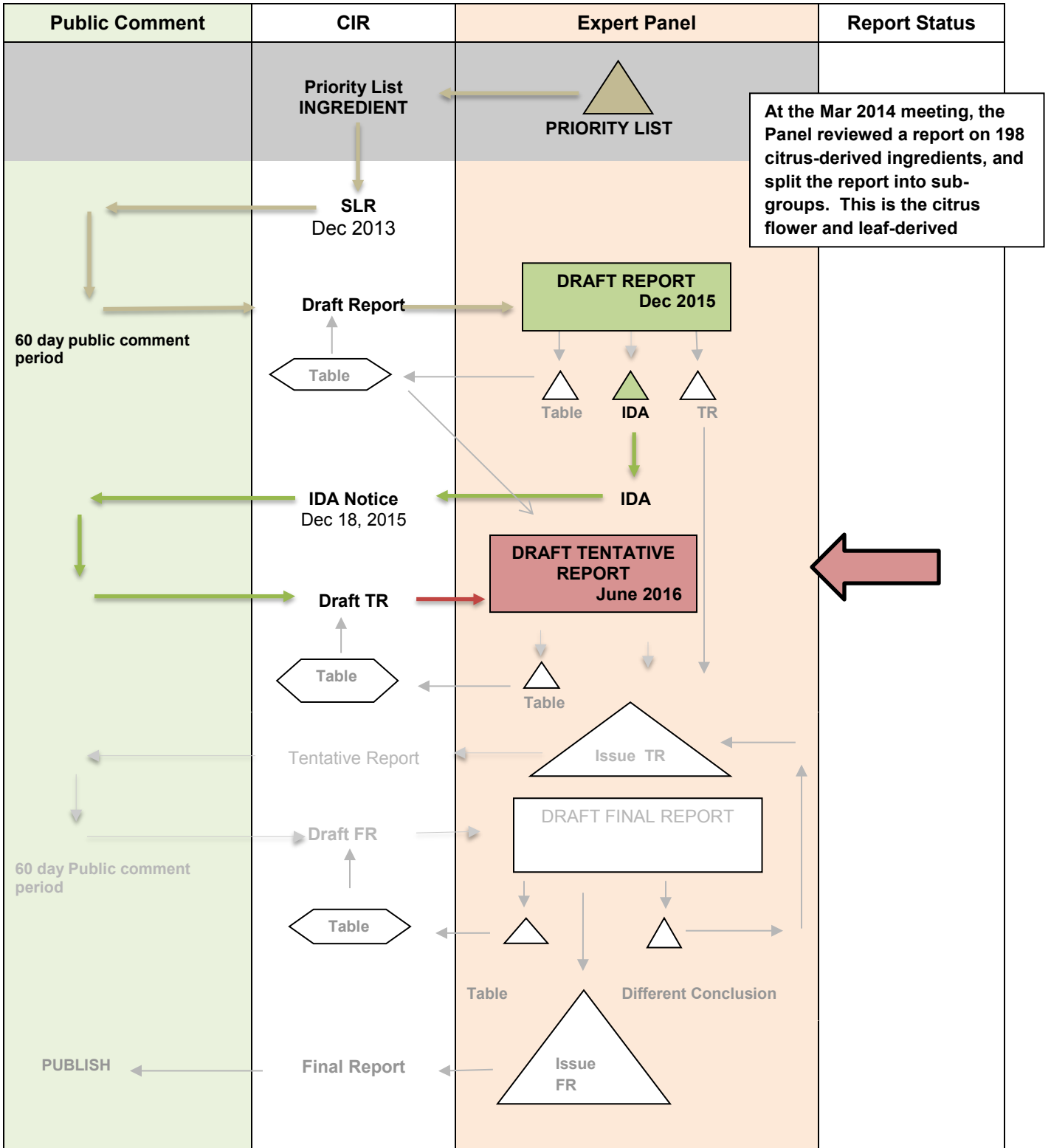
Both the VCRP and the concentration of use data have been updated for these ingredients. Currently, Citrus Aurantium Amara (Bitter Orange) Flower Oil has the most reported uses of the ingredients in this report in cosmetic products, with a total of 99; the majority of the uses are in leave-on skin care preparations. Citrus Aurantium Dulcis (Orange) Flower Extract has the second greatest number of overall uses reported, with a total of 70; a majority of the uses are in rinse-off and leave-on skin care preparations. The results of the concentration of use survey conducted by the Council indicate Citrus Aurantium Dulcis (Orange) Flower Extract has the highest reported maximum concentration of use; it is used at up to 6% in eye shadow. Citrus Aurantium Dulcis (Orange) Flower Oil had the second highest reported maximum concentration of use; it is used at up to 0.66% in a depilatory. 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) Flower Extract was previously reported to be used at up to 5% and Citrus Aurantium Amara (Bitter Orange) Flower Water was previously reported to be used at up to 4%)

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 Flower and Leaf-Derived Ingredients

MEETING June 2016



Citrus Flower- and Leaf-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 32 *Citrus* flower- and leaf-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 amara (bitter orange) flower extract and citrus aurantium amara (bitter orange) flower water at maximum use concentrations or greater

Citrus Flower- and Leaf-Derived Ingredients Data Profile – June 2016 – Writer, Christina Burnett												
	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Genotoxicity	Reproductive and Developmental Toxicity	Carcinogenicity	Irritation/Sensitization - Nonhuman	Irritation/Sensitization - Clinical	Ocular/Mucosal	Phototoxicity	Case Studies
Citrus Aurantifolia (Lime) Flower Extract	X											
Citrus Aurantium Amara (Bitter Orange) Flower Extract	X								X			
Citrus Aurantium Amara (Bitter Orange) Flower Oil	X								X			
Citrus Aurantium Amara (Bitter Orange) Flower Water	X											
Citrus Aurantium Amara (Bitter Orange) Flower wax	X		X	X				X				
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	X											
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	X											
Citrus Aurantium Dulcis (Orange) Flower	X											
Citrus Aurantium Dulcis (Orange) Flower Extract	X	X	X	X								
Citrus Aurantium Dulcis (Orange) Flower Oil	X								X			
Citrus Aurantium Dulcis (Orange) Flower Water	X											
Citrus Aurantium Dulcis (Orange) Flower Wax	X											
Citrus Aurantium Dulcis (Orange) Leaf Extract	X											
Citrus Hystrix Leaf Extract			X	X				X				
Citrus Natsudaiddai Flower Oil			X	X					X			
Citrus Natsudaiddai Flower Water			X									
Citrus Reticulata (Tangerine) Leaf Oil	X											
<i>Citrus unshiu</i> flowers (generic, not INCI)				X								
<i>Citrus depressa</i> leaves (generic, not INCI)				X								
lemon flowers (generic, not INCI)				X								
sweet orange flowers (generic, not INCI)				X								
sweet orange leaves (generic, not INCI)				X								
pomelo flowers (generic, not INCI)				X								
pomelo leaves (generic, not INCI)				X								
grapefruit leaves (generic, not INCI)				X								
mandarin orange leaf oil (generic, not INCI)				X								
mandarin orange leaves (generic, not INCI)												
bitter orange flower oil (generic, not INCI)				X								
bitter orange leaf oil (generic, not INCI)				X				X	X		X	
bitter orange leaves (generic, not INCI)				X								
Kaffir Lime (Citrus Hystrix) Leaf Oil (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 Flower- and Leaf-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 flower AND toxicity”, “citrus AND flower AND irritation”, “citrus AND leaf AND toxicity”, and “citrus AND leaf AND irritation” – 0 new relevant references found.

Updated searches February-May 2016 with “citrus flower composition” and “citrus leaf composition” – 64 hits, 5 relevant references retrieved.

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 Flower- and Leaf-Derived Ingredients
December 14-15, 2015

Dr. Marks' Team

DR. MARKS: So next is citrus flower and leaf. Are we on a roll here? So this is the first time we've seen these 32 ingredients and Tom and Ron, is the ingredients okay?

DR. SLAGA: Yes. The leaf oil and the flower oil, in a way that we -- I thought we dealt with all the oils before.

DR. HILL: I don't think --

DR. SLAGA: No?

DR. MARKS: We did peel oil.

DR. HILL: Peel oil.

DR. MARKS: We didn't do flower oil and we didn't do the other parts of the plant oils. It was just peel oil.

DR. HILL: So in this one we got flower extract, flower oil, flower wax, flower water, leaf extract, leaf oil. I think that's it.

DR. MARKS: Yes, so we have --

DR. HILL: I color coded.

DR. MARKS: -- different citrus, lime, orange, bitter orange, clementine, grapefruit, lemon and (inaudible). And then, as you said, Ron, we had different ingredients from them. One are wax, leaf cell, oil, powder, so we have sort of -- so the ingredients are all okay?

DR. HILL: I mean, it's a cumbersome grouping because clearly flower water is going to be very different than flower oil and but yet --

DR. SLAGA: It's all the leaf and all the flower.

DR. HILL: We agreed when we discussed the grouping we would group leaf and flower which make good sense. It's just we have different preparations so we have subfamilies or something like that. And then, it affects whether we read across, I think, because we've got a flower wax and we've got leaf oil and let's see. Does this capture -- nothing came in wave two on this, right? That's it. We've got --

DR. MARKS: Correct.

DR. HILL: -- some data for sensitization on bitter orange flower wax and bitter orange leaf oil which is not an INCI ingredient but is in use if I understood correctly. We don't know -- we don't capture it in the use survey. So I guess not. No, it's here for read across yes?

DR. MARKS: Yes, I think it's important that when you look at the list of 32 ingredients you go back up what we actually have data on. It's a much smaller subset of this.

DR. SLAGA: It's only on the wax and the leaf oil.

DR. HILL: That's what I got and the leaf oil is not --

MS. BURNETT: We have bergamot leaf oil but we don't have bitter orange leaf oil.

DR. HILL: But we were trying to raise it across for the tangerine leaf oil, I guess.

MS. BURNETT: Right.

DR. HILL: Which is in use but no data.

DR. MARKS: So I have a feeling this is going to be another I'll be moving for an insufficient data announcement. Ron and Tom, does that sound appropriate?

DR. SLAGA: Yes.

DR. HILL: Yes.

DR. SLAGA: Manufacturing and composition.

DR. MARKS: Yep, sounds the same, doesn't it.

DR. ANSELL: I do believe there's quite a bit of composition data that is available with the (inaudible) that.

DR. MARKS: So method of manufacture. We can almost do these ingredients, these composition and then, the -- I picked that the ones that are being used -- I picked a bitter orange flower extract, an HRIPT at five percent since that was a high concentration or a higher concentration and had a number of uses. And then, the bitter orange flower water at four percent and thought that they would be the two ones I would focus on in the HRIPT. Even though it's being used flower oil, flower extract orange.

DR. HILL: Yes, because I wrote -- what I had written in here was that there's no way we'd read across the wax data to the flower oil or leaf oil or flower extract or leaf extract because wax is a very specific kind of substance.

DR. MARKS: Right. So that seem -- does that seem reasonable just for those two HRIPTs?

DR. SHANK: Yes.

DR. MARKS: For the bitter orange flower extract five percent and the bitter orange flower water at four percent.

DR. HILL: And I have a question for Christina and maybe the FDA folks down the table. How is it that flowers and leaves, anything, are GRAS? I mean, we eat preparations made from the flowers and leaves of an orange?

MS. BURNETT: Well --

DR. HILL: Or a lemon?

MS. BURNETT: -- kaffir lime leaves are used in Thai and Indian cooking for flavoring. Flowers, people eat flowers on salad sometimes, teas. Tea.

DR. SLAGA: A lot of flowers are eaten.

DR. HILL: Okay. I just doubted that we ate orange flowers or lime flowers or lemon flowers.

DR. SHANK: We do in tea.

DR. HILL: I mean, I've seen people float them in there but I didn't think that that was the same as eating.

DR. SLAGA: Well, the hot water it would (inaudible).

DR. HILL: I guess. Okay.

DR. SLAGA: Dry herb added to the tea.

DR. MARKS: Okay. Any more with these then? Insufficient data announcement, (inaudible) manufacture, composition and then, those two ingredients get HRIPT and that would address irritation sensitivity. We note that interestingly, even though it has one use, bitter orange leaf oil or bergamot, we do have irritation sensitization, eight percent, which is okay.

DR. HILL: On which?

DR. MARKS: The bitter orange leaf oil.

MS. BURNETT: It's not an INCI.

DR. HILL: Oh, yeah, right. That's why --

DR. MARKS: Yeah, not INCI, yeah. Okay. Any other comments about the citrus flower and leaf? And now we know it's being --

DR. HILL: So on that, I didn't look up the reference specifically on that leaf oil or do we have referencing that can -- how much can we know about the preparation that was used for the study? I can't -- that's not your job to look.

MS. BURNETT: Yeah, I don't know.

DR. HILL: I'll look. Okay.

DR. MARKS: Okay. Can we move on to the next ingredient? Okay.

Dr. Belsito's Team

DR. BELSITO: So then, we move to the citrus, flower, and leaf-derived ingredients. So, again, we've, I guess, discussed the non-INCI ingredients reported to the VCRP, we are just going to continue to deal with them. And then, again, I have the same question, will the extracts, oils, waxes have the same chemical composition, this was another grouping issue. And then we start saying GRAS, but are flowers and leaves or citrus of GRAS?

MS. BURNETT: Some of the flowers are, leaves -- kaffir, lime leaves are used in Thai and Indian cuisine, I believe, that's not technically one of our cosmetic ingredients but --

DR. BELSITO: And then I guess there was, I believe it was Rachel's point on the definition of GRAS before, at one of the meetings?

MS. BURNETT: Right.

DR. BELSITO: It doesn't necessarily mean that --

DR. EISENMANN: There's a lot of composition information in the published literature of leaves and flowers that is not yet in the report, and what I was finding is that these are a lot of linalool, and citral, there's like two main groups of citrus, and the furocoumarin issue is not a part of flowers or leaves as far as I could understand.

DR. BELSITO: No.

DR. EISENMANN: It's completely different issues on these too. But there is a lot of published information that's not yet in the report, on preparations from flowers and leaves.

DR. HELDRETH: And are those preparations specific to cosmetic ingredients. Like, are they using the same (crosstalk)?

DR. EISENMANN: Some of the reports appear to be, but some of them were looking at -- they were looking at the composition of leaves and flowers, to look at where the genetic lines of the plants came from. So, some of them aren't necessarily the cosmetic ingredient, but some of them look like they were.

DR. BELSITO: So, again, here we get manufacturing for the wax, and we know very little about the extract, the oil, the water, and used up to 5 percent in leave-ons. Yes, we do have some of that information, Carol, in Table 5. You know, it's quite clear that, you know, with the flower wax, you know, you are looking at coumarin, geraniol, farnesol, so you are getting into a whole other group of potential, not phototoxins, but sensitizers here.

DR. LIEBLER: So, it looks like we can't really use the GRAS argument to skirt the tox issues, can we?

DR. BELSITO: I didn't think so, but apparently for one leaf we can.

DR. LIEBLER: Only if we can establish that that leaf is indeed the same -- that the leaf that says the cosmetic ingredient is the same as used in Thai cooking, I guess.

DR. BELSITO: I mean I'm -- This, to me, was even more problematic than the last one, where we had sufficient data for any of these if we do it for the wax only. I mean, we don't know how the extracts, oils, waters, or powders are manufactured. We don't know what their impurities are.

DR. SNYDER: Only the flower wax, right?

DR. BELSITO: Only the flower wax. Yes. I mean that's the only one we have some limited data on.

DR. LIEBLER: So, under acute toxicity the paragraph currently said, also as noted earlier essential oils, oleo resins, and natural extractors including distillates derived from citrus, flowers, and leaves, or GRAS, for their intended use in foods for human and animal consumption according to FDA. So, I think what we don't know is how well that actually matches up with the ingredients we are looking at.

Now, I mean, we do know that some of the constituents of concern that are likely to be present based on what Carol just said, are likely to be, you know, skin issues, sensitization, for example. So we are likely to have a pretty, you know, reasonably safe profile for, you know, many of the tox end points that we not only worry about, but without knowing, you know, what's in these, we really can't say that.

DR. BERGFELD: That's true of all the botanicals though.

DR. LIEBLER: Yes.

DR. BERGFELD: That's an issue forever.

DR. LIEBLER: Yes. Right.

DR. BERGFELD: So, are you sending out a use survey on this also?

DR. EISENMANN: Yes. The use survey has gone out for all three of these new citrus reports.

DR. SNYDER: Christina, Table 4 what -- So, Table says, allergens related to flower wax, and Table 4, just says, potential constituents. Is that for all?

MS. BURNETT: It's for citrus in general.

DR. SNYDER: Just for citrus in general. Okay. Thank you.

DR. BELSITO: Okay. So, I guess we've raised a number of issues, first and foremost is the GRAS status of many of these that we are looking at, and then, I guess that would therefore pertain to even ruling on the safety of the waxes. Is that my understanding of what you are saying, Dan?

DR. LIEBLER: Right.

DR. BELSITO: But could we get a -- I mean, would you expect the wax to be absorbed?

DR. LIEBLER: No.

DR. BELSITO: Across the skin?

DR. LIEBLER: No. So, one thing, once we have a better definition of what these are, then we have some information we can work with to, you know, take other factors into consideration, like likely then of absorption, and so forth.

DR. BELSITO: But we know we have safety data on the wax, at least in terms of skin data, we have method of manufacture, we have sense of the impurities?

DR. SNYDER: Flower wax.

DR. BELSITO: Flower wax. Yes, but that's what we are dealing with flower -- as opposed to leaf wax, that's true, we are dealing with flower and leaf.

DR. LIEBLER: Right.

DR. BELSITO: So flower was, but we don't know about -- but is there a leaf wax that's listed?

SPEAKER: No -- (crosstalk) Flower waxes. two flower waxes.

DR. BELSITO: Right. So we can say the flower waxes are safe as used, and say that we don't know whether those specific species are GRAS, but we would not expect the wax to be absorbed.

DR. LIEBLER: Right.

DR. BELSITO: Okay. And for the others we need method of manufacture, impurities, sensitization and irritation.

DR. SNYDER: Constituents.

DR. BELSITO: Constituents, method --

DR. SNYDER: The usual. Method of manufacture, chemical composition, impurities constituents --

DR. BELSITO: So, if we have method of manufacturing, constituents, impurities sensitization and irritation, that still doesn't address the need for potential systemic toxicity. Do we need a 28-day dermal, or proof that they are GRAS, or what do we need here?

DR. BERGFELD: Don't you have -- call for the constituents first, to see what --

DR. BELSITO: Well, that's what I'm saying, I mean, if we got constituents, if we -- We say we want manufacturing constituents impurities, sensitization and irritation for the extracts, oils, waters and powders, if we get that information, do we need specifically to know which of these are GRAS?

DR. LIEBLER: I really don't think the GRAS thing is applicable here, because these aren't things that are normally eaten.

DR. BELSITO: Right. I agree.

DR. LIEBLER: So, once we have the constituents then we can make judgments about what other data we need. So, I think that --

DR. BELSITO: Okay. So, what we'll say is, we need information on the manufacturing constituents, impurities, sensitization and irritation for the extracts, oils, waters and powders, depending upon manufacturing and impurities, additional information may be needed?

DR. LIEBLER: Correct.

DR. SNYDER: Or, they could give us a 28-day dermal, if they one sitting in the closet.

DR. KLAASSEN: And the flower is likely to have very different constituents to the leaf, a special fragrance.

MR. BEST: So, I just have two brief questions. One is so -- I think I'm following this, right. So, phototoxicity is not a concern in this one, because this is not where the psoralens, like in the peel, right? So that one; okay, got you. And the second thing is on GRAS when I was doing a quick Googling, there's a database. I mean, is it possible to sort of just say, definitely what is GRAS, and what isn't GRAS? It's not? Okay. Fair enough. That is just (inaudible) About the question, so there is sort of an art as opposed to a science to sort deciding what it is? Okay.

SPEAKER: Right.

DR. HELDRETH: Well, someone at the CFR would say that a food may be GRAS if it was being eaten before a certain date in the past.

MR. BEST: I got you. Okay. To some extent how do we know.

SPEAKER: Read the old cookbooks, or something, right, that's what you are saying. Okay.

MS. BURNETT: I captured it the best that I could with the way that the CFR has it, and it did say some specific flowers were -- are GRAS, but not -- it doesn't all of them, and of course there's a nomenclature difference, too, and stuff like that.

MR. BEST: Thank you. That's my own ignorance to the procedure, it was not a knock at the report. Thank you.

DR. BELSITO: Okay. So, we are going to go safe for the flower wax, manufacturing and constituents, impurities, sensitization and irritation for the remaining extracts, oils, waters, powders, depending upon impurities in constituents, additional data may be needed.

Full Panel Meeting

DR. BERGFELD: Well, we have voted on this, so we're going to move on then to the citrus flower and leaf. Dr. Marks.

DR. MARKS: So this is the first review of these ingredients. Oh, flower and leaf, hold it, I apologize. The only change in that introduction is there are 32 ingredients for first review. And we'll continue with the insufficient data notice, move for that. The needs are the same as previously: Method of manufacture and composition. And I just wanted to see an HRIPT, the bitter orange flower extract at 5 percent and the bitter orange flower water at 4 percent.

So move for insufficient data announcement.

DR. BERGFELD: Is there a second?

DR. BELSITO: So manufacturing?

DR. MARKS: Yeah, composition.

DR. BELSITO: Impurities.

DR. MARKS: Yeah.

DR. BELSITO: And sensitization and irritation on which one?

DR. MARKS: I wanted to see bitter orange flower extract and the bitter orange flower water. Those were the highest concentrations and uses, I believe, too.

DR. BELSITO: Second.

DR. BERGFELD: So it's been seconded. Any other comments to be added to the insufficient list? Seeing none, I'm going to call the question. All those in favor of insufficient for this ingredient? Thank you. Unanimous.

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Cosmetic Ingredient Review

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DRAFT ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 32 *Citrus* flower- and leaf-derived ingredients, which are most frequently reported to function in cosmetics as fragrances and/or 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 flower- and leaf-derived ingredients are widely used in cosmetics, and are most frequently reported to function in cosmetics as fragrances and/or skin conditioning agents (Table 1).¹ This report assesses the safety of the following 32 ingredients:

Citrus Aurantifolia (Lime) Flower Extract	Citrus Grandis (Grapefruit) Leaf Extract
Citrus Aurantifolia (Lime) Leaf Oil	Citrus Hystrix Leaf Extract
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Citrus Junos Flower Oil
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Citrus Limon (Lemon) Flower Water
Citrus Aurantium Amara (Bitter Orange) Flower Water	Citrus Limon (Lemon) Leaf Extract
Citrus Aurantium Amara (Bitter Orange) Flower Wax	Citrus Limon (Lemon) Leaf Cell Extract
Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract	Citrus Natsudaikai Flower Water
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	Citrus Natsudaikai Flower Oil
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	Citrus Reticulata (Tangerine) Leaf Oil
Citrus Aurantium Dulcis (Orange) Flower Extract	Citrus Reticulata (Tangerine) Leaf Water
Citrus Aurantium Dulcis (Orange) Flower Oil	Citrus Sinensis (Orange) Flower Water
Citrus Aurantium Dulcis (Orange) Flower Wax	Citrus Tamurana Flower Extract
Citrus Aurantium Dulcis (Orange) Flower	Citrus Unshiu Flower Extract
Citrus Aurantium Dulcis (Orange) Leaf Extract	Citrus Unshiu Flower powder
Citrus Clementina Leaf Cell Extract	Citrus Unshiu Flower Water
Citrus Depressa Flower Water	Citrus Unshiu Leaf Extract

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 has also reviewed the safety of Citrus Aurantifolia (Lime) Seed Oil, Citrus Aurantifolia (Lime) Seed Oil unsaponifiables, Citrus Aurantium Dulcis (Orange) Seed Oil, Citrus Aurantium Dulcis (Orange) Seed Oil unsaponifiables, Citrus Grandis (Grapefruit) Seed Oil, Citrus Grandis (Grapefruit) Seed Oil unsaponifiables, Citrus Limon (Lemon) Seed Oil, and Citrus Paradisi (Grapefruit) Seed Oil, and concluded that these ingredients were safe in the present practices of use and concentration as described in the safety assessment of plant-derived fatty acid oils.⁴ The Panel is concurrently reviewing the safety of *Citrus* plant- and seed-derived ingredients and *Citrus* peel-derived ingredients in separate reports.

Some of the *Citrus* flowers and leaves that are used to derive the ingredients described in this safety assessment are used as food ingredients. The U.S. Food and Drug Administration (FDA) determined that the use of some *Citrus* flowers and leaves as direct food additives is generally recognized as safe (GRAS). Additionally, essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from bitter orange flowers, sweet orange leaves and possibly other *Citrus* flowers and leaves 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* flower- and leaf-derived ingredients via oral exposure is not addressed further in this report. The primary focus of the 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 International Cosmetic Ingredient Dictionary and Handbook, 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.

Botanicals such as *Citrus*-derived ingredients contain numerous constituents, some of which have the potential to be toxic. In this assessment, CIR is reviewing the potential toxicity of each *Citrus* flower- or leaf-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* flowers and leaves 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 test substance 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. bitter orange flower oil). If the substance is clearly a cosmetic ingredient, the International Nomenclature of Cosmetic Ingredients (INCI) name will be used (e.g. “Citrus Aurantium Amara (Bitter Orange) Flower Oil”). 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 the 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 3.⁵

CHEMISTRY

Definition and General Characterization

The definitions and functions of the *Citrus* flower- and leaf-derived ingredients included in this report are provided in Table 1. The definition indicates what part(s) of the plant an ingredient is obtained from. In some cases, the definition provides insight on the method(s) of manufacture. Essential oils are the hydrophobic, liquid, volatile aroma compounds in the insoluble condensate fraction. The essential oils are typically small molecules, but their chemical structures can vary rather widely. (Fixed oils, on the other hand are hydrophobic, nonvolatile, fatty compounds from plants, animals or algae. These are primarily composed of glycerides, and to some extent, free fatty acids. Constituents of these *Citrus*-derived ingredients may include both oil types.) The volatile nature of essential oils makes them more likely to be useful as fragrances, but that does not necessitate that fragrance is their only function.

Physical and Chemical Properties

Citrus Aurantium Dulcis (Orange) Flower Extract

As reported by a supplier, *Citrus Aurantium Dulcis* (Orange) Flower Extract is a medium to dark amber liquid with a characteristic odor.⁶ At 25° C, the pH range is 4.0 to 6.5 (actual 4.1). Specific gravity range is 0.99 to 1.01 (1.01 actual) at 25° C. *Citrus Aurantium Dulcis* (Orange) Flower Extract is soluble in any proportion of water, has less than 100 organisms/g, and has a refractive index range of 1.3250 to 1.3450 (1.3385 actual) at 25° C.

No further relevant published physical and chemical properties on *Citrus* flower- and leaf-derived ingredients were identified in a literature search for these ingredients and no unpublished data were submitted.

Method of Manufacturing

Citrus Aurantium Amara (Bitter Orange) Flower Wax

Figure 1 is a generic representation of the method of manufacturing for *Citrus Aurantium Amara* (Bitter Orange) Flower Wax. In the preparation of this ingredient, *Citrus aurantium amara* flowers undergo extraction with an organic solvent to form a “concrete”, which is then dissolved in alcohol. The insoluble portion is the floral wax, which is then further refined.

Citrus Aurantium Dulcis (Orange) Flower Extract

According to a supplier, fresh or dried flowers of *Citrus aurantium dulcis* is extracted with specified eluent under appropriate temperatures to yield a concentrate.⁶ The concentrate is then blended with the desired diluent and preservation systems to produce *Citrus Aurantium Dulcis* (Orange) Flower Extract.

Citrus Hystrix Leaf Extract

A supplier has report that *Citrus Hystrix* Leaf Extract is produced by extracting dried leaves with 80% ethanolic solution, which is then filtered and concentrated before the addition of 70% 1,3-butylene glycolic solution.⁷ The material then undergoes sedimentation, filtration, and adjustment before packaging.

Citrus Natsudaidai Flower Water and Oil

In the preparation of *Citrus Natsudaidai* Flower Water and *Citrus Natsudaidai* Flower Oil, *Citrus natsudaidai* flowers were handpicked and then refrigerated.⁸ Then, approximately 4 to 8 kg of flowers were then distilled with 10 to 20 L

of purified water. The water and oil were then separated and the resulting products were analyzed for heavy metals and bacteria content.

Constituents/Composition/Impurities

The *Citrus* ingredients are complex botanicals made up of numerous constituents. Table 4 lists Citrus constituents that are established contact allergens, according to the European Commission's Scientific Committee on Consumer Safety (SCCS). Table 5 presents the cosmetic allergens certificate of analysis for Citrus Aurantium Amara (Bitter Orange) Flower Wax. Table 6, Table 7, and Table 8 list the composition (%) of several *Citrus* leaf and flower volatiles.

Citrus Aurantium Amara (Bitter Orange) Flower Wax

In data provided by a supplier, Citrus Aurantium Amara (Bitter Orange) Flower Wax had less than 0.1 mg/kg heavy metals (arsenic, cadmium, and lead) and no detectable pesticides (< 0.005 mg/kg) or polycyclic aromatic hydrocarbons (< 0.25 µg/kg).⁹ Concentrations of aflatoxins (B1, B2, G1, G2) were less than 0.1 µg/kg, with the total aflatoxins concentration less than 0.4 µg/kg, and dioxins were less than 0.6 pg/g.

Citrus Aurantium Dulcis (Orange) Flower Extract

According to a supplier, impurities testing on Citrus Aurantium Dulcis (Orange) Flower Extract is performed on the concentrate in alcohol base.⁶ No residual pesticides or heavy metals (including arsenic, lead, and mercury) were detected. In addition, none of the 26 cosmetic allergens listed in Table 5 were detected (detection limit < 1 ppm).

Citrus Hystrix Leaf Extract

A supplier reports that Citrus Hystrix Leaf Extract is composed of tannin and sugar.⁷ Impurities of heavy metals are not more than 20 ppm and arsenic is not more than 2 ppm.

USE

Cosmetic

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

According to 2016 VCRP data, Citrus Aurantium Amara (Bitter Orange) Flower Oil has the most reported uses of the ingredients in this report in cosmetic products, with a total of 99; the majority of the uses are in leave-on skin care preparations (Table 9).¹⁰ Citrus Aurantium Dulcis (Orange) Flower Extract has the second greatest number of overall uses reported, with a total of 70; a majority of the uses are in rinse-off and leave-on skin care preparations. The results of the concentration of use survey conducted by the Council indicate Citrus Aurantium Dulcis (Orange) Flower Extract has the highest reported maximum concentration of use; it is used at up to 6% in eye shadow.¹¹ Citrus Aurantium Dulcis (Orange) Flower Oil had the second highest reported maximum concentration of use; it is used at up to 0.66% in a depilatory.

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

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) Flower Extract is used at 2% in lipstick. Additionally, some of these ingredients were reported to be used in hair sprays, fragrance preparations, and face powders and could possibly be inhaled. For example, Citrus Aurantium Dulcis (Orange) Flower Oil was reported to be used in hair spray at a maximum concentration of 0.015% and Citrus Aurantium Amara (Bitter Orange) Flower Oil was reported to be used in face powders at a maximum concentration of 0.01%. 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.¹²⁻¹⁵ 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.^{13,14} 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.¹⁶⁻¹⁸

The *Citrus* flower- and leaf-derived ingredients in this safety assessment are not restricted from use under the rules governing cosmetic products in the European Union.¹⁹

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).

TOXICOKINETICS

No relevant published toxicokinetics studies on *Citrus* flower- and leaf-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 hundreds of constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity

Some of the *Citrus* ingredients in this assessment are found in foods, and the daily exposure from food use 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 bitter orange flowers, sweet orange leaves, and possibly other *Citrus* flowers and leaves are GRAS for their intended use in foods for human and animal consumption according to the FDA. Consequently, the systemic toxicity potential 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.

Dermal – Non-Human

Bitter Orange Leaf Oil

The dermal LD₅₀ of bitter orange leaf oil (described as “petitgrain bigarade oil”) was reported as greater than 2 g/kg in rabbits; however, only 2 rabbits were used in the study.²⁰ An occlusive patch of undiluted test material was applied for 24 h.

Repeated Dose Toxicity

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

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No relevant published reproductive and developmental studies on *Citrus* flower- and leaf-derived ingredients were identified in a literature search for these ingredients and no unpublished data were submitted.

GENOTOXICITY

No relevant published genotoxicity studies on *Citrus* flower- and leaf-derived ingredients were identified in a literature search for these ingredients and no unpublished data were submitted.

CARCINOGENICITY

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

IRRITATION AND SENSITIZATION

Dermal Irritation

Dermal irritation studies are summarized in Table 11.^{7,20-23} In rabbit studies, moderate, reversible erythema reactions were observed with undiluted Citrus Aurantium Amara (Bitter Orange) Flower Wax and slight erythema was observed after exposure to unreported concentrations of bitter orange leaf oil (described as “petitgrain bigarade oil”). Citrus Hystrix Leaf Extract was not irritating in rabbits at up to 10%. In human subjects, no irritation was observed after topical exposure to bitter orange leaf oil (described as “petitgrain bigarade oil”; up to 8%) or to Citrus Natsudaidai Flower Oil (1% in jojoba seed oil).

Ocular Irritation

Citrus Aurantium Amara (Bitter Orange) Flower Wax

The eye tolerance of Citrus Aurantium Amara (Bitter Orange) Flower Wax (> 50%) was tested in vitro using the SIRC cell model.²⁴ Tolerance was evaluated by measuring cytotoxicity. Negative controls solutions were physiological serum or sample diluent and the positive control solutions were 0.01% to 0.2% SDS. Negligible cytotoxicity was observed.

Sensitization

Sensitization studies are presented in Table 12.^{7,20,25-29} Citrus Hystrix Leaf Extract was not sensitizing in guinea pigs at up to 10%. In human repeated insult patch tests (HRIPT), Citrus Aurantium Amara (Bitter Orange) Flower Extract was considered not sensitizing in formulations at up to 0.0225%. Bitter orange leaf oil (described as “petitgrain bigarade oil”) at up to 8% was not sensitizing. Citrus Aurantium Dulcis (Orange) Flower Oil was not irritating or sensitizing at 0.4% in a face and neck product.

Photosensitization

Photosensitization studies are presented in Table 13.³⁰ Undiluted bitter orange leaf oil (described as “petitgrain bigarade oil”) was not photosensitizing in tests with hairless mice or miniature swine.

CLINICAL STUDIES

No relevant published clinical studies on *Citrus* flower- and leaf-derived ingredients were identified in a literature search for these ingredients and no unpublished data were submitted.

SUMMARY

The 32 *Citrus* flower- and leaf-derived ingredients described in this report function primarily as fragrances and/or skin conditioning agents. Botanicals such as *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, photo-toxic furanocoumarin (psoralen) in *Citrus*. CIR reviewed the information available on each *Citrus* flower- and leaf-derived ingredient as a whole, complex substance; CIR did not review the potential toxicity information on the individual constituents of which the *Citrus* flower- and leaf-derived ingredients are comprised.

Citrus Aurantium Amara (Bitter Orange) Flower Oil has the most reported uses of the ingredients in this report in cosmetic products, with a total of 99; the majority of the uses are in leave-on skin care preparations. Citrus Aurantium Dulcis (Orange) Flower Extract has the second greatest number of overall uses reported, with a total of 70; a majority of the uses are in rinse-off and leave-on skin care preparations. The results of the concentration of use survey conducted by the Council indicate Citrus Aurantium Dulcis (Orange) Flower Extract has the highest reported maximum concentration of use; it is used at up to 6% in eye shadow. Citrus Aurantium Dulcis (Orange) Flower Oil had the second highest reported maximum concentration of use; it is used at up to 0.66% in a depilatory.

The *Citrus* flower- and leaf-derived ingredients in this safety assessment are not restricted from use under the rules governing cosmetic products in the European Union.

Some of the *Citrus* ingredients in this assessment are found in foods, and the daily exposure from food use would result in a much larger systemic dose than that resulting from use in 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.

The dermal LD₅₀ of undiluted bitter orange leaf oil (described as “petitgrain bigarade oil”) was reported as greater than 2 g/kg when tested in 2 rabbits.

In rabbit studies, moderate, reversible erythema reactions were observed with undiluted Citrus Aurantium Amara (Bitter Orange) Flower Wax and slight erythema, after treated with unreported concentrations of bitter orange leaf oil (described as “petitgrain bigarade oil”). Citrus Hystrix Leaf Extract was not irritating in rabbits at up to 10%. In human subjects, no irritation was observed after topical exposure to bitter orange leaf oil (described as “petitgrain bigarade oil”; up to 8%) or to Citrus Natsudaikai Flower Oil (1% in jojoba seed oil).

Essentially no cytotoxicity was observed in an in vitro eye tolerance study of Citrus Aurantium Amara (Bitter Orange) Flower Wax (> 50%) using the SIRC cell strain.

Citrus Hystrix Leaf Extract was not sensitizing in guinea pigs at up to 10%. In human studies, Citrus Aurantium Amara (Bitter Orange) Flower Extract was considered not sensitizing in formulations at up to 0.0225%. Bitter orange leaf oil (described as “petitgrain bigarade oil”) at up to 8% was not sensitizing. Citrus Aurantium Dulcis (Orange) Flower Oil was not irritating or sensitizing at 0.4% in a face and neck product.

Undiluted bitter orange leaf oil (described as “petitgrain bigarade oil”) was not photosensitizing in tests with hairless mice or miniature swine.

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

DISCUSSION

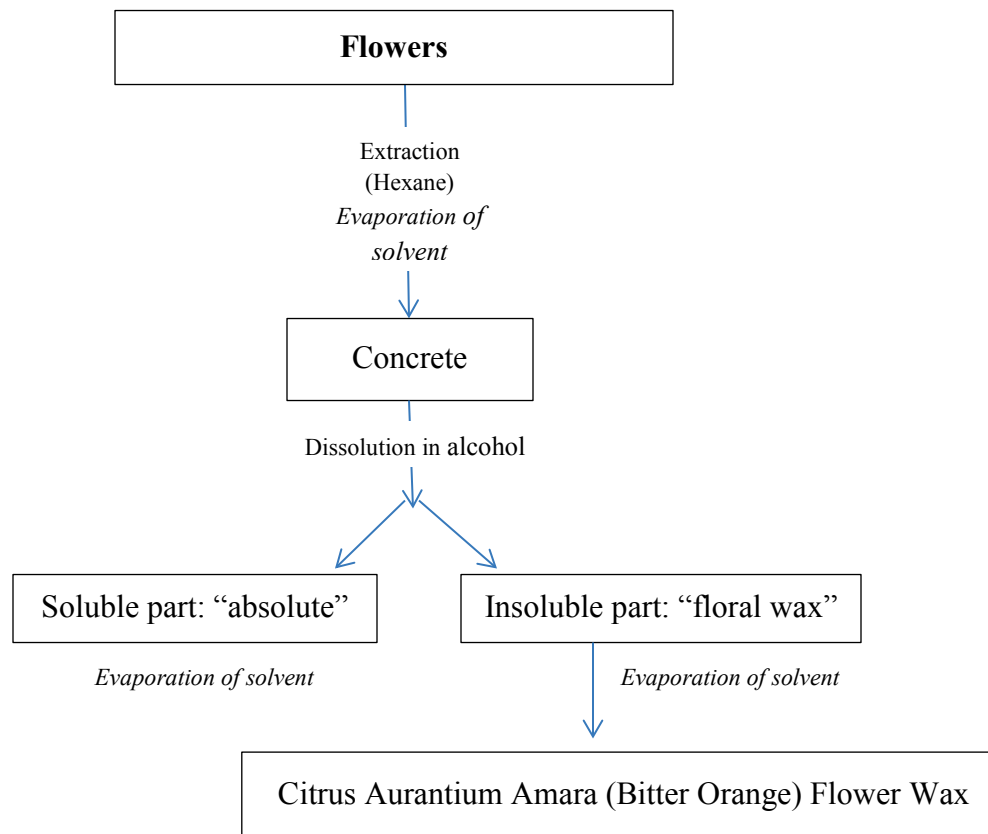
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CONCLUSION

To be determined...

FIGURES

Figure 1. Manufacturing flow chart of Citrus Aurantium Amara (Bitter Orange) Flower Wax.³¹



TABLES**Table 1.** Definitions and functions of Citrus-derived ingredients.

1

Ingredient	Definition	Function
Citrus Aurantifolia (Lime) Flower Extract	Citrus Aurantifolia (Lime) Flower Extract is the extract of the flowers of <i>Citrus aurantifolia</i> .	Cosmetic Astringents; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Leaf Oil	Citrus Aurantifolia (Lime) Leaf Oil is the volatile oil obtained from the leaves of <i>Citrus aurantifolia</i> .	Fragrance Ingredients
Citrus Aurantium Amara (Bitter Orange) Flower Extract CAS No. 72968-50-4	Citrus Aurantium Amara (Bitter Orange) Flower Extract is the extract of the flowers of <i>Citrus aurantium amara</i> .	Skin-Conditioning Agents - Occlusive
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Citrus Aurantium Amara (Bitter Orange) Flower Oil is the volatile oil obtained from the flowers of <i>Citrus aurantium amara</i> .	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Flower Water	Citrus Aurantium Amara (Bitter Orange) Flower Water is an aqueous solution of the steam distillate obtained from the flowers of <i>Citrus aurantium amara</i> .	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Flower Wax	Citrus Aurantium Amara (Bitter Orange) Flower Wax is a wax obtained from the flower of <i>Citrus aurantium amara</i> .	Not reported
Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract	Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract is the extract of a culture of the leaf cells of <i>Citrus aurantium bergamia</i> . The accepted scientific name for <i>Citrus aurantium bergamia</i> is <i>Citrus x limon</i> .	Antioxidants; Skin Protectants
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	Citrus Aurantium Bergamia (Bergamot) Leaf Extract is the extract of the leaves of <i>Citrus aurantium bergamia</i> .	Cosmetic Astringents
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	Citrus Aurantium Bergamia (Bergamot) Leaf Oil is the volatile oil obtained from the leaves of <i>Citrus aurantium bergamia</i> .	Cosmetic Astringents
Citrus Aurantium Dulcis (Orange) Flower	Citrus Aurantium Dulcis (Orange) Flower is the flower of <i>Citrus aurantium dulcis</i> .	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Flower Extract	Citrus Aurantium Dulcis (Orange) Flower Extract is the extract of the flowers of <i>Citrus aurantium dulcis</i> .	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Flower Oil CAS No. 8016-38-4	Citrus Aurantium Dulcis (Orange) Flower Oil is the volatile oil obtained from the flowers of <i>Citrus aurantium dulcis</i> .	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Flower Wax	Citrus Aurantium Dulcis (Orange) Flower Wax is a wax obtained from the flowers of <i>Citrus aurantium dulcis</i> .	Skin-Conditioning Agents - Occlusive
Citrus Aurantium Dulcis (Orange) Leaf Extract	Citrus Aurantium Dulcis (Orange) Leaf Extract is the extract of the leaves of <i>Citrus aurantium dulcis</i> .	Skin-Conditioning Agents - Miscellaneous
Citrus Clementina Leaf Cell Extract	Citrus Clementina Leaf Cell Extract is the extract of a culture of the leaf cells of <i>Citrus clementina</i> . The accepted scientific name for <i>Citrus clementina</i> is <i>Citrus x aurantium</i> .	Antioxidants; Skin Protectants
Citrus Depressa Flower Water	Citrus Depressa Flower Water is the aqueous solution of the steam distillates obtained from the flowers of <i>Citrus depressa</i> . The accepted scientific name for <i>Citrus depressa</i> is <i>Citrus reticulata</i> .	Skin-Conditioning Agents - Humectant
Citrus Junos Flower Oil	Citrus Junos Flower Oil is the volatile oil obtained from the flowers of <i>Citrus junos</i> . The accepted scientific name for <i>Citrus junos</i> is <i>Citrus x junos</i> .	Flavoring Agents; Fragrance Ingredients
Citrus Limon (Lemon) Flower Water	Citrus Limon (Lemon) Flower Water is an aqueous solution of the steam distillates obtained from the flowers of <i>Citrus limon</i> (lemon). The accepted scientific name for <i>Citrus limon</i> is <i>Citrus x limon</i> .	Skin-Conditioning Agents - Humectant
Citrus Grandis (Grapefruit) Leaf Extract	Citrus Grandis (Grapefruit) Leaf Extract is the extract of the leaves of <i>Citrus grandis</i> .	Skin-Conditioning Agents - Miscellaneous
Citrus Hystrix Leaf Extract	Citrus Hystrix Leaf Extract is the extract of the leaves of <i>Citrus hystrix</i> .	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Leaf Cell Extract CAS No. 84929-31-7	Citrus Limon (Lemon) Leaf Cell Extract is the extract of a culture of the leaf cells of <i>Citrus limon</i> . The accepted scientific name for <i>Citrus limon</i> is <i>Citrus x limon</i> .	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Leaf Extract	Citrus Limon (Lemon) Leaf Extract is the extract of the leaves of <i>Citrus limon</i> .	Antioxidants
Citrus Natsudaïdai Flower Oil	Citrus Natsudaïdai Flower Oil is the volatile oil obtained from the flowers of <i>Citrus natsudaïdai</i> . The accepted scientific name for <i>Citrus natsudaïdai</i> is <i>Citrus x aurantium</i> .	Fragrance Ingredients
Citrus Natsudaïdai Flower Water	Citrus Natsudaïdai Flower Water is the aqueous solution of the steam distillates obtained from the flowers of <i>Citrus natsudaïdai</i> .	Fragrance Ingredients
Citrus Reticulata (Tangerine) Leaf Oil CAS No. 8014-17-3	Citrus Reticulata (Tangerine) Leaf Oil is the volatile oil derived from the leaves of <i>Citrus reticulata</i> .	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Reticulata (Tangerine) Leaf Water	Citrus Reticulata (Tangerine) Leaf Water is an aqueous solution of the steam distillate obtained from the leaves of <i>Citrus reticulata</i> .	Skin-Conditioning Agents - Miscellaneous

Table 1. Definitions and functions of Citrus-derived ingredients. ¹

Ingredient	Definition	Function
Citrus Sinensis (Orange) Flower Water	Citrus Sinensis (Orange) Flower Water is an aqueous solution of the steam distillates obtained from the flowers of <i>Citrus sinensis</i> . The accepted scientific name for <i>Citrus sinensis</i> is <i>Citrus x aurantium</i> .	Skin-Conditioning Agents - Humectant
Citrus Tamurana Flower Extract	Citrus Tamurana Flower Extract is the extract of the flowers of <i>Citrus tamurana</i> .	Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu Flower Extract	Citrus Unshiu Flower Extract is the extract of the flowers of <i>Citrus unshiu</i> . The accepted scientific name for <i>Citrus unshiu</i> is <i>Citrus reticulata</i> .	Skin Protectants; Skin-Conditioning Agents - Humectant
Citrus Unshiu Flower Powder	Citrus Unshiu Flower Powder is the powder obtained from the dried, ground flowers of <i>Citrus unshiu</i> .	Exfoliants
Citrus Unshiu Flower Water	Citrus Unshiu Flower Water is an aqueous solution of the steam distillates obtained from the flowers of <i>Citrus unshiu</i> .	Fragrance Ingredients
Citrus Unshiu Leaf Extract	Citrus Unshiu Leaf Extract is the extract of the leaves of <i>Citrus unshiu</i> . The accepted scientific name for <i>Citrus unshiu</i> is <i>Citrus reticulata</i> .	Skin Protectants; Skin-Conditioning Agents - Humectant

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

Citrus Aurantifolia (Lime) Leaf Oil
Citrus Natsudaikai Flower Oil
Citrus Natsudaikai Flower Water
Citrus Unshiu Flower Water

Table 3. Review of *Citrus* genus species names.⁵

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

Table 4. Potential constituents that are established 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)³²
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)
terpineol (mixture of isomers)/ α -terpineol	≤ 10
terpinolene	11-100

Table 5. Cosmetic allergens certificate from a manufacturer of Citrus Aurantium Amara (Bitter Orange) Flower Wax.³³

Allergen	Amount
Amyl cinnamal	< 5 ppm
Benzyl alcohol	< 20 ppm
Cinnamyl alcohol	< 1 ppm
Citral	< 10 ppm
Eugenol	< 5 ppm
Hydroxycitronellal	< 5 ppm
Isoeugenol	< 5 ppm
Amylcinnamyl alcohol	< 1 ppm
Benzyl salicylate	< 5 ppm
Cinnamal	< 5 ppm
Coumarin	< 15 ppm
Geraniol	< 5 ppm
Hydroxyisohexyl 3-cyclo hexane carboxaldehyde	< 5 ppm
Anise alcohol	< 30 ppm
Benzyl cinnamate	< 15 ppm
Farnesol	< 50 ppm
Butylphenyl methylpropional	< 1 ppm
Linalool	< 50 ppm
Benyl benzoate	< 5 ppm
Citronellol	< 5 ppm
Hexyl cinnamal	< 1 ppm
Limonene	< 200 ppm
Methyl 2-octynoate	< 1 ppm
Alpha-isomethyl ionone	< 1 ppm
Evernia prunastri	ND
Evernia furfuracea	ND
Detection limit 2 ppm.	
ND = unable to be detected by GCSM	

Table 6. Composition (%) of *Citrus* flower and leaves.³⁴⁻³⁶

	Citrus Natsudaikai Flower Oil	<i>Citrus reticulata</i> leaf oil (mandarin)	<i>Citrus aurantium</i> L. flower oil (bitter orange)	<i>Citrus aurantium</i> L. leaf oil (bitter orange)
β-pinene	4.49	4.71	19.08	1.90-3.58
sabinene	0.65	0.57	2.01	0.22-0.37
β-myrcene	1.26	0.63	1.59	1.63-2.74
α-terpinene	0.35	NR	NR	NR
limonene	23.48	3.63	12.04	0.53-0.77
citronellol	NR	5.19	NR	NR
eucalyptol	0.55	NR	NR	NR
α-phellandrene	NR	0.49	NR	NR
β-phellandrene or β-thujene	0.17	NR	NR	NR
α-pinene	NR	3.91	1.35	0.19
γ-terpinene or 3-carene	9.56	20.15	0.36/0.17	NR
β-cis-ocimene	4.69	NR	0.77	0.71-1.22
(E)-β-ocimene	NR	1.74	6.06	3.11-4.08
p-cymene	14.53	16.29	NR	NR
caryophyllene oxide	0.24	NR	NR	NR
dihydropseudoionone	0.34	NR	NR	NR
germacrene A	0.96	NR	0.13	NR
(E)-β-farnesene	0.06	NR	NR	00-0.13
β-bisabolene	0.93	NR	NR	NR
δ-elemene	NR	NR	0.12	NR
elemene	2.90	NR	NR	NR
α-caryophyllene	0.47	NR	NR	NR
β-selinene	0.24	NR	NR	NR
α-selinene	0.83	NR	NR	NR
γ-cadinene	2.90	NR	NR	NR
α-farnesene	1.81	NR	NR	NR
β-cubebene	0.19	NR	NR	NR
α-humulene	NR	NR	NR	0-0.10
caryophyllene	1.40	NR	0.42	0.22-1.09
linalool	7.57	9.55	29.14	36.03-58.21
linalool oxide	NR	NR	0.29	NR
nerolidol	13.99	NR	1.76	0-0.10
farnesol	0.40	NR	5.14	NR
α-terpineol	NR	0.85	4.56	7.11-12.89
(-)-4-terpineol	0.58	7.13	0.68	0.13-0.17
α-terpinolene	NR	NR	0.47	0.40-0.70
carvacrol	0.80	NR	NR	NR
nerol	NR	0.21	0.83	1.45-2.89
neral	NR	0.36	NR	NR
geranial	NR	0.83	NR	NR
geraniol	0.26	NR	4.31	NR
geraniol or geranyl isopentanoate	0.25	NR	NR	NR
phenylethyl alcohol	NR	NR	NR	NR
nonanal	NR	NR	NR	NR
linalyl acetate	NR	NR	3.88	12.42-23.00
linalyl propanoate	0.67	NR	NR	NR
methyl anthranilate	1.41	NR	0.19	NR
geranyl acetate	NR	2.13	2.59	4.49-8.70
bornyl acetate	NR	0.24	NR	NR
terpinyl acetate	NR	NR	0.20	0-0.11
neryl acetate	NR	NR	1.30	2.18-4.46
eicosane	0.35	NR	NR	NR
benzeneacetonitrile	NR	NR	NR	NR
bicyclogermacrene	NR	NR	NR	0.18-0.20

NR = not reported

Table 7. *Citrus* flower volatiles composition (%), identified by headspace-solid phase microextraction gas chromatography-mass spectrometry.³⁷

	<i>Citrus reticulata</i> (mandarin orange)	<i>Citrus unshiu</i>	<i>Citrus sinensis</i> (sweet orange)	<i>Citrus limon</i> (lemon)	<i>Citrus grandis</i> (pomelo)
hexanal	0.1-1	NR	0.1-1	0.1-1	0.1-1
2-hexanal	0.1-1	0.1-2.84	1.19-2.36	0.1-1.45	0.1-1.68
benzaldehyde	trace-1	trace-1	trace-1	trace	trace
benzene acetaldehyde	0.1-1.08	NR	0.1-1.31	0.1-1	1.34
lilac aldehyde B	NR	NR	trace	NR	trace-1
myrtenal	NR	0.1-1	trace	NR	trace
decanal	trace	trace	trace	trace-1	trace-1
undecanal	NR	NR	NR	trace-1	NR
α -thujene	0.1-1	0.1-1	0.1-1	trace-1	trace-2.18
α -pinene	0.1-1	0.1-2.80	0.1-1.42	0.1-1	0.1-1
camphene	NR	NR	NR	NR	trace-4.48
sabinene	NR	NR	6.07-11.15	NR	NR
β -pinene	6.59-9.20	2.92-6.51	3.53-11.88	0.1-2.07	1.67-7.49
β -myrcene	1.11-1.46	1.53-2.55	1.48-2.53	2.01-2.42	0.1-8.08
α -terpinene	0.1-1	0.1-1	0.1-1.62	NR	trace-1
<i>p</i> -cymene	0.1-1	6.538.56	0.1-1	NR	1.01
limonene	1.07-1.48	1.69	1.54-4.64	44.95-52.53	2.19-4.92
(<i>Z</i>)-ocimene	trace	NR	0.1-1.71	0.1-1	0.1-1
(<i>E</i>)-ocimene	2.16-3.03	2.27-6.37	1.18-8.40	5.35-6.35	1.97-9.14
γ -terpinene	1.44-1.90	0.1-13.79	0.1-1	1.97-3.17	trace-11.06
terpinolene	NR	NR	0.1-1	0.1-1	NR
2,4,6-octatriene,3,4-dimethyl	0.1-1	trace-1	trace-1	trace-1	trace-1
1,8-cineol	NR	3.15-6.05	NR	NR	NR
<i>cis</i> - β -terpineol	1.08-1.99	0.1-1	0.1-3.60	trace-1	trace-1
<i>cis</i> -linalol oxide	NR	NR	NR	NR	trace-1
linalool	46.76-50.43	17.41-42.76	24.95-46.98	3.94-7.95	21.59-56.16
limonene oxide, <i>cis</i>	NR	NR	NR	NR	trace-1.15
limonene oxide, <i>trans</i>	NR	NR	NR	2.58-3.04	NR
citronellal	0.1-1	0.1-1	0.1-1	0.1-1.05	trace-1
umbellulone	trace	NR	NR	NR	NR
terpinen-4-ol	0.1-1	0.1-1	0.1-1	0.1-1	0.1-1
<i>p</i> -cymen-8-ol	trace-1	0.1-1	NR	NR	NR
α -terpineol	1.96-3.83	1.01-5.58	0.1-4.59	1.54	0.1-1
<i>trans</i> -dihydrocarvone	NR	NR	NR	0.1-1	NR
<i>p</i> -menth-1-en-9-al	trace-1	0.1-1	NR	0.1-1	0.1-1
<i>cis</i> -carveol	NR	0.1-1	trace	0.1-1	trace
<i>cis</i> -geraniol	NR	0.1-1	0.1-1	trace-1	0.1-2.84
β -citronellol	trace-1	0.1-1	trace-1	trace	0.1-1
methyl thymyl ether	1.07-1.93	NR	trace-5.74	trace	NR
β -citral	trace-1	0.1-1	0.1-2.55	0.1-1	0.1-2.28
<i>trans</i> -geraniol	0.1-2.47	0.1-1	trace-6.80	NR	0.1-6.52
α -citral	trace-1	0.1-1	0.1-11.17	0.1-1.24	0.1-3.07
α -thujenal	NR	0.1-1.33	NR	NR	NR
carvacrol	NR	NR	NR	0.1-1	NR
E,E-farnesal	NR	0.1-1	NR	trace-1	0.1-1
δ -elemene	0.1-1.36	NR	0.1-1	0.1-1	0.1-1.23
α -cubebene	trace	NR	NR	trace-1	NR
copaene	NR	NR	NR	0.1-1	NR
β -elemene	trace-1	2.13-5.40	0.1-19.43	6.02-7.53	0.1-4.98
zingiberene	0.1-1	NR	NR	NR	0.1-1
bergamotene	NR	NR	trace-1	trace	0.1-1
<i>trans</i> - α -bergamotene	trace-1	0.1-1	trace-1	trace	NR
caryophyllene	0.1-1	2.11-2.61	0.1-1.34	3.14-3.93	trace-2.18
α -santalene	NR	NR	NR	trace	NR
β -cubebene	trace	0.1-1	0.56	trace	0.06-1.64
γ -elemene	0.1-1.16	0.1-1	1.37	trace	trace-1.77
bicyclosquiphellandrene	0.1-1	NR	0.1-1	NR	trace-1
β -farnesene	2.24-3.53	NR	2.03-3.89	1.64-2.26	trace-5.16
α -elemene	NR	NR	NR	trace	0.1-1
germacrene D	trace-1	trace-1	1.36	0.1-1	0.1-1.17
β -eudesmene	NR	NR	trace	0.1-1	NR
α -selinene	NR	trace-1	0.1-1	0.1-1	0.1-1
allo-aromadendrene	NR	NR	trace	0.1-1	NR
bicyclogermacrene	NR	trace-1	trace	NR	trace-1

Table 7. *Citrus* flower volatiles composition (%), identified by headspace-solid phase microextraction gas chromatography-mass spectrometry.³⁷

	<i>Citrus reticulata</i> (mandarin orange)	<i>Citrus unshiu</i>	<i>Citrus sinensis</i> (sweet orange)	<i>Citrus limon</i> (lemon)	<i>Citrus grandis</i> (pomelo)
α -muurolene	0.1-1	NR	NR	NR	trace-1
α -bulnesene	trace-1	NR	trace	0.1-1	trace
(<i>Z,E</i>)- α -farnesene	NR	NR	NR	0.1-1	trace-1
α -farnesene	0.1-1	NR	trace	0.1-1	NR
β -bisabolene	NR	NR	NR	2.34-2.82	NR
δ -cadinene	1.30-2.17	NR	0.1-1.07	NR	0.1-1.13
β -sesquiphellandrene	0.1-1	4.31-6.41	0.1-1	trace	0.1-1
eudesma-3,7(11)-diene	NR	NR	0.1-1	NR	NR
cis- α -bisabolene	NR	NR	NR	trace	trace
nerolidol	trace-1	0.1-1	0.1-3.64	trace-1	0.1-8.75
caryophyllene oxide	NR	0.1-1	NR	NR	NR
β -eudesmol	trace	NR	NR	NR	NR
tetradecanal	NR	NR	0.1-1	NR	NR
farnesol	0.1-1	0.1-1.07	0.1-1.54	0.1-1	0.1-2.38
α -sinensal	0.1-1	NR	0.1-1	NR	NR
chrysanthenone	NR	0.1-1	0.1-1	NR	NR
cis-jasmone	0.1-1	0.1-1.44	0.1-1	trace-1	0.1-1
methyl geranate	NR	0.1-1	1.79-15.81	0.1-1	0.1-1
citronellyl acetate	NR	NR	NR	trace	NR
nerol acetate	NR	trace	trace	NR	0.1-1
geranyl acetate	NR	trace-1	NR	NR	NR
<i>p</i> -thymol	4.03-4.96	0.1-1	NR	0.1-1.05	trace
methyl jasmonate	NR	NR	trace	NR	trace
1-octanol	NR	NR	NR	trace	NR
phenylethyl alcohol	trace-1	0.1-1	trace-1	NR	0.1-1
styrene	NR	NR	NR	trace	NR
α,p -dimethylstyrene	0.1-1	1.33-2.17	NR	trace	0.1-1
benzyl nitrile	0.1-4.61	1.20-3.43	0.1-2.49	trace	0.1-1
indole	2.28-4.99	3.69-5.00	4.45-10.41	0.1-1.01	4.79-8.84
methyl anthranilate	0.1-1	1.12-17.91	1.77	trace-2.47	2.79-8.21
pentadecane,3-methyl	NR	2.56	trace-1.14	trace	NR
hexadecane,2-methyl	NR	trace	trace-1	NR	NR
8-heptadecene	1.70-2.23	0.1-1.26	trace-2.76	0.1-1.65	1.03
octadecane, 2-methyl	trace	NR	trace-1	NR	0.1-1

NR = not reported

Table 8. Volatile organic compounds (%) in *Citrus* leaves, identified by gas chromatography-mass spectroscopy.³⁸

	<i>Citrus aurantium</i> (bitter orange)	<i>Citrus sinensis</i> (sweet orange)	<i>Citrus grandis</i> (pomelo)	<i>Citrus paradisi</i> (grapefruit)	<i>Citrus depressa</i>	<i>Citrus reticulata</i> (mandarin orange)
sabinene	NR	1.33	NR	1.38	NR	4.38
myrcene	6.42	1.09	NR	0.00	0.96	4.06
limonene	2.08	2.51	NR	2.68	11.18	2.52
citronellol	NR	NR	11.68	NR	4.67	NR
α -pinene	NR	2.90	NR	NR	NR	1.01
β -pinene	NR	NR	NR	NR	1.03	NR
γ -terpinene	NR	0.40	NR	NR	NR	1.85
δ -3-carene	1.99	NR	NR	NR	NR	NR
2-carene	0.59	NR	NR	NR	NR	NR
(E)- β -ocimene	4.82	3.75	1.45	1.34	1.86	4.14
ocimene	0.87	NR	NR	NR	NR	NR
o-Isopropenyltoluene	NR	NR	NR	NR	NR	NR
α -farnesene	NR	NR	NR	NR	1.59	NR
(E)- β -farnesene	NR	0.43	NR	2.28	NR	0.57
α -bisabolene	NR	NR	NR	NR	NR	NR
β -bisabolene	NR	NR	NR	NR	1.11	NR
β -elemene	NR	0.97	NR	1.99	NR	NR
γ -elemene	NR	NR	NR	NR	NR	0.43
α -selinene	NR	0.34	NR	1.26	NR	NR
δ -cadinene	NR	NR	0.40	NR	NR	0.29
ledene	NR	NR	NR	NR	NR	0.47
α -humulene	NR	0.20	0.23	0.70	NR	NR
β -caryophyllene	1.07	0.52	2.16	0.91	2.16	0.31
linalool	56.93	14.45	5.76	8.26	23.56	67.27
β -fenchyl alcohol	NR	NR	NR	NR	NR	NR
2-cyclohexen-1-ol	NR	0.36	NR	NR	NR	NR
α -terpineol	0.91	0.87	NR	NR	4.22	2.04
α -terpinolene	0.82	0.99	NR	NR	1.00	1.44
terpinen-4-ol	NR	NR	NR	NR	NR	1.49
citronella	0.78	3.60	54.26	17.33	12.51	NR
nerol	1.65	4.14	NR	6.27	NR	NR
neral	2.31	16.14	NR	11.35	5.78	NR
geranial	3.33	23.24	NR	16.25	8.26	NR
geraniol	NR	2.07	NR	2.07	0.96	NR
nonanal	NR	NR	NR	NR	NR	NR
linalyl acetate	5.12	NR	NR	NR	NR	NR
linalyl propanoate	NR	NR	NR	1.19	NR	NR
citronellyl propionate	NR	NR	NR	0.37	NR	NR
geranyl acetate	4.72	0.43	NR	NR	NR	NR
neryl acetate	2.08	0.19	NR	0.46	NR	NR
citronellyl acetate	NR	NR	1.22	NR	NR	NR
α -bergamotene	NR	NR	NR	NR	0.57	NR
aromadendrene	NR	NR	0.52	NR	NR	NR
propanoic acid	NR	0.40	0.31	NR	NR	0.38
1,3,8-p-menthatriene	NR	NR	NR	NR	NR	NR
2-octene	NR	2.29	NR	NR	NR	NR
1,5-hexadiene	NR	NR	NR	NR	NR	NR
1,5-heptadiene	NR	NR	NR	NR	NR	NR
isopulegol	NR	NR	10.36	4.34	2.71	NR
neo-isopulegol	NR	NR	1.33	NR	NR	NR
bicyclogermacrene	NR	NR	0.86	NR	NR	NR
bicycloelemene	NR	NR	0.40	NR	NR	NR
spiro[2.5]octane	NR	NR	4.07	2.29	1.64	NR
cyclooctane	NR	7.12	NR	NR	NR	NR
3-cyclohexene-carboxaldehyde	NR	4.18	NR	4.61	NR	NR
thymyl methyl ether	NR	NR	NR	NR	6.94	1.14

NR = not reported

Table 9. Frequency and concentration of use according to duration and type of exposure for *Citrus* flower- and leaf-derived ingredients.^{10,11}

	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>
	Citrus Aurantium Dulcis (Orange) Flower Extract^b		Citrus Aurantium Dulcis (Orange) Flower Oilⁱ		Citrus Aurantium Dulcis (Orange) Flower Water		Citrus Aurantium Dulcis (Orange) Flower Wax^l	
Totals[†]	70	0.0000016-6	67	0.000011-0.66	16	NR	4	0.12
<i>Duration of Use</i>								
Leave-On	36	0.00003-6	44	0.000035-0.21	9	NR	2	0.12
Rinse Off	33	0.0000016-0.04	19	0.000011-0.66	7	NR	2	NR
Diluted for (Bath) Use	1	0.01-0.1	4	NR	NR	NR	NR	NR
<i>Exposure Type</i>								
Eye Area	NR	0.01-6	1	NR	2	NR	NR	NR
Incidental Ingestion	NR	2	NR	NR	NR	NR	NR	0.12
Incidental Inhalation-Spray	2; 19 ^b ; 9 ^a	0.01	8; 13 ^b ; 15 ^a	0.015; 0.032 ^b	1; 4 ^b ; 1 ^a	NR	2 ^b	NR
Incidental Inhalation-Powder	9 ^a	0.002-0.75 ^c	15 ^a	0.04-0.21 ^c	1 ^a	NR	NR	NR
Dermal Contact	70	0.0000016-6	60	0.000011-0.66	14	NR	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.0002-0.005	6	0.015-0.069	2	NR	2	NR
Hair-Coloring	NR	0.0018	NR	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	NR	NR	NR	NR
Mucous Membrane	14	0.01-2	11	0.0099-0.12	NR	NR	NR	0.12
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Citrus Aurantium Dulcis (Orange) Leaf Extract		Citrus Reticulata (Tangerine) Leaf Oil^k		Kaffir Lime (Citrus Hystrix) Leaf Oil^l			
Totals[†]	1	0.1	35	0.02-0.1	26	NR		
<i>Duration of Use</i>								
Leave-On	1	0.1	18	0.02-0.1	12	NR		
Rinse Off	NR	NR	12	0.066-0.069	12	NR		
Diluted for (Bath) Use	NR	NR	5	NR	2	NR		
<i>Exposure Type</i>								
Eye Area	NR	NR	NR	NR	NR	NR		
Incidental Ingestion	NR	NR	1	0.02	NR	NR		
Incidental Inhalation-Spray	1 ^b	NR	3; 4 ^b ; 6 ^a	0.027 ^b	2; 3 ^b ; 1 ^a	NR		
Incidental Inhalation-Powder	NR	NR	6 ^a	0.1 ^c	1 ^a	NR		
Dermal Contact	1	0.1	31	0.1	21	NR		
Deodorant (underarm)	NR	NR	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	3	0.027-0.069	5	NR		
Hair-Coloring	NR	NR	NR	NR	NR	NR		
Nail	NR	NR	NR	NR	NR	NR		
Mucous Membrane	NR	NR	11	0.02	9	NR		
Baby Products	NR	NR	1	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 Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^b It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

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

^d Includes generic lime blossom extract in the VCRP database.

^e Listed as Citrus Aurantium (Bitter Orange) in the VCRP database.

^f Listed as Citrus Bergamia (Bergamot Orange) in the VCRP database.

^g Includes uses listed under Orange Blossom in the VCRP database.

^h Includes uses listed under Citrus Sinensis (Sweet Orange) Flower Extract in the VCRP database.

ⁱ Includes uses under Citrus Sinensis (Sweet Orange) Flower Oil; Oil of Orange Flowers; and Orange Flower Oil, Sweet in the VCRP database.

^j Includes uses listed under Orange Blossom Wax in the VCRP database.

^k Includes uses listed under Citrus Reticulata (Mandarin Orange) Leaf Oil in the VCRP database.

^l Only listed in the VCRP database, not an INCI ingredient. Included because of similarity.

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

Citrus Aurantifolia (Lime) Leaf Oil
Citrus Grandis (Grapefruit) Leaf Extract
Citrus Hystrix Leaf Extract
Citrus Limon (Lemon) Leaf Extract
Citrus Natsudaikai Flower Water
Citrus Reticulata (Tangerine) Leaf Water
Citrus Tamurana Flower Extract
Citrus Unshiu Flower Powder
Citrus Unshiu Flower Water

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

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
NON-HUMAN					
Citrus Aurantium Amara (Bitter Orange) Flower Wax	neat	6 New Zealand male rabbits	primary cutaneous tolerance test ; test material applied to scarified and intact shaved skin with 2.5 cm ² occluded patches for 24 h	moderate irritation reactions (erythema) that were totally reversible by 72 h; reactions were accompanied by minor, isolated structural modifications	21
bitter orange leaf oil (described as "petitgrain bigarade oil")	2g/kg	2 rabbits	24-h occlusive, single dose study	slight erythema	20
Citrus Hystrix Leaf Extract	10%	3 rabbits	primary skin irritation test, details not provided	no irritation	7
Citrus Hystrix Leaf Extract	10%	Details not provided	cumulative application test, details not provided	no irritation	7
HUMAN					
Citrus Natsudaïdai Flower Oil	1% in jojoba seed oil	20 subjects	24 h human insult patch test using Finn chambers; control patches of white petrolatum, normal saline and distilled water	not irritating	23
bitter orange leaf oil (described as "petitgrain bigarade oil")	0.1%, 2% or 5%; multiple vehicles	48 subjects at 0.1%, 30 subjects at 2%, and 30 subjects at 5%	24-72 h occlusive patch tests	no irritation	22
bitter orange leaf oil (described as "petitgrain bigarade oil")	8%, vehicle not specified	25 subjects	48 h occlusive patch applied to the forearm or back	no irritation	20

Table 12. Sensitization studies for Citrus-derived ingredients.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			ANIMAL		
Citrus Hystrix Leaf Extract	10%	25 guinea pigs	dermal sensitization test, details not provided	not sensitizing	7
			HUMAN		
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0225% in a cream	108 subjects	HR IPT; 0.2 g; occlusive patch	as many as 17 subjects had a ± (faint, minimal erythema) reactions during induction (7 th patch); as many as 7 subjects had a 1 (erythema) reaction (4 th patch) during induction; as many as 3 subjects had a 1 E reaction (3 rd patch) during induction; during challenge as many as 14 subjects had a ± reaction (2 nd challenge reading) and as many as 6 subjects had a 1 reaction (1 st challenge reading); study authors concluded test material was non-sensitizing	26
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0225% in a body cream	106 subjects	HR IPT; 0.2 g; semi-occlusive patch	one subject had a ± reaction on the 1 st challenge reading; study authors concluded test material was non-sensitizing	25
Citrus Aurantium Amara (Bitter Orange) Flower Oil	0.089%	108 healthy subjects	modified Marzulli and Maibach method with 0.02 ml over 50 mm ² ; occlusive patch	not irritating; not sensitizing	27
Citrus Aurantium Dulcis (Orange) Flower Oil	0.4% in a face and neck product	104 subjects	modified HR IPT; semi-occlusive patch; 150 µl over 2 cm ²	not irritating, not sensitizing	28
bitter orange leaf oil (described as "petitgrain bigarade oil")	2% in paraffin	200 patients with dermatitis tested with 35 essential oils plus an additional 50 patients with balsam sensitivity	sensitization patch study, details not provided	3 positive reactions, details not provided	29
bitter orange leaf oil (described as "petitgrain bigarade oil")	8% in petrolatum	25 subjects	maximization study, details not provided	not sensitizing	20

Table 13. Photosensitization studies.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
NON-HUMAN					
bitter orange leaf oil (described as "petitgrain bigarade oil")	undiluted	hairless mice (#/group not stated)	test material was applied, and the test sites were irradiated with UVA irradiation by blacklight or xenon lamp	not photosensitizing	30
bitter orange leaf oil (described as "petitgrain bigarade oil")	undiluted	miniature swine (#/group not stated)	test material was applied, and the test sites were irradiated with UVA irradiation by blacklight or xenon lamp	not photosensitizing	30

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2016 VCRP Raw Data for Citrus Flower- and Leaf-Derived Ingredients

05F - Shampoos (non-coloring)	CITRUS AURANTIFOLIA (LIME) FLOWER EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS AURANTIFOLIA (LIME) FLOWER EXTRACT	1
03D - Eye Lotion	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	5
03G - Other Eye Makeup Preparations	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	1
04A - Cologne and Toilet waters	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	1
05F - Shampoos (non-coloring)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	1
08F - Nail Polish and Enamel Removers	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	2
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	1
12A - Cleansing	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	3
12C - Face and Neck (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	11
12D - Body and Hand (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	8
12F - Moisturizing	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	3
12G - Night	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	3
12H - Paste Masks (mud packs)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	1
12J - Other Skin Care Preps	CITRUS AURANTIUM (BITTER ORANGE) FLOWER EXTRACT	4
01A - Baby Shampoos	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	1
01B - Baby Lotions, Oils, Powders, and Creams	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	2
02A - Bath Oils, Tablets, and Salts	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	3
03G - Other Eye Makeup Preparations	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	4
04A - Cologne and Toilet waters	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	1
04B - Perfumes	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	2
05I - Other Hair Preparations	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	1
07I - Other Makeup Preparations	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	2
10A - Bath Soaps and Detergents	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	3
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	2
11D - Preshave Lotions (all types)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	1
11E - Shaving Cream	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	1
12A - Cleansing	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	3
12C - Face and Neck (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	23
12D - Body and Hand (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	9
12F - Moisturizing	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	18
12G - Night	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	7
12H - Paste Masks (mud packs)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	2

12I - Skin Fresheners	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	1
12J - Other Skin Care Preps	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	6
13A - Suntan Gels, Creams, and Liquids	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	1
13B - Indoor Tanning Preparations	CITRUS AURANTIUM (BITTER ORANGE) FLOWER OIL	5
03D - Eye Lotion	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	3
03E - Eye Makeup Remover	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	1
03G - Other Eye Makeup Preparations	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	4
04A - Cologne and Toilet waters	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	1
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	1
12A - Cleansing	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	6
12C - Face and Neck (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	2
12D - Body and Hand (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	1
12F - Moisturizing	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	4
12G - Night	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	3
12I - Skin Fresheners	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	3
12J - Other Skin Care Preps	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WATER	2
03F - Mascara	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WAX	1
12D - Body and Hand (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WAX	2
12F - Moisturizing	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WAX	1
12J - Other Skin Care Preps	CITRUS AURANTIUM (BITTER ORANGE) FLOWER WAX	1
02B - Bubble Baths	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	1
04A - Cologne and Toilet waters	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	2
07C - Foundations	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	2
07F - Makeup Bases	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	6
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	7
12A - Cleansing	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	11
12B - Depilatories	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	6
12C - Face and Neck (exc shave)	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	4
12D - Body and Hand (exc shave)	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	4
12F - Moisturizing	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	13

12G - Night	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	4
12H - Paste Masks (mud packs)	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	3
12I - Skin Fresheners	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	1
12J - Other Skin Care Preps	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER EXTRACT	2
03D - Eye Lotion	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER WATER	1
03E - Eye Makeup Remover	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER WATER	1
04A - Cologne and Toilet waters	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER WATER	1
05A - Hair Conditioner	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER WATER	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER WATER	1
07H - Makeup Fixatives	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER WATER	1
12A - Cleansing	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER WATER	5
12C - Face and Neck (exc shave)	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER WATER	1
12I - Skin Fresheners	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER WATER	3
12J - Other Skin Care Preps	CITRUS AURANTIUM DULCIS (ORANGE) FLOWER WATER	1
12G - Night	CITRUS AURANTIUM DULCIS (ORANGE) LEAF EXTRACT	1
12C - Face and Neck (exc shave)	CITRUS BERGAMIA (BERGAMOT ORANGE) LEAF OIL	1
12D - Body and Hand (exc shave)	CITRUS BERGAMIA (BERGAMOT ORANGE) LEAF OIL	1
12A - Cleansing	CITRUS RETICULATA (MANDARIN ORANGE) LEAF OIL	2
12D - Body and Hand (exc shave)	CITRUS RETICULATA (MANDARIN ORANGE) LEAF OIL	1
01C - Other Baby Products	CITRUS RETICULATA (TANGERINE) LEAF OIL	1
02A - Bath Oils, Tablets, and Salts	CITRUS RETICULATA (TANGERINE) LEAF OIL	3
02B - Bubble Baths	CITRUS RETICULATA (TANGERINE) LEAF OIL	1
02D - Other Bath Preparations	CITRUS RETICULATA (TANGERINE) LEAF OIL	1
04E - Other Fragrance Preparation	CITRUS RETICULATA (TANGERINE) LEAF OIL	3
05A - Hair Conditioner	CITRUS RETICULATA (TANGERINE) LEAF OIL	1
05F - Shampoos (non-coloring)	CITRUS RETICULATA (TANGERINE) LEAF OIL	2
07E - Lipstick	CITRUS RETICULATA (TANGERINE) LEAF OIL	1
10A - Bath Soaps and Detergents	CITRUS RETICULATA (TANGERINE) LEAF OIL	3
10E - Other Personal Cleanliness Products	CITRUS RETICULATA (TANGERINE) LEAF OIL	2
12A - Cleansing	CITRUS RETICULATA (TANGERINE) LEAF OIL	2
12D - Body and Hand (exc shave)	CITRUS RETICULATA (TANGERINE) LEAF OIL	5
12F - Moisturizing	CITRUS RETICULATA (TANGERINE) LEAF OIL	1
12G - Night	CITRUS RETICULATA (TANGERINE) LEAF OIL	2
12J - Other Skin Care Preps	CITRUS RETICULATA (TANGERINE) LEAF OIL	3

13A - Suntan Gels, Creams, and Liquids	CITRUS RETICULATA (TANGERINE) LEAF OIL	1
11B - Beard Softeners	CITRUS SINENSIS (SWEET ORANGE) FLOWER EXTRACT	1
12D - Body and Hand (exc shave)	CITRUS SINENSIS (SWEET ORANGE) FLOWER EXTRACT	1
12F - Moisturizing	CITRUS SINENSIS (SWEET ORANGE) FLOWER EXTRACT	1
02A - Bath Oils, Tablets, and Salts	CITRUS SINENSIS (SWEET ORANGE) FLOWER OIL	1
04E - Other Fragrance Preparation	CITRUS SINENSIS (SWEET ORANGE) FLOWER OIL	1
05A - Hair Conditioner	CITRUS SINENSIS (SWEET ORANGE) FLOWER OIL	1
05F - Shampoos (non-coloring)	CITRUS SINENSIS (SWEET ORANGE) FLOWER OIL	1
10A - Bath Soaps and Detergents	CITRUS SINENSIS (SWEET ORANGE) FLOWER OIL	4
11B - Beard Softeners	CITRUS SINENSIS (SWEET ORANGE) FLOWER OIL	1
12C - Face and Neck (exc shave)	CITRUS SINENSIS (SWEET ORANGE) FLOWER OIL	1
12D - Body and Hand (exc shave)	CITRUS SINENSIS (SWEET ORANGE) FLOWER OIL	1
12H - Paste Masks (mud packs)	CITRUS SINENSIS (SWEET ORANGE) FLOWER OIL	1
02A - Bath Oils, Tablets, and Salts	KAFFIR LIME (CITRUS HYSTRIX) LEAF OIL	1
02D - Other Bath Preparations	KAFFIR LIME (CITRUS HYSTRIX) LEAF OIL	1
04A - Cologne and Toilet waters	KAFFIR LIME (CITRUS HYSTRIX) LEAF OIL	1
04E - Other Fragrance Preparation	KAFFIR LIME (CITRUS HYSTRIX) LEAF OIL	1
05A - Hair Conditioner	KAFFIR LIME (CITRUS HYSTRIX) LEAF OIL	2
05F - Shampoos (non-coloring)	KAFFIR LIME (CITRUS HYSTRIX) LEAF OIL	3
10A - Bath Soaps and Detergents	KAFFIR LIME (CITRUS HYSTRIX) LEAF OIL	7
12D - Body and Hand (exc shave)	KAFFIR LIME (CITRUS HYSTRIX) LEAF OIL	1
12F - Moisturizing	KAFFIR LIME (CITRUS HYSTRIX) LEAF OIL	3
12J - Other Skin Care Preps	KAFFIR LIME (CITRUS HYSTRIX) LEAF OIL	6
02D - Other Bath Preparations	LIME BLOSSOM EXTRACT	3
12C - Face and Neck (exc shave)	LIME BLOSSOM EXTRACT	1
12J - Other Skin Care Preps	LIME BLOSSOM EXTRACT	4
02A - Bath Oils, Tablets, and Salts	OIL OF ORANGE FLOWERS	2
02D - Other Bath Preparations	OIL OF ORANGE FLOWERS	1
03D - Eye Lotion	OIL OF ORANGE FLOWERS	1
04A - Cologne and Toilet waters	OIL OF ORANGE FLOWERS	2
04B - Perfumes	OIL OF ORANGE FLOWERS	1
04E - Other Fragrance Preparation	OIL OF ORANGE FLOWERS	3
05A - Hair Conditioner	OIL OF ORANGE FLOWERS	1
05B - Hair Spray (aerosol fixatives)	OIL OF ORANGE FLOWERS	1
05F - Shampoos (non-coloring)	OIL OF ORANGE FLOWERS	2
10A - Bath Soaps and Detergents	OIL OF ORANGE FLOWERS	1
10E - Other Personal Cleanliness	OIL OF ORANGE FLOWERS	1

Products

11A - Aftershave Lotion	OIL OF ORANGE FLOWERS	1
11E - Shaving Cream	OIL OF ORANGE FLOWERS	1
12A - Cleansing	OIL OF ORANGE FLOWERS	5
12C - Face and Neck (exc shave)	OIL OF ORANGE FLOWERS	4
12D - Body and Hand (exc shave)	OIL OF ORANGE FLOWERS	9
12F - Moisturizing	OIL OF ORANGE FLOWERS	8
12G - Night	OIL OF ORANGE FLOWERS	1
12J - Other Skin Care Preps	OIL OF ORANGE FLOWERS	4
13B - Indoor Tanning Preparations	OIL OF ORANGE FLOWERS	3
02A - Bath Oils, Tablets, and Salts	ORANGE BLOSSOM	1
03G - Other Eye Makeup Preparations	ORANGE BLOSSOM	1
12D - Body and Hand (exc shave)	ORANGE BLOSSOM	1
12F - Moisturizing	ORANGE BLOSSOM	3
05F - Shampoos (non-coloring)	ORANGE BLOSSOM WAX	2
12F - Moisturizing	ORANGE BLOSSOM WAX	2
08B - Cuticle Softeners	ORANGE FLOWER OIL, SWEET	1
10A - Bath Soaps and Detergents	ORANGE FLOWER OIL, SWEET	1
13A - Suntan Gels, Creams, and Liquids	ORANGE FLOWER OIL, SWEET	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

A handwritten signature in blue ink that reads "Beth A. Lange".

DATE: February 10, 2016

SUBJECT: Citrus Hystrix Leaf Extract

Anonymous. 2016. Summary information: Citrus Hystrix Leaf Extract.

February 2016

Citrus Hystrix Leaf Extract

- ◆ Method of manufacture
- ◆ Chemical composition and impurities
- ◆ Dermal irritation and sensitization data on products containing the highest concentrations of these ingredients, especially human repeated insult patch tests (HRIPT) on Citrus Aurantium Amara (Bitter Orange) Flower Extract and Citrus Aurantium Amara (Bitter Orange) Flower Water

Trade name: Citrus Hystrix Leaf Extract BG70

Method of manufacture	Dried raw material⇒extract with 80vol% ethanolic solution⇒filtrate⇒concentration ⇒ add 70vol% 1,3-butylene glycolic solution ⇒ sedimentation⇒filtrate⇒adjustment⇒packaging
Chemical composition	Tannin and sugar
Impurities	Heavy metals : Not more than 20ppm , Arsenic : Not more than 2ppm
Dermal irritation data	Primary skin irritation test (10%) (negative) (tested in 3 rabbits), Cumulative application test (10%) (negative)
Dermal sensitization data	Dermal sensitization test (10%) (negative) (tested in 25 guinea pigs)



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 Flower- and Leaf-Derived Ingredients

Concentration of Use by FDA Product Category – Citrus Flower- and Leaf-Derived Ingredients*

Citrus Aurantifolia (Lime) Flower Extract	Citrus Tamurana Flower Extract
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Citrus Unshiu Flower Extract
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Citrus Unshiu Flower Powder
Citrus Aurantium Amara (Bitter Orange) Flower Water	Citrus Unshiu Flower Water
Citrus Aurantium Amara (Bitter Orange) Flower Wax	Citrus Aurantifolia (Lime) Leaf Oil
Citrus Aurantium Dulcis (Orange) Flower	Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract
Citrus Aurantium Dulcis (Orange) Flower Extract	Citrus Aurantium Bergamia (Bergamot) Leaf Extract
Citrus Aurantium Dulcis (Orange) Flower Oil	Citrus Aurantium Bergamia (Bergamot) Leaf Oil
Citrus Aurantium Dulcis (Orange) Flower Wax	Citrus Clementina Leaf Cell Extract
Citrus Depressa Flower Water	Citrus Aurantium Dulcis (Orange) Leaf Extract
Citrus Junos Flower Oil	Citrus Grandis (Grapefruit) Leaf Extract
Citrus Limon (Lemon) Flower Water	Citrus Hystrix Leaf Extract
Citrus Natsudaikai Flower Oil	Citrus Limon (Lemon) Leaf Cell Extract
Citrus Natsudaikai Flower Water	Citrus Limon (Lemon) Leaf Extract
Citrus Sinensis (Orange) Flower Water	Citrus Reticulata (Tangerine) Leaf Oil
	Citrus Reticulata (Tangerine) Leaf Water
	Citrus Unshiu Leaf Extract

Ingredient	Product Category	Maximum Concentration of Use
Citrus Aurantifolia (Lime) Flower Extract	Bubble baths	0.0005%
Citrus Aurantifolia (Lime) Flower Extract	Other bath preparations	0.0005%
Citrus Aurantifolia (Lime) Flower Extract	Other fragrance preparations	0.0005%
Citrus Aurantifolia (Lime) Flower Extract	Hair sprays Aerosol	0.00001%
Citrus Aurantifolia (Lime) Flower Extract	Shampoos (noncoloring)	0.005%
Citrus Aurantifolia (Lime) Flower Extract	Tonics, dressings and other hair grooming aids	0.00001%
Citrus Aurantifolia (Lime) Flower Extract	Bath soaps and detergents	0.0005%
Citrus Aurantifolia (Lime) Flower Extract	Body and hand products Not spray	0.0005%
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Colognes and toilet waters	0.001%
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Hair sprays Pump spray	0.000000072%
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Shampoos (noncoloring)	0.001%
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Tonics, dressings and other hair grooming aids	0.032%
Citrus Aurantium Amara (Bitter Orange)	Bath soaps and detergents	0.00028-0.001%

Flower Extract		
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Deodorants Not spray	0.00001-0.0099%
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Body and hand products Not spray	0.001-0.023%
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Moisturizing products Not spray	0.001%
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Hair conditioners	0.001-0.0026%
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Shampoos (noncoloring)	0.001-0.003%
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Tonics, dressings and other hair grooming aids	0.049%
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Face powders	0.01%
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Bath soaps and detergents	0.019%
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Face and neck products Not spray	0.00098%
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Body and hand products Not spray Spray	0.005% 0.0024%
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Moisturizing products Not spray	0.008%
Citrus Aurantium Amara (Bitter Orange) Flower Water	Bubble baths	0.000033%
Citrus Aurantium Amara (Bitter Orange) Flower Water	Eye lotions	0.0023%
Citrus Aurantium Amara (Bitter Orange) Flower Water	Eye makeup removers	0.0017%
Citrus Aurantium Amara (Bitter Orange) Flower Water	Hair conditioners	0.00014%
Citrus Aurantium Amara (Bitter Orange) Flower Water	Shampoos (noncoloring)	0.00005%
Citrus Aurantium Amara (Bitter Orange) Flower Water	Bath soaps and detergents	0.00018-0.05%
Citrus Aurantium Amara (Bitter Orange) Flower Water	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.000076%
Citrus Aurantium Amara (Bitter Orange) Flower Water	Face and neck products Not spray	0.00021%
Citrus Aurantium Amara (Bitter Orange) Flower Water	Suntan products Not spray	0.00016%
Citrus Aurantium Dulcis (Orange) Flower	Colognes and toilet waters	0.01%
Citrus Aurantium Dulcis (Orange) Flower	Hair conditioners	0.001%
Citrus Aurantium Dulcis (Orange) Flower	Shampoos (noncoloring)	0.00008-0.005%
Citrus Aurantium Dulcis (Orange) Flower	Other personal cleanliness products	0.01%

Citrus Aurantium Dulcis (Orange) Flower	Shaving cream	0.0000025%
Citrus Aurantium Dulcis (Orange) Flower	Body and hand products Not spray	0.01%
Citrus Aurantium Dulcis (Orange) Flower Extract	Bubble baths	0.1%
Citrus Aurantium Dulcis (Orange) Flower Extract	Other bath preparations	0.01%
Citrus Aurantium Dulcis (Orange) Flower Extract	Eyeliners	0.68%
Citrus Aurantium Dulcis (Orange) Flower Extract	Eye shadows	6%
Citrus Aurantium Dulcis (Orange) Flower Extract	Other eye makeup preparations	0.01%
Citrus Aurantium Dulcis (Orange) Flower Extract	Colognes and toilet waters	0.01%
Citrus Aurantium Dulcis (Orange) Flower Extract	Hair conditioners	0.005%
Citrus Aurantium Dulcis (Orange) Flower Extract	Shampoos (noncoloring)	0.0002-0.005%
Citrus Aurantium Dulcis (Orange) Flower Extract	Hair rinses (coloring)	0.0018%
Citrus Aurantium Dulcis (Orange) Flower Extract	Lipstick	2%
Citrus Aurantium Dulcis (Orange) Flower Extract	Bath soaps and detergents	0.01-0.04%
Citrus Aurantium Dulcis (Orange) Flower Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0000016-0.01%
Citrus Aurantium Dulcis (Orange) Flower Extract	Depilatories	0.007%
Citrus Aurantium Dulcis (Orange) Flower Extract	Face and neck products Not spray	0.002-0.056%
Citrus Aurantium Dulcis (Orange) Flower Extract	Body and hand products Not spray	0.01-0.75%
Citrus Aurantium Dulcis (Orange) Flower Extract	Paste masks and mud packs	0.0002%
Citrus Aurantium Dulcis (Orange) Flower Extract	Suntan products Not spray	0.0045%
Citrus Aurantium Dulcis (Orange) Flower Oil	Hair conditioners	0.066%
Citrus Aurantium Dulcis (Orange) Flower Oil	Hair sprays Aerosol	0.015%
Citrus Aurantium Dulcis (Orange) Flower Oil	Shampoos (noncoloring)	0.069%
Citrus Aurantium Dulcis (Orange) Flower Oil	Tonics, dressings and other hair grooming aids	0.032%
Citrus Aurantium Dulcis (Orange) Flower Oil	Blushers	0.000035%

Citrus Aurantium Dulcis (Orange) Flower Oil	Bath soaps and detergents	0.0099-0.12%
Citrus Aurantium Dulcis (Orange) Flower Oil	Skin cleansing (cold creams, cleansing lotions, liquid and pads)	0.000011-0.1%
Citrus Aurantium Dulcis (Orange) Flower Oil	Depilatories	0.66%
Citrus Aurantium Dulcis (Orange) Flower Oil	Face and neck products Not spray	0.1-0.21%
Citrus Aurantium Dulcis (Orange) Flower Oil	Body and hand products Not spray	0.04-0.05%
Citrus Aurantium Dulcis (Orange) Flower Wax	Lipstick	0.12%
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	Hair conditioners	0.002%
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	Shampoos (noncoloring)	0.002%
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	Face and neck products Not spray	0.002%
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	Body and hand products Not spray	0.002%
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	Hair conditioners	0.002%
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	Shampoos (noncoloring)	0.002%
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	Face and neck products Not spray	0.002%
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	Body and hand products Not spray	0.002%
Citrus Aurantium Dulcis (Orange) Leaf Extract	Makeup bases	0.1%
Citrus Reticulata (Tangerine) Leaf Oil	Hair conditioners	0.066%
Citrus Reticulata (Tangerine) Leaf Oil	Shampoos (noncoloring)	0.069%
Citrus Reticulata (Tangerine) Leaf Oil	Tonics, dressings and other hair grooming aids	0.027%
Citrus Reticulata (Tangerine) Leaf Oil	Lipstick	0.02%
Citrus Reticulata (Tangerine) Leaf Oil	Face and neck products Not spray	0.1%

*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 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 19, 2016

SUBJECT: Citrus Aurantium Amara (Bitter Orange) Flower Oil

Institut D'Expertise Clinique. 2008. Sensitisation and cutaneous compatibility study (face serum containing 0.089% Citrus Aurantium Amara (Bitter Orange) Flower Oil).



INSTITUT D'EXPERTISE CLINIQUE

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I.E.C. BULGARIE

REPORT: SENSITISATION AND CUTANEOUS COMPATIBILITY STUDY

DT 026091

CLINICAL STUDY FOR THE VERIFICATION OF THE ABSENCE OF THE SENSITISING POTENTIAL AND OF THE GOOD CUTANEOUS COMPATIBILITY OF A COSMETIC INVESTIGATIONAL PRODUCT, BY REPEATED EPICUTANEOUS APPLICATIONS UNDER OCCLUSIVE PATCH, IN 108 HEALTHY ADULT SUBJECTS
(modified Marzulli and Maibach method)

**INVESTIGATIONAL
PRODUCT**

Citrus Aurantium Amara (Bitter Orange) Flower Oil 0.089% Face Serum - batch n° 707285 of 02/08/2007)

**STANDARD EXPERIMENTAL
PROTOCOL**

N° EN_P_STD_CLITP_5021_01, of 20 January 2005

**SPECIFIC EXPERIMENTAL
PROTOCOL**

N° B072004PE, of 2 January 2008

REPORT

N° B072004RD1- Version 1, of 7 April 2008

START OF OBSERVATIONS

15 January 2008

END OF OBSERVATIONS

23 February 2008

STUDY MONITOR	TECHNICAL AND SCIENTIFIC DEPUTY MANAGER	DERMATOLOGIST INVESTIGATORS
[REDACTED]	Miss E. ATANASSOVA Engineer in Biotechnology I.E.C. Bulgarie Lozenetz - 16A, Kichinev street 1407 SOFIA- BULGARIA	- Dr. Z. PANOVA, M.D. (Coordinator) - Dr. G. BOCHEVA, M.D. Address of Investigations: I.E.C. Bulgarie Lozenetz - 16A, rue Kichinev 1407 SOFIA - BULGARIA

Document of 57 pages

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AUTHENTICATION

The study subject of the present report was conducted under my responsibility, in compliance with standard and specific experimental protocols, and in accordance with I.E.C. Standard Operating Procedures and in the spirit of the general principles of the Good Clinical Practices.

All observations and numerical data obtained during this study are reported in the present document.

Dr. Zoya PANOVA, M.D.
Dermatologist Investigator
Coordinator

I have read this report, I certify that these data are an accurate reflection of the results obtained and I agree with its content.

Elitsa ATANASSOVA
Technical and Scientific Deputy Manager

PERSONNEL INVOLVED IN THE REALISATION OF THE STUDY

(for I.E.C. France)

<p><u>President</u> Name: J.P. GUILLOT Senior Toxicologist- Pharmacologist (Eurotox Registered Toxicologist) Address: Route de Bibost 69690 Bessenay - France +33 (0) 4.74.70.93.39</p>	<p><u>Deputy General Director- Vice- President</u> Name: E. CAMEL Pharm. D., D.E.A. in Skin Biology and Cosmetology, Senior Toxicologist (Eurotox Registered Toxicologist) Address: 88, boulevard des Belges 69006 Lyon - France +33 (0) 4.72.69.89.61</p>
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<p><u>Administration, Finance and Human Resources</u> Director Name: Y. POHLMANN D.U.E.L. in English Address: 88, boulevard des Belges 69006 Lyon - France +33 (0) 4.72.69.70.91</p>	<p><u>Head of Studies Management performed in I.E.C. Bulgarie</u> Name: J.R. CAMPOS Graduate in Dermocosmetology Doctor of Cellular Biology and Microbiology Address: 88, boulevard des Belges 69006 Lyon - France +33 (0) 4.72.69.89.66</p>
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(for I.E.C. Bulgarie)

<p><u>Executive Director</u> Name: G. VELEY Graduate of High School of Economy Address: Lozenetz- 16A, rue Kichinev 1407 Sofia- Bulgaria + (359) 2.868.35.82</p>	<p><u>Administrative Manager</u> Name: K. CHTEREVA Master in French Address: Lozenetz- 16A, rue Kichinev 1407 Sofia- Bulgaria + (359) 2.868.53.11</p>
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<p><u>Dermatologist Investigators</u> Names: Dr. Z. PANOVA, M.D. (Coordinator) Dr. G. BOCHEVA, M.D. Graduate in Dermatology & Venerology Address: Lozenetz - 16A, rue Kichinev 1407 Sofia - Bulgaria + (359) 2.868.53.11</p>	<p><u>Technical and Scientific Manager</u> Name: M. VASSILEVA Post-Graduate in Life and Health Sciences Address: Lozenetz- 16A, rue Kichinev 1407 Sofia- Bulgaria + (359) 2.868.53.11</p>
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<p><u>Technical and Scientific Deputy Manager</u> Name: E. ATANASSOV A Engineer in Biotechnology Address: Lozenetz- 16A, rue Kichinev 1407 Sofia- Bulgaria + (359) 2.868.53.11</p>

<p><u>Technicians</u> Names: G. KOSTADINOVA, Nurse K. IVANOVA, Nurse S. KABAKCHIEVA, Master in Chemistry V. DIMITROVA, Master in Chemistry A. KRASTANOV A, Master in Biology Address: Lozenetz- 16A, rue Kichinev 1407 Sofia- Bulgaria + (359) 2.868.53.11</p>	<p><u>Technicians</u> Names: B. HRISTOVA, Master in Biology K. RANGELOVA, Master in Chemistry M. VALCHANOVA, Nurse J. YORDANOVA, Master in Chemistry K. NIKOLOVA, Master in Biology Address: Lozenetz- 16A, rue Kichinev 1407 Sofia- Bulgaria + (359) 2.868.53.11</p>
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ENGLISH SUMMARY OF THE REPORT

SPONSOR:



INVESTIGATIONAL PRODUCT:

Citrus Aurantium Amara (Bitter Orange)
Flower Oil 0.089% Face Serum- batch n°
707285 of 02/08/2007)

DT 026091

SENSITISATION AND CUTANEOUS COMPATIBILITY STUDY

**CLINICAL STUDY FOR THE VERIFICATION OF THE ABSENCE
OF THE SENSITISING POTENTIAL AND OF THE GOOD CUTANEOUS
COMPATIBILITY OF A COSMETIC INVESTIGATIONAL PRODUCT,
BY REPEATED EPICUTANEOUS APPLICATIONS
UNDER OCCLUSIVE PATCH, IN 108 HEALTHY ADULT SUBJECTS
(modified Marzulli and Maibach method)**

STUDY OBJECTIVE	To check the absence of sensitising potential and the good cutaneous compatibility, of a cosmetic investigational product, by repeated applications on the skin, under occlusive patch, in the healthy adult subject.
TYPE OF STUDY	Compatibility study (modified Marzulli and Maibach method), under Dermatological control.
STUDY RELEVANCE	Cutaneous allergy is an individual phenomenon, of immune origin, of which setting off activating 3 phases (penetration of the foreign substance in the skin and forming of the allergen; development of the immune reaction; activating of the reaction, by a new application of the allergenic molecule to the skin). These 3 phases are thus required to check, in 50 or 100 subjects, the absence of sensitising potential of an investigational product, and are the basis of the method described by Marzulli and Maibach (<i>protocol in conformity to note dated 4 August 1997 of the French "Repression des Fraudes" to the "Federation Française des Industries de la Parfumerie"</i>).
<u>INCLUSION CRITERIA SPECIFIC TO THE STUDY</u> <i>(in addition to the general criteria)</i>	<ul style="list-style-type: none"> . Number of subjects: 100 . Sex: female and male . Age: 18 to 70 years old . Origin: Caucasian . Healthy subjects: 100%

<p><u>METHODOLOGY</u></p>	<p>-Application modalities of the investigational product: -<i>area</i>: back -<i>quantity</i>: 0.02 ml over a 50 mm² surface (occlusive patch) -<i>application conditions</i>: the investigational product as supplied, being under a liquid form was put onto a disc of filter paper (7 mm in diameter) previously inserted into the cupule of the occlusive patch (Finn Chambers on Scanpor). -<i>frequency and duration</i>: Induction period: 9 applications of about 48 or 72 hours (for the week-ends), over a period of 3 weeks. rest period: 13 days "challenge" period: single application, for about 24 or 48 hours N.B.: the patches were removed by the Laboratory staff.</p> <p>- Modalities of evaluations: - <i>Clinical observations</i>: readings performed according to the Sponsor's specificities (D2, D35, D37 and D39 performed by the Dermatologist Investigator): <i>induction</i>: 15 to 30 minutes after removal of the patches <i>"challenge"</i>: 30 min to 60 min and 48 hours ± 3 hours after removal of the patches - <i>Evaluation of the good cutaneous compatibility and of sensitising potential</i>, according to a given numerical scale (irritation scale: "challenge": 0 to 4 & scale of the International Contact Dermatitis Research Group: I.C.D.R.G.; 0 to 3[+++]).</p>
<p><u>ANALYSIS OF THE RESULTS AND EVALUATION CRITERIA</u></p>	<p>-<i>Determination of the Mean Irritation Index (M.I.I)</i>: mean of the induction readings quotations, divided by the number of readings performed -<i>Interpretation of the results obtained</i>, under the experimental conditions adopted: . For cumulative irritation: arbitrary classification of the investigational product ("non-irritating" to "severely irritating"); . For sensitisation: An erythema, of intensity higher than or equal to 2 during the "challenge" phase, with or without palpable lesions, had to be evaluated in the following days to note if the reaction decreases or increases in order to precise if the reaction observed is of allergical or irritative type. A quick decrease of the reaction indicates an irritation (decrecendo reaction). A reaction with presence of infiltration/redema, which persists and/or which increases within time generally indicates a reaction of allergical type, an additional application (rechallenge) was performed 3 to 6 weeks after the "challenge" phase. . also on the base of the type of investigational products and the I.E.C. statistics established on about 3,100 investigational products at I.E.C. Bulgarie between 2002 and 2006 (positioning of the cumulative irritation and/or sensitisation in comparison of investigational products of the same type). The additional examinations, in case of positive reaction(s) (photography, additional revelation ...) can be carried out according to the modalities specified by the Sponsor.</p>

RESULTS AND CONCLUSION

STUDIED POPULATION

Number of subjects recruited	151
Number of subjects who came to I.E.C.	111
Number of subjects included by the Dermatologist Investigator	108
Number of subjects discontinued from the study	0
Number of subjects for the analysis of the results	
. for the evaluation of Primary Cutaneous Irritation	108
. for the evaluation of Cumulative Irritation	108
. for the evaluation of Cutaneous Sensitisation	108

The physical characteristics of the subjects are summarized in the following table.

Subjects	Primary Cutaneous Irritation	Cumulative Irritation	Cutaneous Sensitisation
Number	108	108	108
Females	90	90	90
Males	18	18	18
Age minimum (y.o.)	18	18	18
Age maximum (y.o.)	67	67	67

RESULTS

Percentage of subjects having presented with one or several well visible to severe irritation reactions (score ≥ 2), during the induction	0%
Mean Irritation Index (M.I.I.) of the induction Classification of the investigational product	0 ✓ non-irritant: M.I.I. < 0.25 slightly irritant: M.I.I. [0.25 - 1] moderately irritant: M.I.I. [1 - 2] very irritant: M.I.I. [2 - 3] severely irritant: M.I.I. [3 - 4]
Percentage of the sensitisation reactions observed	0%
Reactions considered as serious adverse events linked to the investigational product	0%

CONCLUSION

In conclusion and given the results obtained under the experimental conditions adopted, the single and repeated epicutaneous applications of this investigational product, under occlusive patch, in the healthy adult subject, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitisation.

Lyon and Sofia,

J.R. CAMPOS
Graduate in Dermocosmetology
Doctor in Cellular Biology and
Microbiology
Head of Studies Management
performed in I.E.C. Bulgarie

E. ATANASSOVA
Engineer in Biotechnology
Technical and Scientific
Deputy Manager

Dr. Z. PANOVA, M.D.
Dermatologist Investigator
Coordinator

This study was conducted by INSTITUT D'EXPERTISE CLINIQUE- BULGARIE,
registered by the Bulgarian Health Authorities
Scientific Member of the Board of Directors of I.E.C. Bulgarie:
Professor Romyana YANKOVA, MD., Ph. D., Head of the Dermatology
and Allergology Department of Plovdiv Medical University

QUALITY CONTROL

This study was conducted in conformity with the standard operating procedures of the Clinical Research Centre, the general procedures of I.E.C. Bulgarie, the signed protocol and "in the spirit" of the general principles of the Good Clinical Practices published by I.C.H. (CPMP/ICH/135/95).

The quality control of the clinical studies is carried out periodically. It is designed to ensure that all critical phases (investigational product applications and examinations or measurements) of a particular study type are controlled, at least once quarterly, for the studies carried out during this time period. Dates of these controls and study type concerned are given below.

The results of these quality controls were reported to the Dermatologist Investigators and to the General Management.

Types of study	Dates of quality controls	Dates of reports to the Dermatologist Investigators	Dates of reports to the General Management
. Identical study:	22 January 2008	23 January 2008	29 January 2008
. Raw data:	Induction: 6 February 2008	7 February 2008	13 February 2008
	Challenge: 26 February 2008	27 February 2008	4 March 2008

This report has been controlled by I.E.C. France Quality Unit, it is an accurate account of the procedures followed, and accurately records the raw laboratory data generated in this study.

	Dates of quality control	Dates of reports to the Dermatologist Investigators	Dates of report to the General Management
Report (vs. Compiled Data):	31 March 2008	31 March 2008	31 March 2008

Signature:

 07/04/08

Aurelie CHAMBERAUD
Quality Executive Deputy Manager



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 25, 2016

SUBJECT: Citrus Reticulata (Tangerine) Leaf Oil

Published papers concerning the composition of Citrus Reticulata (Tangerine) Leaf Oil.

Title: Mandarin Leaf Oil (Citrus reticulata Blanco); Aromatic Plants of the Holy Land and the Sinai. Part III

Authors: Zhenia Fleishera & Alexander Fleisherb

Source: Journal of Essential Oils, Vol. 2, Issue 6, pages 331-334; 1990

Abstract: The leaf oils of seven major commercial mandarin varieties which are cultivated in Israel were investigated using GC/MS. Seventy-three components were identified in the oils, which could be grouped into three distinct chemical types. These were type A: (classic mandarin petitgrain) an oil rich in methyl-N-methyl anthranilate (variety Balady); type B: (varieties Yussuf Effendy, Dancy and Maya) containing thymol, reduced amounts of sabinene and a large amount of linalool; type C: (varieties Clementine, Michal and Nectarine) which is characterized by high concentrations of sabinene and terpinen-4-ol, moderate amounts of linalool and by the absence of thymol.

http://www.tandfonline.com/na101/home/literatum/publisher/tandf/journals/content/tjeo20/1990/tjeo20.v002.i06/10412905.1990.9697893/production/10412905.1990.9697893.fp.png_v03 (first page)

Title: Leaf Volatile Oil Composition of Mandarin (Citrus reticulata) from Nigeria

Authors: Olusegun Ekundayoa, Oladapo Bakarea, Akinbo Adesomjua & Elisabeth Stahl-Biskupb

Source: Journal of Essential Oils, Vol. 2, Issue 6, pages 329-330; 1990

Abstract: A combination of GC and GC/MS was used to characterize the chemical composition of the leaf oil of mandarin (*Citrus reticulata*) from Nigeria. A total of twenty-two compounds were identified in the oil. The main compounds were found to be α -terpinene (20.15%), p-cymene (16.29%), linalool (9.55%) and terpinen-4-ol (7.13%).

http://www.tandfonline.com/na101/home/literatum/publisher/tandf/journals/content/tjeo20/1990/tjeo20.v002.i06/10412905.1990.9697892/production/10412905.1990.9697892.fp.png_v03 (first page)



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 29, 2016

SUBJECT: Citrus Aurantium Dulcis (Orange) Flower Extract

Anonymous. 2016. Method of manufacture, impurities and specifications Citrus Aurantium Dulcis (Orange) Flower Extract.

February 2016

Citrus Aurantium Dulcis (Orange) Flower Extract**Manufacturing Process:**

The fresh/dried flower is extracted with specified eluent under appropriate temperature conditions, to yield a concentrate. Concentrate containing the phytochemical constituents is then blended with the desired diluent and preservation systems to produce the final ingredient. The ingredient is evaluated for physiochemical properties according to the specification requirements for the batch to be released. In addition, the concentrate is also evaluated for contaminants and physiochemical properties as needed.

Impurities/ Heavy metal & Pesticides/ Allergens:

The following data are obtained based on the testing done on the concentrate in alcohol base:

Pesticides: There were no residual pesticides detected. (Parameters: EPA Analytical Method 8081 GCS Pesticides and EPA Analytical Method 8141A GCS, O/P Pesticides)

Heavy metals:	Heavy Metal	Result	Detection/Reporting Limit	Heavy Metal	Result	Detection/Reporting Limit
	Antimony	Not Detected	0.25 mg/kg	Iron	Not Detected	25.0 mg/kg
Arsenic	Not Detected	0.25 mg/kg	Lead	Not Detected	0.100 mg/kg	
Cadmium	Not Detected	0.040 mg/kg	Mercury	Not Detected	0.0035 mg/kg	
Chromium	Not Detected	0.100 mg/kg	Nickel	Not Detected	0.1 mg/kg	

Presence of the 26 allergens defined by the 7 th amendment to the EU Cosmetic Directive:	Fragrance Ingredient		Fragrance Ingredient	
	Fragrance Ingredient	Result	Fragrance Ingredient	Result
	Amyl Cinnamal	None detected	Anise Alcohol	None detected
	Benzyl Alcohol	None detected	Benzyl Cinnamate	None detected
	Cinnamyl Alcohol	None detected	Farnesol	None detected
	Citral	None detected	Butylphenyl Methylpropional	None detected
	Eugenol	None detected	Linalool	None detected
	Hydroxycitronellal	None detected	Benzyl Benzoate	None detected
	Isoeugenol	None detected	Citronellol	None detected
	Amylcinnamyl Alcohol	None detected	Hexyl Cinnamal	None detected
	Benzyl Salicylate	None detected	Limonene	None detected
	Cinnamal	None detected	Methyl 12-octynoate	None detected
	Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde	None detected	Alpha-Isomethyl Inone (Other Name: Methyl Lonone Gamma)	None detected
	Coumarin	None detected	Evernia Prunastri (Oak Moss) Extract	Not Detected
	Geraniol	None detected	Evernia Furfuracea (Tree Moss) Extract	Not Detected

*Detection Limit: <1 ppm

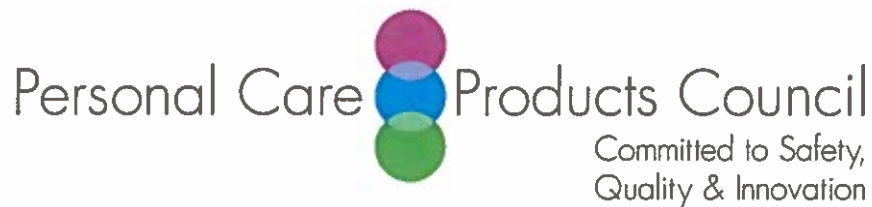
HRIPT Testing: Not available

Additional information:

A typical product with the Citrus Aurantium Dulcis (Orange) Flower Extract prepared in water has the following specifications:

Analysis:

Specification	Range	Actual
APPEARANCE	Medium to dark amber liquid	PASS
MICROBIAL PLATE COUNT	Less than 100 organisms per gram	PASS
ODOR	Characteristic	PASS
PH	4.0 - 6.5 at 25° C	4.1
REFRACTIVE INDEX	1.3250 - 1.3450 at 25° C	1.3385
SOLUBILITY	Soluble in any proportion in water	PASS
SPECIFIC GRAVITY	0.99 - 1.01 at 25° C	1.01



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 Natsudaikai Flower Water and Oil

Nerola Aroma & Cosmetics, Ltd. 2016. Manufacture flowchart of the Citrus Natsudaikai Flower Water and Oil.

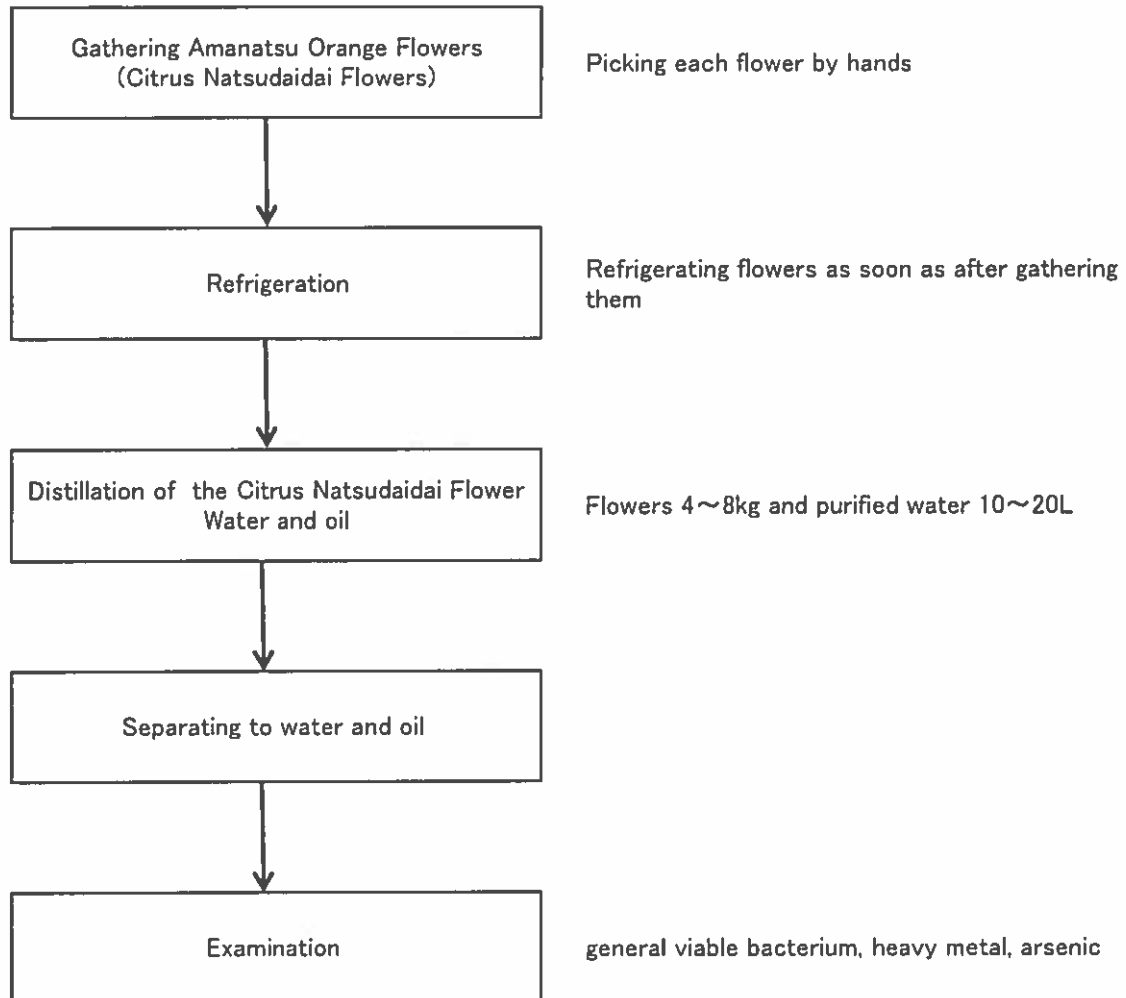
Nerola Aroma & Cosmetics, Ltd. 2016. Composition of Citrus Natsudaikai Flower Oil.

Nerola Aroma & Cosmetics, Ltd. 2011. Certificate of 24 hours human insult patch test for "Citrus Natusdaikai Flower Oil".

2016

Manufacture Flowchart of the Citrus Natsudaikai Flower Water and Oil

Nerola Aroma & Cosmetics Ltd.,



Nerola Aroma + Cosmetics, Ltd

2016

Compositio of the Ingredients

結果 I ~各サンプルの成分組成~

compounds	composition(%)		
	ネロリ (オーガニ エッセンシャルオイル)	Citrus Natsudaikai Flower Oil	甘夏ネロリ ユースドホホバオイル
Monoterpenes			
.beta.-Pinene		4.49	
sabinene		0.65	
.beta.-Myrcene		1.26	
α -terpinene		0.35	
Limonene		23.48	
Eucalyptol		0.55	
.beta.-Phellandrene or β -thujene		0.17	
.alpha.-Pinene		—	
γ -terpinene or 3-Carene		9.56	
β -cis-ocimene		4.69	
p-cimene		14.53	
Sesquiterpene			
Caryophyllene oxide		0.24	
Dihydropseudoionone		0.34	
Germacrene A		0.96	
(E)- β -Farnesene		0.06	
β -Bisabolene		0.93	
δ -Elemene		—	
Elemene	—	2.90	
α -Caryophyllene	—	0.47	
β -Selinene	—	0.24	
α -Selinene	—	0.83	—
γ -Cadinene		2.90	—
α -Farnesene		1.81	—
β -Cubebene		0.19	—
Caryophyllene		1.40	—
Alchols			
linalool		7.57	
nerolidol		13.99	
Farnesol		0.40	
(-)-4-terpineol		0.58	
Carvacrol		0.80	
Geraniol		0.26	
Geraniol or Geranyl isopentanoate		0.25	—
Phenylethyl Alcohol		—	
Aldehyde			
Nonanal		—	
Esters			
Linalyl propanoate		0.67	
Methyl anthranilate		1.41	
Others			
Eicosane	—	0.35	—
Benzeneacetonitrile	—	—	

Test No. 110124-1
January 5th, 2011

Certificate of 24 hours Human Insult Patch Test
for "Citrus Natsudaikai Flower Oil"

Consigner: Nerola Aroma & Cosmetic Ltd.

Consignee: DRC Co.,Ltd. (seal)

Concerning persons:

Dermatological Medical Doctor Hirohiko Akamatsu (seal)

Dermatological Medical Doctor Yachiyo Akitomo (seal)

Director of the DRC Keiji Takano (seal)

Director of the test Hiromi Michinuki (seal)

Test Matter

Sample No.2: Neroli Jojoba Oil

(Jojoba seed oil with extracted Citrus Natsudaikai Flower Oil)

Test periodBeginning on December 15th, 2010Ending on December 17th, 2010**Method of the test****1. Subjects**

Japanese persons, 20 or older and 60 or younger, subscribing to this test.

2. Number of the examinees

20 persons

3. Part of the patch

On their back

4. Patch test unit

Finn Chambers on Scanpor Tape with ICDRG on standard (SmartPractice Japan Co., Ltd.)

5. Method of patch

24 hours closed patch test

6. Quantity of patch

Proper quantity

7. Concentration of the matterNo concentration (Citrus Natsudaikai Flower Oil 1%) in *Jojo ba seed oil***8. Control matter**

White vaseline (Nikko Rica Corporation)

Normal Saline (Otsuka Pharmaceutical Co., Ltd.)

Distilled water to injection (Otsuka Pharmaceutical Co., Ltd.)

9. Observation

Visible observation at 24 and 48 hours later from disposal of the unit

10. Criteria and Skin Irritation

The criteria and skin irritation were approved in accordance with the following standards.

Chart 1 criteria of patch test	
national standard	
-	no reaction
+ -	small erythematous patch
+	obvious erythematous patch
+ +	erythematous patch and edema
+ + +	erythematous patch, edema and blister
+ + + +	big blister

Chart 2 ratio of skin irritation

national standard		score	ratio of skin irritation	
-	no reaction	0.0	gross score number of the examinees	× 100
+ -	small erythematous patch	0.5		
+	obvious erythematous patch	1.0		
++	erythematous patch and edema	2.0		
+++	erythematous patch, edema and blister	3.0		
++++	big blister	4.0		

Chart 3 classification of the ratio of aroma and cosmetic products in Japan

ratio of SI	classification
less than 5.0	safe
5.0 ~ 15.0	acceptable
15.0 ~ 30.0	demanding improvement
30.0 ~ 60.0	dangerous
more than 60.0	

Result of the test

Chart 4 result of the ratio SI

test matter	Neroli Jojoba Oil	
	24 hours	48 hours
criteria of hours		
-number	20/20	20/20
+ - number	0/20	0/20
+number	0/20	0/20
++ number	0/20	0/20
ratio of SI	0.0	0.0

Sample No.2

ネローラ花香房オイル(NEROLI-J EXTRA OIL) Lot.0710 の結果一覧表

被験者番号	年齢	性別	24時間後	48時間後
1	34	F	—	—
2	36	F	—	—
3	47	F	—	—
4	36	F	—	—
5	38	F	—	—
6	48	F	—	—
7	33	M	—	—
8	42	F	—	—
9	41	F	—	—
10	22	F	—	—
11	37	F	—	—
12	45	F	—	—
13	37	F	—	—
14	50	F	—	—
15	36	M	—	—
16	37	F	—	—
17	49	F	—	—
18	21	F	—	—
19	22	F	—	—
20	36	F	—	—



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 Aurantium Dulcis (Orange) Flower Oil

Product Investigations, Inc. 2007. Determination of the irritating and sensitizing propensities of a face and neck product containing 0.4% Citrus Aurantium Dulcis (Orange) Flower Oil.

Citrus Aurantium Dulcis (Orange) Flower Oil @ 0.4% in a face/neck product [MT#2250510]



PRODUCT INVESTIGATIONS, INC.

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

REPORT: PII N° 21870

**DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF
MT# 2250510 ON HUMAN SKIN**



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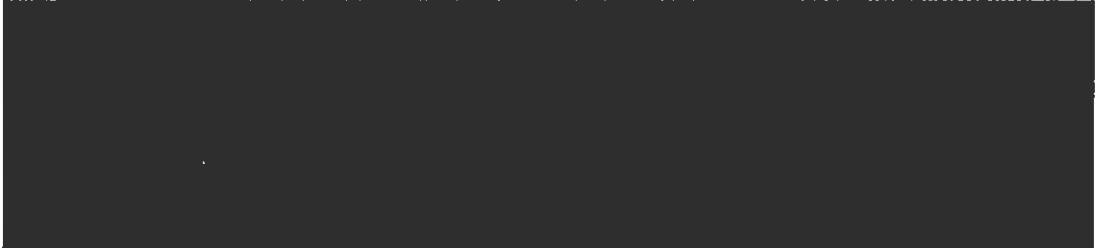
**DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES
OF MT# 2250510 ON HUMAN SKIN**

1.00 OBJECTIVES:

- .01 To identify and characterize the skin-damaging propensities that MT# 2250510 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.



4.00 STUDY PRODUCT:

Sponsor Identification: MT# 2250510
 Date received: 2/9/07
 Quantity rec'd: > 600 g. gross wt.
 Form used in study: as supplied
 PIN^e: 21870

5.00 SITE OF STUDY:

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

Study Personnel:

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

6.00 DATES OF STUDY:

Started: 12 February 2007
Completed: 14 March 2007

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 N^o: 07065

b. Demographics:

SEX	Number	Age Range
Female	80	18 - 67
Male	34	18 - 63

8.00 SITE INFORMATION:**.01 LOCATION:**

MT# 2250510 was assigned Band #2 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.

<u>Morphology</u>	<u>Visible Change</u>	<u>Grade</u>
<u>Subclinical Stage</u>	None	0
<u>Inflammation</u>		
<u>Vascular Dilatation:</u>	Faint redness with poorly defined margins	1
	<u>Redness with well-defined margins</u>	2
<u>Infiltration:</u>	Redness plus well-defined edema	3
	<u>Redness plus papules, or vesicles or ulceration</u>	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. The time at which the patch was removed on Saturday was recorded.
- iii. a) If the subject had undergone all nine induction applications, she/he was dismissed after being instructed as follows:
 - i) to report back to the clinic on the following Monday to receive the challenge applications, and
 - ii) to notify the investigator without delay should any significant changes occur in the skin of the contact site before Monday of the challenge week.
- b) If the subject had not received the required number of induction applications and was deficient without valid reason, applications were continued. As many as two missed applications could be made up during this week. When the subject had undergone the required number of make up applications, she/he was dismissed after being instructed as in section a) ii, above.

.02 HIATUS/MAKE UP PHASE-**Week # 4:**

After the examination on Monday of Week 4, no procedures were scheduled during this period.

.03 CHALLENGE PHASE-**Week #5:****Monday:**

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

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

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

Wednesday:

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

.04 FOLLOW-UP PHASE:**Week No. 6 and Week No.7:**

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

13.00 PROCEDURE DEVIATIONS:

None were necessary.

14.00 COMPLIANCE:

PHASE	No. Of AEC's Required	EXCUSED	COMPLIANT	
			YES	NO
Induction	8	0	104	10
Challenge	1/1	0	104	10

104 of the 114 Subjects were in compliance with the number of required application/examination cycles during induction.
104 of the 114 Subjects were in compliance with the number of required application/examination cycles during challenge.

15.00 INCIDENCE OF RESPONSES :

GRADE	TYPE OF RESPONSE	INDUCTION PHASE	CHALLENGE PHASE	
			Original Contact Site	Naive Contact Site
0	No visible change	110 subjects	104 subjects	104 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	4 subjects	10 subjects	10 subjects

16.00 SIGNIFICANCE OF THE RESPONSES:**.01 INITIAL/INDUCTION PHASE:**

No responses were noted on any of the 110 subjects who underwent at least one post-application examination. The absence of responses 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 104 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 104 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.

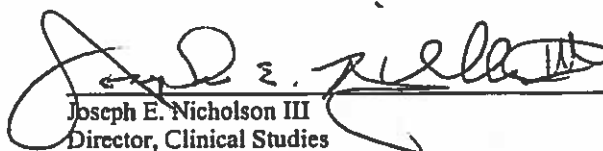
17.00 CONCLUSIONS:

.01 MT# 2250510 was found to be neither a clinically significant skin irritant nor a skin sensitizer under the conditions of this study.

.02 MT# 2250510 is not contraindicated for usages entailing repeated applications on human skin under conditions appropriate for such products.

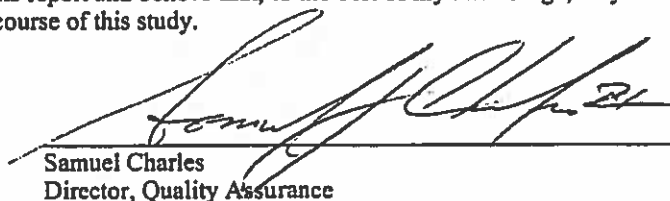
PRODUCT INVESTIGATIONS, INC.

4/27/07
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

Subj #	Sponsor Code: MT#2250510 (DA)										PI-21870					Site: L2										
	INDUCTION PHASE										HIATUS/MAKEUPS					CHALLENGE WEEK										
	WEEK 1			WEEK 2			WEEK 3			WEEK 4			WEEK 5			WEEK 5										
M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M	T	W	TH	F	M						
091	B/O				0	0	0					0			0	0	0	0			B/O	0/0	0/0			
092	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
093	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
094	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
095	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
096	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
097	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
098	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
099	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
100	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
101	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
102	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
103	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
104	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
105	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
106	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
107	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
108	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
109	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
110	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
111	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
112	B/O				0	0	0					0			0	0	0	0								
113	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0		
114	B/O				0	0	0					0			0	0	0	0				B/O	0/0	0/0	A	

LEGEND
 A = Absent
 D = Dropped
 Monday week 6: Only if any reactions on the last Friday week 5 (challenge week)



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 8, 2016

SUBJECT: Citrus Aurantium Amara (Bitter Orange) Flower Extract

Harrison Research Laboratories, Inc. 2008. Repeated insult patch test on a cream containing Citrus Aurantium Amara (Bitter Orange) Flower Extract.

Harrison Research Laboratories, Inc. 2009. Repeated insult patch test on a body cream containing Citrus Aurantium Amara (Bitter Orange) Flower Extract.



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FINAL REPORT REPEATED INSULT PATCH TEST (RIPT) Page 1 of 12

HRL Panel #08-110
Test Material #7:

*Contains 0.0225% Citrus Aurantium Amara (Bitter Orange)
Flower Extract*

PURPOSE: To evaluate the potential of the Test Material, as a result of repeated applications, to induce dermal sensitization in human subjects.

IRB APPROVAL: Both the HRL Standard Protocol #100 and the Informed Consent were approved by the New England Institutional Review Board (NEIRB) on 1/24/08.

SPONSOR:

AUTHORIZATION: Sponsor authorization dated April 3, 2008

PRINCIPAL INVESTIGATOR: Lynne B Harrison, PhD
DERMATOLOGISTS: Deborah R Spey, MD, FAAD
Kimberly K Ruhl, MD, PhD, FAAD
TEST FACILITY: Harrison Research Laboratories, Inc. (HRL)

TEST MATERIAL: Cream, , a tan creme, was received on April 4, 2008 with the following instructions: Test as received; allow volatiles to evaporate from the patch for at least 30 minutes prior to application to skin. Patch occlusively.

SUBJECTS: 115 subjects were inducted; 108 subjects completed the test. Seven subjects discontinued. No subject discontinued due to test material reaction.

METHOD: This test was conducted according to HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations). See pages 3 - 4.

-CONTINUED-



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FINAL REPORT REPEATED INSULT PATCH TEST (RIPT) Page 2 of 12

**HRL Panel #08-110
Test Material #7:**

TEST DATES: April 9, 2008 through May 16, 2008

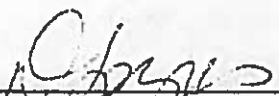
SCORING SYSTEM: See Tables I-II.

RESULTS: See Tables I-II. During the Induction Phase, five subjects, #019 (HRL #03184), #038 (HRL #23893), #052 (HRL #30113), #096 (HRL #31224) and #105 (HRL #20834) exhibited 1-level plus edema reactions; the test sites were changed. The new test sites of Subjects #038 and #105 exhibited 1-level plus edema reactions and patching of this test material, on these subjects, was discontinued for the remainder of the Induction Phase. The new test sites of Subjects #019, #052 and #096 exhibited low-level (± 1) reactions. Other subjects exhibited low-level (± 1) reactions.


At the Challenge, low-level (± 1) reactions were exhibited.

CONCLUSION: In this Repeated Insult Patch Test, test material Cream, Code 1011685-008, did not induce dermal sensitization in human subjects.

The etiology of the edematous reactions exhibited during the Induction Phase by Subjects #019, #038, #052, #096 and #105, is unknown.


Deborah R Spey, MD, FAAD
Medical (Dermatological) Investigator

5/21/08
Date


Lynne B Harrison, PhD
Principal Investigator

FINAL REPORT – REPEATED INSULT PATCH TEST (RIPT)

Page 3 of 12

HRL Panel #08-110
Test Material #7: Cream,

SUBJECTS: Each potential subject completed an HRL Subject History Form (HRL Form:SHF), including relevant medical history. (An updated Subject History Form is secured approximately every two years.) Each accepted subject was assigned a permanent HRL Identification Number. No subject was used if he or she exhibited any dermatological or other medical or physical condition that would preclude topical application of the Test Material. No known pregnant nor nursing women were used on this RIPT.

An appropriate clearance period had elapsed since a subject was patched on a Repeated Insult Patch Test (RIPT) or a Photoallergy Test (PA) before being used in this RIPT.

Legally valid written informed consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

METHOD: Induction Phase: A webril/adhesive patch (Kendall Healthcare Products Company Patch #4022) was used occlusively. Approximately 0.2 gm of Test Material was applied to each patch. The test site was wiped with a dry Kimwipe® prior to each patching. As per HRL Standard Operating Procedures (SOP) (HRL Form:SOP/RIPT), the left side of the back was usually the test area for the Induction Phase. The subject's skin was marked with gentian violet surgical marker at the left side of the test site. The test site was recorded on the anatomical diagram of each subject's individual Data Form, HRL Form: Data RIPT. In addition, at this time, the prospective placement of the Challenge test site was also recorded on the anatomical diagram.

Each subject was instructed that the patch was to remain in place and kept dry for approximately 24 hours, at which time the patch was to be removed by the subject. A 24 hour period, during which no test material was applied, followed the weekday patch removals; a 48 hour period followed the weekend patch removal.

Each subject returned to HRL on the appropriate day. The test site was observed by the HRL technician, and the reaction scored and recorded (see **SCORING SYSTEM**, below). The identical test site was then repatched until the nine Induction patchings were completed.

If a subject was unable to make up a missed patching during the same week, the subject was either patched four days the following week or was repatched at the end of the Induction Phase (tenth test day). Any absences and repatchings are noted by the dates on the individual Data Form.

A series of nine (9) Induction patchings was completed over a period of approximately three weeks.

Subject #076 (HRL #23675) received nine Induction patchings but was unable to return to HRL for the final Induction reading/scoring; she was therefore given a reading of N9R (no 9th reading). (See Table II.)

Rest Period: A Rest Period of approximately two weeks followed the last Induction patching; no test material was applied during the Rest Period.

HRL Form:FR/RIPT(3)-08/07

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FINAL REPORT – REPEATED INSULT PATCH TEST (RIPT)

Page 4 of 12

HRL Panel #08-110
Test Material #7: Cream,

METHOD: (continued)

Challenge Phase: At the Challenge Phase, the original Induction test site was observed and each subject queried as to whether any reaction was experienced during the Rest Period. A webriil/adhesive patch (Kendall Healthcare Products Company Patch #4022) was used occlusively. Approximately 0.2 gm of Test Material was applied to each patch. As per HRL RIPT SOP, the right side of the back was usually the virgin test site for the Challenge Phase.

As per HRL RIPT SOP, the Challenge patch was applied to the virgin site only. Each subject was again instructed to keep the patch on and dry.

Each subject reported to HRL approximately 24 hours later (C1 visit), at which time the patch was removed and the Challenge site scored and recorded by the HRL technician. The original test site was also observed. (See RESULTS, below.)

Subject #076 (HRL #23675) returned to HRL at the C1 visit without her patch on; she was therefore re-patched at the C2 visit.

Each subject reported to HRL at approximately 48 hours (C2 visit), 72 hours (C3 visit) and 96 hours (C4 visit) post-patching for additional observations; reactions were scored and recorded.

Subjects #076 (HRL #23675), #081 (HRL #29409) and #096 (HRL #31224) missed the C4 visit. Subjects #076 and #081 returned to HRL on May 19, 2008 and their test sites were negative. Subject #096 was unable to return to HRL. A verbal report from each of these subjects (including Subject #096) stated 'no reaction present' at what would have been his or her C4 visit.

SCORING SYSTEM: See Tables I-II, pages 5-11. The test sites were scored using the modified scoring scale of the International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 1986: p 26.

RESULTS: See Tables I-II. This test was conducted under the supervision of a Board-Certified Dermatologist, the Co-Investigator. At the C3 visit Challenge reading, the Dermatologist participated in the scoring of the subjects. A total of 108 subjects completed the test; 33 male and 75 female. The subjects range in age from 19 to 76.

RETENTION: All original Data Forms will be retained at HRL for a period of three years, or such other time as may be required by law. A laboratory retainer bottle of the Test Material shall be retained for at least two years, or as required by law. Return or disposal of unused Test Material shall be as per the Sponsor's instructions—to be communicated within 30 days of receipt of this Final Report. HRL shall appropriately dispose of any test material after six months if no Sponsor instructions have been communicated.

HRL Form:FR/RIPT(4)-08/07

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FINAL REPORT – REPEATED INSULT PATCH TEST (RIPT)

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HRL Panel #08-110
 Test Material #7: Cream,

TABLE I: SUMMARY OF REACTIONS

TOTAL NUMBER OF SUBJECTS INDUCTED: 115

Reaction	Induction Reading									Challenge Reading			
	Grade	1	2	3	4	5	6	7	8	9	C1	C2	C3
0	106	100	94	90	94	92	90	96	94	97	90	89	94
±	3	10	11	13	12	15	17	11	11	6	14	13	11
1	2	3	4	7	3	2	2	1	2	6	5	4	
1E	2		3	1	1								
2													
2E													
3													
4													
-				1	1	2	2	2	2			2	3
N9R									1				
Total	113	113	112	112	111	111	111	110	110	109	109	108	108

SCORING SYSTEM:

- 0 No visible reaction
- ± Faint, minimal erythema
- 1 Erythema
- 2 Intense erythema, induration
- 3 Intense erythema, Induration, vesicles
- 4 Severe reaction with erythema, Induration, vesicles, pustules (may be weeping)
- E Edema
- No reading
- N9R No 9th reading

HRL Panel #08-110
 Test Material #7: Cream,

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading										Challenge Reading			
					1	2	3	4	5	6	7	8	9	9	C1	C2	C3	C4
001	31309	RH	M	59	0	0	0	0	±	±	±	1	1	1DR [^]	0	0	0	0
002	24777	SJ	F	46	X	X	X	X	X	X	X	X	X	X	X	X	X	X
003	19360	JP	M	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0
004	31654	AJ	M	47	0	0	0	0	0	0	0	0	0	0	0	0	0	0
005	30270	WB	M	50	±DR	±DR	0DR	0 [^]	0 [^]	0 [^]	0 [^]	0 [^]	0 [^]	0	0	0	0	0
006	17593	VB	F	40	0	0	0	0	0	0	0	0	0	0	0	0	0	0
007	15702	CJ	F	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0
008	18132	ML	F	55	0	0	0	0	0	0	0	0	0	0	0	0	0	0
009	31443	HS	M	65	0	0	0	0	0 [^]	0 [^]	0 [^]	0 [^]	0 [^]	0 [^]	0	0	0	0
010	28794	IF	F	50	0	0	0	0	0	0	0	0	0	0 [^]	0	0	0	0
011	29367	NB	F	40	0	0	0	0	0	0	0	0	0	0 [^]	0	0	0	0
012	31183	EB	M	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0
013	24184	MB	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0	0
014	30784	NS	F	45	±	1	1	1	1	1	±	±	±	±	0	0	±	±
015	25195	MM	F	62	0	0	0	±	0	0	0	±	±	±	0	0	0	0
016	10794	BT	F	28	0	0	0	0	0	0	0	0	0	0	0	0	0	0
017	10600	JR	F	52	0	0	0	0	0	0	0	0	0	0	0	0	0	0
018	31539	LW	F	44	0	0	0	0	X	X	X	X	X	X	X	X	X	X
019	03184	LD	F	63	1	±	0	1EC	±	±	±	±	±	0	0	0	0	0
020	27966	BD	F	69	0	0	±DR	±	±	±	±	±	±	±	0	±	±	0 [^]
021	28896	NG	F	59	0	0	0	±	0	0	0	0	0	0	0	0	0	±
022	26512	NG	F	58	0	0	0	0	0	0	0	0	0	0	0	0	0	0
023	26709	SL	F	23	0	0	0	0	0	0	0	0	0	0	0	0	0	0
024	26308	SB	F	47	0	0	0	0	0	0	0	0	0	0	0	0	0	0
025	23823	LS	F	74	0	0	0	0	0	0	0	0	0	0	0	0	0	0

HRL Panel #08-110
 Test Material #: Cream,

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading										Challenge Reading					
					1	2	3	4	5	6	7	8	9	C1	C2	C3	C4			
026	21976	TB	M	37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
027	31655	KH	M	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
028	19438	CS	F	74	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
029	30899	RJ	F	41	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	X
030	27614	JF	M	50	0	0	0	1	±	0	0	0	0	0	0	0	0	0	0	0
031	31065	RH	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
032	01195	KB	F	76	0	0	0	0	0	0	0	0	0	0	0	0	0	±	0	0
033	31647	AD	M	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	±
034	13094	HD	F	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
035	31342	SR	F	48	0	0	0	0	0	0	0	0	0	0	0	X	X	X	X	X
036	29845	NC	F	39	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
037	23400	CV	F	40	0	0	±	±	0	0 ^A	0 ^A	0 ^A	0 ^A	0 ^A	0 ^A	0	0	0	0	0
038	23893	OO	M	23	1EC	0	1E	-	-	-	-	-	-	-	-	-	-	-	-	-
039	30180	JA	M	49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
040	16849	KG	F	32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
041	31618	SB	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
042	31489	DG	F	46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
043	21955	IQ	F	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
044	19005	CO	F	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
045	19296	MF	F	64	0	±	0	0	0	0	0	0	0	0	0	0	0	±	0	0
046	01388	CB	F	58	0	0	±	0	0	0	0	0	0	0	0	0	0	0	0	0
047	27534	DV	M	45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
048	31641	DM	M	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
049	31659	MM	F	58	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0DR	0
050	29197	OS	F	43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

HRL Panel #08-110
 Test Material #7: Cream,

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading										Challenge Reading									
					1	2	3	4	5	6	7	8	9	C1	C2	C3	C4							
051	24640	DM	F	39	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
052	30113	SQ	F	39	0	0	1EC	0	±DR	±DR	±	0	0	0	0	0	0	0	0	0	0	0	0	0
053	31660	GS	F	49	0	±	±	±	0	0	0	0 [^]	0	0	0	0	0	0	0	0	0	0	0	±
054	31006	CN	F	26	±	±	±	1	±DR	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0
055	31005	MC	F	38	0	0	0	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
056	30686	MS	F	47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
057	26748	LL	F	46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
058	23278	KW	F	40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
059	27042	KM	F	66	1	1	1	1	1	1	±	±	±	±	±	±	±	±	±	±	±	±	±	±
060	22216	MR	F	61	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
061	29366	AS	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
062	29363	DM	F	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
063	26198	EG	F	32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
064	26681	DG	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
065	30935	CG	M	19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
066	29116	MG	M	42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
067	26258	AM	M	26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
068	29268	MR	M	43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
069	29265	SA	F	29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
070	22288	MR	F	60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
071	28228	NO	F	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	±
072	31500	AW	M	42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
073	29429	LC	F	53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
074	31085	JM	F	43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
075	31270	CN	F	52	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	X

HRL Panel #08-110
 Test Material #7: Cream

TABLE II: INDIVIDUAL SUBJECT DATA																			
(see Scoring System, page 11)																			
Sub	HRL	Ini	Sex	Age	Induction Reading										Challenge Reading				
					1	2	3	4	5	6	7	8	9	N9R	C1	C2	C3	C4	
076	23675	LL	F	59	0	0	0	0	0	0	0	0	0	0	0	±	±	±	-
077	26108	DF	F	43	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
078	29177	JP	M	49	0	±	±	±	±DR	1	1	1	0^	±^	±	1	±	±	±^
079	31209	MM	M	41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
080	27555	SW	F	47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
081	29409	CJ	F	64	0	±	±	±	±	±	±	±	±	±	±	0	0	0	0
082	31318	EA	F	39	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
083	25606	EP	M	70	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
084	25604	VP	F	62	0	0	±	±	±	±	±	±	±	±	±	±	±	±	±
085	26901	EL	F	23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
086	31323	MF	F	35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
087	11386	JR	M	22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
088	21249	JR	F	22	0	0	0	0	0	0	0	0	0	0	0	±	±	±	±
089	31623	EE	M	26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
090	14583	SS	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
091	05049	WE	M	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
092	31219	LP	F	51	0	0	0	0	±DR	0DR	0DR	0DR	0DR	0DR	0DR	0	0	0	0
093	14898	LH	M	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
094	14127	BH	F	71	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
095	14128	PH	F	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
096	31224	KB	M	57	1EC	±	±	±	±	±	±	±	±	±	±	±	±	±	±
097	21576	SK	F	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
098	27225	JM	F	66	0	1	1	1	1DR	±	±	±	±	±	±	±	±	±	±
099	31622	VJ	F	19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
100	00035	JK	F	36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

HRL Panel #08-110
 Test Material #7: Cream,

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading										Challenge Reading				
					1	2	3	4	5	6	7	8	9	C1	C2	C3	C4		
101	29207	LP	F	34	0	±	±	±	±	0 [^]	0 [^]	0 [^]	0 [^]	0 [^]	0 [^]	0	±	±	±
102	22100	LG	M	57	0	0	0	0	0	0	0	0	0	0	0	0	0	0	±
103	24935	JR	M	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	±
104	30089	TB	F	36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
105	20834	LM	F	41	0	0	1EC	1	1E	-	-	-	-	-	-	1	±	0	0
106	31393	HP	M	64	0	0	0	0	0	0	0	0	0	0	0	±	±	±	±
107	30662	MP	F	59	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
108	01991	LH	M	73	±	±	1	1	±	±	±DR	0	0	0	±	0	0	0	0
109	28871	JW	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
110	20132	SA	F	41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
111	20133	LG	F	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
112	17406	AA	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
113	19479	PD	M	52	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
114	28515	DW	F	47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
115	28513	MS	M	50	0	0	±	0	0	±	0	0	0	0	0	0	±	0	0

FINAL REPORT -- REPEATED INSULT PATCH TEST (RIPT)

HRL Panel #08-110
Test Material #7: Cream,

SCORING SYSTEM:

- 0 No visible reaction
- + Faint, minimal erythema
- 1 Erythema
- 2 Intense erythema, induration
- 3 Intense erythema, induration, vesicles
- 4 Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
- E Edema
- DR Dryness
- ^ Hyperpigmentation
- ST Staining
- P Peeling
- C Change of test site
- No reading
- N9R No 9th reading
- X Discontinued



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FINAL REPORT – REPEATED INSULT PATCH TEST (RIPT) Page 12 of 12

HRL Panel #08-110
Test Material #7: Cream,

QUALITY ASSURANCE MEMORANDUM

This Final Report was reviewed for accuracy and conformity with both HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations).

Inspections were accomplished as determined by a random sampling approach and reported to the Project Manager and the Principal Investigator immediately following their completion.

The raw data for this study are retained at Harrison Research Laboratories, Inc.

HARRISON RESEARCH LABORATORIES, INC.

SUSAN LAUCK
Quality Assurance Manager

INTERNAL QUALITY ASSURANCE UNIT

Dated: 5/21/08

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FINAL REPORT – REPEATED INSULT PATCH TEST (RIPT)

Page 1 of 12

PURPOSE: HRL Panel #09-104
Test Material #7B: Body Cream,
Contains 0.0225% Citrus Aurantium Amara (Bitter Orange) Flower Extract
 To evaluate the potential of the Test Material, as a result of repeated applications, to induce dermal sensitization in human subjects.

IRB APPROVAL: Both the HRL Standard Protocol #100 and the Informed Consent were approved by the Clarus Institutional Review Board (CIRB) on 1/15/09. A Sponsor-signed Protocol is retained in HRL files.

SPONSOR:

AUTHORIZATION AND SAFETY ASSURANCE: Sponsor authorization dated January 27, 2009 and Safety Assurance dated February 3, 2009.

PRINCIPAL INVESTIGATOR: Lynne B Harrison, PhD
CO-INVESTIGATORS: Deborah R Spey, MD, FAAD
 Kimberly K Ruhl, MD, PhD, FAAD

TEST FACILITY: Harrison Research Laboratories, Inc. (HRL)
 2497 Vauxhall Road
 Union, New Jersey 07083

TEST MATERIAL: Body Cream, a beige creme, was received on January 28, 2009, with the following instructions: Test as received; spread Test Material evenly on the webril of the patch. Allow volatiles to evaporate from the patch prior to application to skin; patch semi-occlusively.

SUBJECTS: The even-numbered subjects of this 200-subject panel were patched with this Test Material: 116 subjects were inducted; 106 subjects completed the test. Ten subjects discontinued due to personal reasons. No subject discontinued due to Test Material reaction.

-CONTINUED-



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FINAL REPORT – REPEATED INSULT PATCH TEST (RIPT)

HRL Panel #09-104
Test Material #7B: Body Cream,

METHOD:

This test was conducted according to HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations).

TEST DATES:

February 9, 2009 through March 20, 2009.

SCORING SYSTEM:

See Tables I-II.

RESULTS:

See Tables I-II. No serious adverse events occurred during this test.

During the Induction Phase, no reactions were exhibited.

At the Challenge, one subject exhibited a low-level (±) reaction.

CONCLUSION:

In this Repeated Insult Patch Test, Test Material Body Cream, did not induce dermal sensitization in human subjects.

QUALITY ASSURANCE (QA):

The QA Unit performed an in-phase audit of this study.

		
Deborah R Spey, MD, FAAD Co-Investigator (Dermatologist)	Debra Harrison, MA Project Manager	Lynne B Harrison, PhD Principal Investigator

Date: 3/25/09

FINAL REPORT – REPEATED INSULT PATCH TEST (RIPT)

Page 3 of 12

HRL Panel #09-104

Test Material #7B: Body Cream,

SUBJECTS: Each potential subject completed an HRL Subject History Form (HRL Form:SHF), including relevant medical history. (An updated Subject History Form is secured approximately every two years.) Each accepted subject was assigned a permanent HRL Identification Number. No subject was used if he or she exhibited any dermatological or other medical or physical condition that would preclude topical application of the Test Material. No subject reported using any medication that would interfere with sensitization results. No known pregnant nor nursing women were used on this RIPT. No minor subjects were used on this RIPT.

An appropriate clearance period had elapsed since a subject was patched on a Repeated Insult Patch Test (RIPT) or a Photoallergy Test (PA) before being used in this RIPT.

Legally valid written IRB-approved Informed Consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

METHOD: Induction Phase: A webril/adhesive patch (Kendall Healthcare Products Company Patch #4022), or equivalent, was used semi-occlusively. Approximately 0.2 gm of the Test Material was applied to each patch. As per HRL Standard Operating Procedures (SOP) (HRL Form:SOP/RIPT), the left side of the back was usually the test area for the Induction Phase. The subject's skin was marked with gentian violet surgical marker at the left side of the test site. The test site was recorded on the anatomical diagram of each subject's individual Data Form. In addition, at this time, the prospective placement of the Challenge test site was also recorded on the anatomical diagram.

Each subject was instructed that the patch was to remain in place and kept dry for approximately 24 hours, at which time the patch was to be removed by the subject. A 24-hour period, during which no Test Material was applied, followed the weekday patch removals; a 48-hour period followed the weekend patch removal.

Each subject returned to HRL on the appropriate day. The test site was observed by the HRL technician, and the reaction scored and recorded (see **SCORING SYSTEM**, below). The identical test site was then repatched until the nine Induction patchings were completed.

In accordance with HRL SOP, if a subject was unable to make up a missed patching during the same week, the subject was either patched four days the following week or was patched at the end of the Induction Phase. Any absences and make-up days are noted by the dates on the individual Data Form.

A series of nine (9) Induction patchings was completed over a period of approximately three weeks.

Rest Period: A Rest Period of approximately two weeks followed the last Induction patching; no Test Material was applied during the Rest Period.

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FINAL REPORT – REPEATED INSULT PATCH TEST (RIPT)

Page 4 of 12

HRL Panel #09-104

Test Material #7B: Body Cream, :

METHOD: (continued)

Challenge Phase: At the Challenge Phase, the original Induction test site was observed and each subject queried as to whether any reaction was experienced during the Rest Period. Any reactions were recorded on the Data Form. A webril/adhesive patch (Kendall Healthcare Products Company Patch #4022), or equivalent, was used semi-occlusively. Approximately 0.2 gm of the Test Material was applied to each patch. As per HRL RIPT SOP, the right side of the back was usually the virgin test site for the Challenge Phase.

As per HRL RIPT SOP, the Challenge patch was applied to the virgin site only. Each subject was again instructed to keep the patch on and dry.

Each subject reported to HRL approximately 24 hours later (Challenge Reading 1), at which time the patch was removed and the Challenge site scored and recorded by the HRL technician. The original test site was also observed. (See RESULTS, below.)

Each subject reported to HRL at approximately 48 hours (Challenge Reading 2), approximately 72 hours (Challenge Reading 3) and approximately 96 hours (Challenge Reading 4) post-patching for additional observations; reactions were scored and recorded.

Subjects #016 (HRL #33271), #020 (HRL #27635) and #144 (HRL #33299) missed Challenge Reading 4. All of the subjects returned to HRL on March 23, 2009 and their test sites were negative. A verbal report from each of these subjects stated 'no reaction present' at what would have been his or her Challenge Reading 4.

SCORING SYSTEM: See Tables I-II. The test sites were scored using the modified scoring scale of the International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 1986: p 26.

RESULTS: See Tables I-II. No serious adverse events related to the Test Material occurred during this test. Erythema, edema, dryness, staining, peeling and hyperpigmentation are possible, expected endpoints and not considered Adverse Reactions. This test was conducted under the supervision of a Board-Certified Dermatologist, a Co-Investigator. At the C3 visit Challenge reading, the Dermatologist participated in the scoring of the subjects. A total of 106 subjects completed the test; 26 male and 80 female. The subjects range in age from 18 to 69.

RETENTION: All original Data Forms will be retained at HRL for a period of three years, or such other time as may be required by law. A laboratory retainer bottle of the Test Material shall be retained, in ambient conditions, for at least two years, or as required by law. Return or disposal of unused Test Material shall be as per the Sponsor's instructions—to be communicated within 30 days of receipt of this Final Report. HRL shall appropriately dispose of any Test Material after six months if no Sponsor instructions have been communicated.

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FINAL REPORT – REPEATED INSULT PATCH TEST (RIPT)

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HRL Panel #09-104

Test Material #7B: Body Cream,

TABLE I: SUMMARY OF REACTIONS

TOTAL NUMBER OF SUBJECTS INDUCTED: 116

TOTAL NUMBER OF SUBJECTS COMPLETED: 106

Reaction	Induction Reading									Challenge Reading			
	1	2	3	4	5	6	7	8	9	1	2	3	4
0	115	112	111	111	109	108	107	107	107	105	106	105	103
±										1			
1													
1E													
2													
2E													
3													
4													
-												1	3
N9R													
Total	115	112	111	111	109	108	107	107	107	106	106	106	106

SCORING SYSTEM:

- 0 No visible reaction
- ± Faint, minimal erythema
- 1 Erythema
- 2 Intense erythema, induration
- 3 Intense erythema, induration, vesicles
- 4 Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
- E Edema
- C Change of test site
- No reading
- N9R No 9th reading

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FINAL REPORT - REPEATED INSULT PATCH TEST (RIPT)

HRL Panel #09-104
 Test Material #7B: Body Cream,

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading										Challenge Reading						
					1	2	3	4	5	6	7	8	9	1	2	3	4				
002	32707	TK	F	41	0	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X
004	33254	LK	F	28	0	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
006	29248	RT	M	39	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
008	33256	RV	F	42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
010	25299	KC	M	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
012	32473	KS	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
014	31949	MR	F	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
016	33271	WG	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
018	32170	SJ	F	42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
020	27635	EF	F	63	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
022	20788	PR	F	52	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
024	33272	BM	F	53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
026	33267	RP	F	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
028	30311	RR	F	56	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
030	25995	AS	F	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
032	30082	AF	F	36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
034	20649	BD	F	44	0	0	0	0	0	0	0	0	0	X	X	X	X	X	X	X	X
036	11712	TH	F	41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
038	29057	MA	F	54	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
040	29261	JM	F	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
042	28840	GM	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
044	24117	VS	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
046	32537	SK	F	42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
048	24390	AL	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
050	33264	JC	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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FINAL REPORT - REPEATED INSULT PATCH TEST (RIPT)

HRL Panel #09-104
 Test Material #7B: Body Cream,

TABLE II: INDIVIDUAL SUBJECT DATA
 (see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading									Challenge Reading					
					1	2	3	4	5	6	7	8	9	1	2	3	4		
052	30662	MP	F	60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
054	21946	YD	F	41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
056	29173	WR	M	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
058	32690	MP	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
060	24163	EW	F	52	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
062	33030	SA	M	35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
064	16409	JR	M	69	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
066	11206	CL	F	32	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X
068	21133	AB	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
070	32212	JL	M	43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
072	31332	MS	F	61	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
074	21286	RD	F	56	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
076	24624	IR	F	65	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
078	32901	RV	M	68	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
080	11231	JR	F	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
082	18191	TD	M	46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
084	26308	SB	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
086	19159	LV	M	63	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
088	33282	MB	F	53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
090	13367	FS	F	56	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
092	23279	YH	F	60	0	X	X	X	X	X	X	X	X	X	X	X	X	X	X
094	32127	KH	F	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
096	32349	ZH	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
098	20464	LE	F	34	0	X	X	X	X	X	X	X	X	X	X	X	X	X	X
100	23562	MZ	F	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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FINAL REPORT - REPEATED INSULT PATCH TEST (RIPT)

HRL Panel #09-104

Test Material #7B: Body Cream,

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading										Challenge Reading					
					1	2	3	4	5	6	7	8	9	1	2	3	4			
102	21012	LP	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
104	17056	RC	M	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
106	32286	OA	F	38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
108	32478	MC	F	42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
110	33244	JW	M	18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
112	23180	CS	F	64	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
114	26227	LC	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
116	23744	AD	M	53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
118	30686	MS	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
120	22762	ML	F	36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
122	31388	AS	F	22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
124	10769	SD	M	54	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
126	16849	KG	F	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
128	27712	AK	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
130	24509	TD	F	58	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
132	26165	EA	F	59	0	0	0	0	0	0	0	X	X	X	X	X	X	X	X	X
134	23611	CC	F	47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
136	18440	SS	M	53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
138	24929	SF	F	38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
140	27866	SH	F	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
142	20073	JR	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
144	33299	AN	M	18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
146	32423	AG	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
148	32387	PC	M	43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	28228	NO	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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HRL Panel #09-104

Test Material #7B: Body Cream,

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading									Challenge Reading					
					1	2	3	4	5	6	7	8	9	1	2	3	4		
152	30724	DE	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
154	29323	SH	F	28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
156	29936	CL	M	34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
158	20518	MR	F	47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
160	21243	JP	M	41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
162	33085	MO	F	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
164	29990	TS	F	28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
166	32005	CZ	F	53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
168	30108	PM	M	43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
170	26966	MC	M	46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
172	32506	DP	F	19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
174	32482	DD	F	56	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
176	07103	CL	F	57	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
178	29650	SC	M	45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
180	29265	SA	F	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
182	23417	CS	M	44	0	0	0	0	0	0	0	0	0	0	±	0	0	0	0
184	14128	PH	F	51	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
186	29207	LP	F	35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
188	33203	JS	M	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
190	14892	VH	F	49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
192	28967	PA	F	18	0	0	0	0	0	0	0	0	0	0	0	X	X	X	X
194	22119	DA	M	26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
196	05633	MM	F	61	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
198	30325	ML	M	32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
200	19699	AE	F	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

HRL Panel #09-104
 Test Material #7B: Body Cream, :

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub	HRL	Ini	Sex	Age	Induction Reading									Challenge Reading					
					1	2	3	4	5	6	7	8	9	1	2	3	4		
202	32555	LJ	F	35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
204	29937	CA	F	58	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
206	22097	MP	F	53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
208	32649	MM	F	27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
210	21160	BF	F	60	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
212	19027	PF	F	59	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
214	32500	AM	F	54	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
216	32666	KG	F	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
218	23494	SD	F	57	0	0	0	0	0	0	0	X	X	X	X	X	X	X	X
220	33279	EG	F	54	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
222	33213	GA	F	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
224	28515	DW	F	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
226	29468	TJ	F	41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
228	30561	IE	F	45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
230	33308	JW	M	18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
232	31891	CG	F	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

FINAL REPORT -- REPEATED INSULT PATCH TEST (RIPT)

HRL Panel #09-104

Test Material #7B: Body Cream,

SCORING SYSTEM:*

- 0 No visible reaction
- + 1 Faint, minimal erythema
- 2 Intense erythema, induration
- 3 Intense erythema, induration, vesicles
- 4 Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
- E. Edema
- DR Dryness
- ^ Hyperpigmentation
- S Staining
- P Peeling
- C Change of test site
- No reading
- N9R No 9th reading
- X Discontinued

*International Contact Dermatitis Research Group System: Fisher, Alexander A., Contact Dermatitis, Lea & Febiger, Philadelphia, 1986: p 26

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FINAL REPORT – REPEATED INSULT PATCH TEST (RIPT)

Page 12 of 12

HRL Panel #09-104
Test Material #7B: Body Cream,

QUALITY ASSURANCE MEMORANDUM

This Final Report was reviewed for accuracy and conformity with both HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations) and any written communication from the Sponsor.

Inspections were accomplished by a random sampling approach and reported to the Project Manager and the Principal Investigator immediately following their completion.

The raw data for this study are retained at Harrison Research Laboratories, Inc.

HARRISON RESEARCH LABORATORIES, INC.

SUSAN LAUCK
Quality Assurance Manager

QUALITY ASSURANCE UNIT


Dated: 3/25/09

This report is only submitted for the use of the party to whom it is addressed, and neither it nor the name of our company or any member of our staff may be used in connection with any advertising, promotional material, or sale without our written authorization



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* Flower-and Leaf-Derived Ingredients as Used in Cosmetics (draft prepared for the December 2015 CIR Expert Panel meeting)

Key Issues

This report gives the impression that there is little known about the composition of citrus flowers and leaves, when there are numerous published studies about composition. Below is list of example references (arranged alphabetically by author) that may be helpful. A few of these references are open access and available on the internet. With the exception of the book, the references were found by searching PubMed for "citrus flowers" and "citrus leaves composition". The references suggest that ingredients made from citrus flowers and leaves (especially the essential oils) are primarily limonene or citral based. These references do not suggest the presence of furocoumarins in the flowers or leaves so that the relevance of the information on furocoumarins in this report is not clear.

Ammar AH, Bouajila J, Lebrihi A, et al. 2012. Chemical composition and in vitro antimicrobial and antioxidant activities of *Citrus aurantium* L. flowers essential oil (Neroli oil). *Pak J Biol Sci* 15(21) 1034-1040.

Azam M, Song M, Fan F, et al. 2013. Comparative analysis of flower volatiles from nine citrus at three blooming stages. *Int J Mol Sci* 14: 22346-22367.

Duan L, Guo L, Dou LL, et al. 2014. Comparison of chemical profiling and antioxidant activities of fruits, leaves, branches, and flowers of *Citrus grandis* 'Tomentosa'. *J Agric Food Chem* 62(46): 11122-11129.

- Dugo G, DiGiacomo A (eds.). 2004. *Citrus: The Genus Citrus*. Taylor & Francis, Inc, New York, NY.
- Ellouze I, Abderrabba M, Sabaou N, et al. 2012. Season's variation impact on *Citrus aurantium* leaves essential oil: chemical composition and biological activities. *J Food Sci* 77(9): T173-180.
- Gancel AL, Ollitrault P, Froelicher Y, et al. 2003. Leaf volatile compounds of seven citrus somatic tetraploid hybrids sharing willow leaf mandarin (*Citrus deliciosa* Ten.) as their common parent. *J Agric Food Chem* 51(20): 6006-6013.
- Gholivand MB, Piryaei M. 2013. A method for fast analysis of components of *Citrus aurantium* L. leaves. *Nat Prod Res* 27(14): 1315-1318.
- Gholivand MB, Piryaei M, Abolghasemi MM. 2013. Analysis of volatile oil composition of *Citrus aurantium* L. by microwave-assisted extraction coupled to headspace solid-phase microextracton with nanoporous based fibers. *J Sep Sci* 36(5): 872-877.
- Hsouna AB, Hamadi N, Halima NB, et al. 2013. Characterization of essential oil from *Citrus aurantium* L. flowers: Antimicrobial and antioxidant activities. *J Oleo Sci* 62(10): 763-772.
- Kim MJ, Yang KW, Kim SS, et al. 2014. Chemical composition and anti-inflammation activity of essential oils from *Citrus unshiu* flower. *Nat Prod Commun* 9(5): 727-730.
- Lin SY, Roan SF, Lee CL, et al. 2010. Volatile organic components of fresh leaves as indicators of indigenous and cultivated citrus species in Taiwan. *Biosci Biotechnol Biochem* 74(4): 806-811.
- Lota ML, de Rocca Serra D, Tomi F, et al. 2002. Volatile components of peel and leaf oils of lemon and lime species. *J Agric Food Chem* 50(4): 796-805.
- Luro F, Venturini N, Costantino G, et al. 2012. Genetic and chemical diversity of citron (*Citrus medica* L.) Based on nuclear and cytoplasmic markers and leaf essential oil composition. *Phytochemistry* 77: 186-196.
- Menichini F, Loizzo MR, Bonesi M, et al. 2011. Phytochemical profile, antioxidant, anti-inflammatory and hypoglycemic potential of hydroalcoholic extracts from *Citrus medica* L. cv Diamante flowers, leaves and fruits at two maturity stages. *Food Chem Toxicol* 49(7): 1549-1555.

Sarrou E, Chatzopoulou P, Dimassi-Theriou K, et al. 2013. Volatile constituents and antioxidant activity of peel, flowers and leaf oils of *Citrus aurantium* L. growing in Greece. *Molecules* 18: 10639-10647.

Vekiari SA, Protopapadakis EE, Papadopoulou P, et al. 2002. Composition and seasonal variation of the essential oil from leaves and peel of a Cretan lemon variety. *J Agric Food Chem* 50(1): 147-153.

Waikedre J, Dugay A, Barrachina I, et al. 2010. Chemical composition and antimicrobial activity of the essential oils from New Caledonian *Citrus macroptera* and *Citrus hystrix*. *Chem Biodivers* 7(4): 871-877.

Zhao HY, Yang L, Wei J, et al. 2012. Bioactivity evaluations of ingredients extracted from the flowers of *Citrus aurantium* L. var. *amara* Engl. *Food Chem* 135(4): 2175-2181.

Unless evidence is found that furocoumarins are contained in citrus flowers and leaves, the information about furocoumarins, e.g., bergapten (or 5-MOP) in the Use section and Summary should be deleted. If it is left in the report, the presentation of the European limit for furocoumarins needs to be corrected and cited to Annex II of the cosmetic regulations not to the 2005 SCCP opinion (reference 11). 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.”

Where is the information that citrus flowers and leaves contain 7-methoxycoumarin? If the CIR report does not present information on the presence of 7-methoxycoumarin in citrus flowers and leaves, the IFRA standard for 7-methoxycoumarin does not need to be presented in the CIR report.

Additional Considerations

Definition and General Considerations - The Dictionary description of how waters are prepared should also be added to this section.

Table 1 - The 2014 edition of the Dictionary (reference 1) should be cited for the definitions rather than the 2012 edition (reference 24).

Table 3 - As presented in Table 1, accepted genus species names are now part of the Dictionary definitions and should be cited to the Dictionary rather than reference 3. Is it necessary to present the accepted names in both Table 1 and Table 3? They are easier to review in Table 3.