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

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

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

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina Burnett, Senior Scientific Writer/Analyst
Date: September 2, 2016
Subject: Draft Final Report of the Safety Assessment of *Citrus* Flower- and Leaf-Derived Ingredients

Enclosed is the draft final report of the Safety Assessment of *Citrus* Flower- and Leaf-Derived Ingredients as Used in Cosmetics. (It is identified as *cleaf092016rep* in the pdf document.)

At the June meeting, the Panel issued a tentative report with the conclusion that the available data are insufficient to make a determination that the 33 *Citrus* flower- and leaf-derived ingredients included in this safety assessment are safe under the intended conditions of use in cosmetic formulations. The data requested by the Panel included:

- Clarification of the generally recognized as safe (GRAS) food status of these ingredients and/or verification of accepted food use
- Genotoxicity data if these ingredients are not GRAS foods or recognized as being an accepted food
- Concentration of use data for Citrus Aurantium Amara (Bitter Orange) Flower Wax and Citrus Hystrix Leaf Oil
- Composition and impurities data for Citrus Aurantium Dulcis (Orange) Flower Extract.

Since the June meeting, unpublished data on Citrus Aurantium Dulcis (Orange) Flower Wax (chemical properties and composition), Citrus Aurantium Amara (Bitter Orange) Flower Water (composition, manufacturing process, and dermal and ocular irritation studies), and Citrus Aurantium Amara (Bitter Orange) Flower Extract (chemical properties, composition, manufacturing process, and safety toxicity data) have been received. While no further authoritative information clarifying GRAS status was received or discovered by staff, information stating that *Citrus hystrix* leaves are a recognized seasoning in food was discovered. These data have been incorporated into the report and highlighted with |brackets| in text or shaded in tables. Safety reports on Citrus Aurantium Amara (Bitter Orange) Flower Water and a raw material containing Citrus Aurantium (Bitter Orange) Flower Extract were received in the unpublished data submissions. The information in the former submission was determined to be redundant to other data in the same submission and thus was not included in this report. Not much of information in the latter submission was specific to the ingredient, so only some manufacturing and composition data were included in this report. No other requested data have been received or identified by CIR staff. Comments provided by Council on the draft tentative and tentative reports have been considered. The comments and the unpublished data can be found in this report's package (*cleaf092016pcpc1-2 and cleaf092016data1-8,* respectively*)*.

The concentration of use data have been updated for these ingredients. The results of the most recent survey conducted by the Council indicate Citrus Aurantium Dulcis (Orange) Flower Oil has the highest reported maximum concentration of use; it is used at up to 0.66% in a depilatory. Citrus Aurantium Dulcis (Orange) Flower Wax had the second highest reported maximum concentration of use; it is used at up to 0.12% in a lipstick. At the June meeting, Citrus Aurantium Dulcis (Orange) Flower Extract had the highest reported maximum concentration of use; it was used at up to 6% in eye shadow: this use is no longer being reported. At the June meeting, the Panel had expressed concern regarding the use of this ingredient at 6% as it was an order of magnitude greater than the next highest maximum concentration. The Council has previously surveyed Citrus Aurantium Amara (Bitter Orange) Flower Wax in 2013 and 2016: no concentrations of use were reported. A use survey for Citrus Hystrix Leaf Oil (a non-INCI ingredient) is still under way.

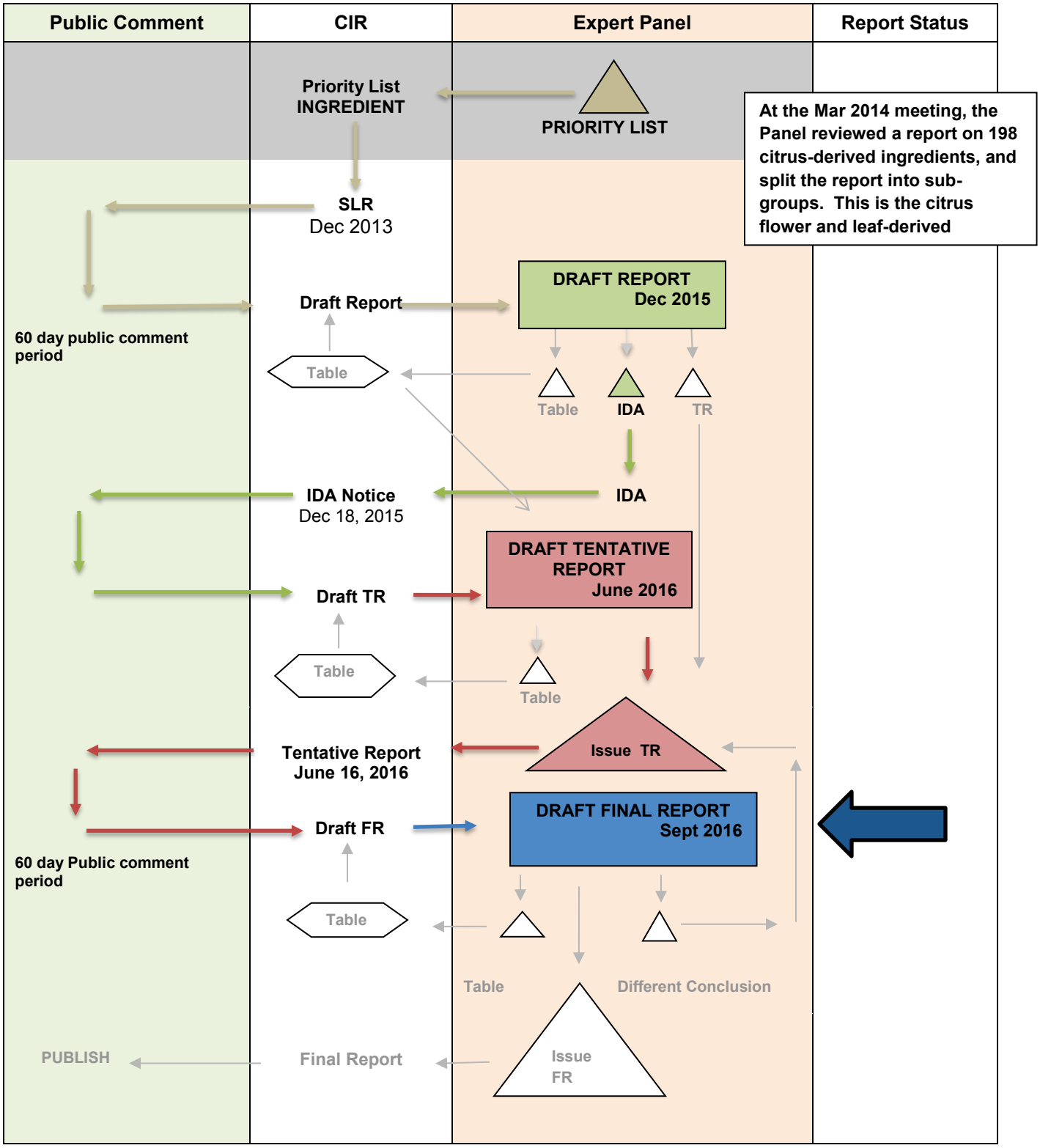
The Panel should carefully review all new information, the abstract, discussion, and conclusion of this report. If the data are now sufficient, the Panel should issue a revised Tentative Safety Assessment with an appropriate discussion and new

conclusion. If the data are still insufficient, the Panel should issue a Final Safety Assessment with the current conclusion of insufficient.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Citrus Flower and Leaf-Derived Ingredients

MEETING Sept 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

June 2016 - The Panel issued a tentative report with the conclusion that the available data are insufficient to make a determination that the *Citrus* flower- and leaf-derived ingredients included in this safety assessment are safe under the intended conditions of use in cosmetic formulations. The data requested by the Panel included:

- Clarification of the generally recognized as safe (GRAS) food status of these ingredients and/or verification of accepted food use
- Genotoxicity data if these ingredients are not GRAS foods or recognized as being an accepted food
- Concentration of use data for Citrus Aurantium Amara (Bitter Orange) Flower Wax and Citrus Hystrix Leaf Oil
- Composition and impurities data for Citrus Aurantium Dulcis (Orange) Flower Extract.

Citrus Flower- and Leaf-Derived Ingredients Data Profile –September 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	X	X					X			
Citrus Aurantium Amara (Bitter Orange) Flower Oil	X								X		X	
Citrus Aurantium Amara (Bitter Orange) Flower Water	X		X	X				X		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	X		X								
Citrus Aurantium Dulcis (Orange) Leaf Extract	X											
Citrus Hystrix Leaf Extract			X	X				X				
Citrus Natsudaidai Flower Oil			X	X					X			
Citrus Natsudaidai Flower Water			X									
Citrus Reticulata (Tangerine) Leaf Oil	X											
Citrus unshiu flowers (generic, not INCI)				X								
Citrus depressa 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.
Updated searches August 1, 2016

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.

- General Google Search on food use/GRAS status (**updated JULY/AUGUST 2016**)

Citrus Flower- and Leaf-Derived Ingredients
June 6-7, 2016

Dr. Marks' Team

DR. MARKS: We have a series of citrus ingredients. The first one is citrus flower and leaf. Then we will be moving on to the citrus peels and then the citrus plant and seed. Christina, you will probably be glad to never see citrus again. (Laughter) Last time I said, well, let's just recombine them altogether again.

We have before us the draft tentative report of the safety assessment of citrus flower and leaf. At the December 2015 meeting, the Panel issued an insufficient data announcement for the 32 citrus flower and leaf derived ingredients. From that May 13 memo, manufacture, chemical composition and impurities, and HRIPT on several of the ingredients, which are listed there, bitter orange.

We received some data. We were told these ingredients do not contain pure coumarins, in the memo. That's important from a phototox point of view. There has been an updated VCRP.

MS. BURNETT: Right. The important thing there is between the VCRP and the update to the concentration use, what you requested data on, based on concentration, might have changed the concentrations up and down.

DR. HILL: Thank you for pointing that out to us.

DR. MARKS: Ron, Ron and Tom, are the needs now met?

DR. SLAGA: I have data needs have been met, method of manufacturing, impurities, and we have information on the ingredients, non-irritating and non-sensitizing.

DR. MARKS: It's kind of interesting because that's the conclusion we used in the previous citrus ingredients, formulated to be non-irritating and non-sensitizing. I guess I still had one sensitization need for citrus aurantium dulcis, which is orange flower extract that is being used up to 6 percent in an eye shadow, and everything else where we had sensitization data, it is significantly less concentrations.

I thought we could have 31 safe when formulated to be non-irritating and non-sensitizing, and an insufficient for the orange flower extract. I'd like to see an HRIPT at 6 percent just to confirm it, but then if you have a conclusion, formulated to be non-irritating and non-sensitizing, it's almost contradictory.

DR. SHANK: How about more composition data? I thought that was still insufficient.

DR. MARKS: Yes, chemical composition, insufficient?

DR. SHANK: Need for sensitization on the 6 percent?

DR. MARKS: Yes, that was the flower extract; yes.

DR. SHANK: I'd also like to ask FDA to clarify the GRAS status for these, are these recognized as GRAS, in food?

MS. BURNETT: Some of them are.

DR. SHANK: Some are.

MS. BURNETT: Like orange flower is.

DR. HILL: Because we are making use of GRAS on some of these ingredient groups, and even though we keep seeing literature banter, public banter about the limitations of that, it is still really useful information.

In the read across table, would it be possible in the future -- since Bart is sitting here -- to think about adding a column that indicates that?

In one of them, we had a CFR column. I didn't cross check that 100 percent.

MS. BURNETT: I'm sorry?

DR. HILL: I'm looking for a column in the read across table indicating GRAS, with an X in a box, something like that, that would be helpful. Otherwise, I have to make that myself which I did in several instances, but I didn't in this one because I wasn't sure about the limitations of the meaning in some cases.

DR. ANSELL: Can you be a little more precise? You're not asking about GRAS, you're asking about whether it's a food --

DR. HILL: A direct food additive, yes, I'm sorry, you're right, more precise. A direct food additive where presumably there is a range of oral toxicity data that has been captured and systemic or at least a confidence oral was okay. Maybe I shouldn't even bring that in.

It's already in the document, in the leaf cross table, and I'm looking to try --

MS. BURNETT: For future botanicals.

DR. HILL: For future botanicals and then GRAS is a big issue.

MS. BURNETT: You're talking about the data profiles?

DR. HILL: I'm talking about the data profiles.

MS. BURNETT: Which is a PDF file.

DR. HILL: PDF file, not in the final report.

DR. ANSELL: We think if it is used as a food or traditionally used as a food is an important question to ask as well. GRAS is an unique status within the U.S. You can end up with it being a common food additive in China and India, and answer not to is it GRAS.

DR. HILL: Well, then maybe a way of capturing both pieces of information, we don't always have the global picture, but often we do, right?

DR. HELDRETH: Saying whether it is GRAS or not, the CFR is not necessarily going to say citrus aurantium is GRAS. Basically, it will give you a saying that if people were eating this before 1950, it's GRAS. I think that specificity and including it in a table will be really challenging unless someone from FDA would go through and do the evaluation for us, which I don't think is going to be likely.

MS. BURNETT: That's what we found once it was -- they won't.

DR. HILL: I know uses included sometimes capture but it hasn't been consistently always captured, so I think I made the comment last time we looked at this ingredient, I don't remember exactly what I said without going back to the transcript, and then somebody said yes, and then the question is is it always in baking, we have cooked it, it's raw. That could have a difference in terms of any kind of read across.

That is what I was looking for here because let's look at the table and see how many of these we actually have data on that are like versus what we have zero data on and are unlike.

For example, in the flower oil, I was reading across only from that generic and saying tends to be very similar in composition, and on that basis, I don't have any concern. I'm counting seven ingredients where I

think they are insufficient and still insufficient. If I had a little more information about the limitations of what we know from food uses in some of these, I might feel a little better.

The other part, of course, that is important is the very low concentrations of use, and that goes to our boilerplate and our conclusions where we say if in the future ingredients of a similar nature are used, then does that person look and see the.005 percent use or do they say well, there are ingredients in this class up to 6 percent, I can put this use substance in there at 6 percent and I will be fine. I'm trusting industry would not be so foolish as to do that, but you never know.

MS. DEWAN: (off mic)

DR. HILL: No, ma'am.

DR. MARKS: My understanding, Ron Shank, correct me if it's GRAS, perhaps the oral toxicity we like to see in ingredients, you can say it's safe because it's being ingested commonly, and there is no systemic toxicity. Obviously, that doesn't apply to topical applications for irritation or sensitization. Perhaps, I don't know, Tom, you can comment, whether GRAS would be also a carry over for carcinogenicity.

DR. SLAGA: Only for internal.

DR. MARKS: Right.

DR. SLAGA: You have no idea --

DR. MARKS: Exactly.

DR. SLAGA: If it's non-irritating, then I would say GRAS would be --

DR. HILL: Again, skin is not as good a metabolic barrier as gut for certain substances that cannot be absorbed dermally because the characteristics match, which is a lot of natural products. If you have something and you are creating or 15 percent and smear it over large portions of the body, then we might again have to worry about systemic, but I think we all know that.

DR. ANSELL: Our position is it's an important data point, it's not the only data point.

DR. HILL: Agreed.

DR. MARKS: Let's go back. Ron Shank, you first mentioned we need composition, is there anything more specific or just any of these?

DR. SHANK: We have a lot.

DR. SLAGA: We have a good bit.

MS. BURNETT: I do have a few more outstanding sources that I've located, it's just a matter of organizing it, the references. I got a little bit more comp data, possibly on orange. I can't remember. I wrote it all down.

DR. ANSELL: Citrus oils.

DR. HILL: I gave you my list of ones I questioned whether we had enough data, maybe you could shoot me down one by one, and that would be fine with me.

MS. BURNETT: If you want comp data, I have lemon leaf oil, amara, which is bitter orange, bitter orange flower, bitter orange flower water, orange leaf, bitter orange leaf. Mandarin leaves, Kaffir lime leaf, and that's it.

DR. HILL: Could you read that list one more time?

MS. BURNETT: Essentially, I have lemon leaf oil, orange blossom, I'm not sure if that is bitter or sweet orange.

DR. HILL: Straight blossom?

MS. BURNETT: Yes. Orange flower, again, I don't know which one, orange flower water, orange leaf, bitter orange leaf, Mandarin leaf, and Kaffir lime leaf.

DR. HELDRETH: Since this is tentative --

MS. BURNETT: Yes, I can still add data.

DR. MARKS: I'm going to be seconding a motion, presumably it is going to be a tentative report with an insufficient conclusion, so the question is in the chemical composition.

The other thing, Christina, when you looked at it, was there significant differences in chemical composition? This gets back to the database, highlight certain chemicals that are in the composition that may be ones we are concerned about.

Are there significant differences between the ingredient composition in this report compared to what we have approved before, with the peel and fruit derived ingredients?

MS. BURNETT: I can honestly say I've not done a comparative analysis of them.

In terms of the ones I have data for, they all have very similar qualities, they might have a few constituents that probably make them their own unique fragrance or whatever. They might all have linalyl acetate --

DR. MARKS: What I found interesting is you state there are no pure coumarins in these ingredients.

MS. BURNETT: I did not see any --

DR. HELDRETH: Seems to be limited.

DR. MARKS: In fact, tested at a neat concentration and had no further toxicity. There is a significant difference. Okay, a tentative report with an insufficient conclusion at this point. Shall we just put "generally" in there, Ron Shank, chemical composition?

DR. SLAGA: More detailed maybe.

DR. HILL: The key point is if you have made extracts of anything, having the composition in the bulk leaf, for example, tells you everything that is in there, but until you know what they are using to extract, in other words, what temperature and for how long, and how much of the thing is concentrated at the end to get down to something that fits that definition, which may or may not be the same for different suppliers.

You don't know how much of those substances are in the final product, and you don't know how much gets formulated, the main margin of safety here for me is that the vast majority of these are used at very low concentrations, dermally, so we have to keep that in mind, and even assuming we have 6, 8, or 10 of these botanicals, we are still probably never getting the high enough concentrations to worry about, and then we have a loophole for sensitization, formulated to be non-sensitizing because it is a botanical.

I still have seven of these ingredients that for me I feel like we don't have sufficient data, and again, I'd like to tell you what they are and you can shoot me down.

DR. MARKS: Why don't you do that? Chemical composition, we want more data on that. Go ahead.

DR. ANSELL: We have additional chemicals in the data that we provided, so I don't know that is going to be very helpful to say you need more data. Can we at least cite one that we think we have sufficient data, and say the others should be -- otherwise, we won't know for the ones we think are sufficient why you consider that to be insufficient.

MS. BURNETT: On that point, for a specific ingredient, the ones I have are in the published literature, they are not specifically -- these are extracts that some college grad students extracted in a lab, this is what they pulled off the orchard.

DR. HILL: We have four ingredients that are here.

MS. BURNETT: There's more.

DR. HILL: Figure out what we have and complete the array of data. I am looking at the read across table way back at the beginning of the document where you have a little "x" in the box where we have the ingredient itself and method of manufacture and composition. We know how they got to whatever extract.

MS. BURNETT: Right, and I divided that table. The top part is INCI ingredient names, the lower part are the general names. I do have a bunch ticked off. They might not actually have an INCI name, because I don't necessarily know where to go.

DR. HILL: I was looking down there as well. Again, when we just say flowers, but then the ingredient is extract, missing some key piece of information. Actually, with the method of manufacture, in conjunction with that information, now you have something that you can begin to make decisions, including read across.

Again, we only have data on like five of these in the table, so flower wax, flower extract, for the dulcis, Hystrix leaf extract, Natsudaidai flower oil and Natsudaidai flower water, which we don't even have indication is in use, but we suspect they are.

DR. MARKS: Chemical composition, Tom, Ron, at this point after discussion, do you think we have enough there, that that shouldn't be a hurdle?

DR. SHANK: Probably not. I'm not sure all of them were a GRAS, if they are, then the composition data is not so important, if you say formulated to be non-irritating or sensitizing.

DR. MARKS: Okay. The second point, Ron Shank, a while ago, and we got a long discussion, you want clarification of which are GRAS?

DR. SHANK: Yes.

DR. MARKS: And food additive?

DR. SHANK: Yes.

DR. HILL: I would still like to read my list of six or so. It is the lime flower extract --

MS. BURNETT: These are the ones you consider to be safe?

DR. HILL: These are the ones I think are sketchy.

DR. MARKS: As far as?

DR. HILL: As far as assessing safety by read across in absence of any data, which we are absent any data. Lime flower extract, bitter orange flower water, Bergamot leaf extract, Bergamot leaf oil. Do I need to slow down?

MS. BURNETT: Yes, please.

DR. HILL: I'm almost done.

MS. BURNETT: Lime flower extract, bitter orange flower water?

DR. HILL: Lime flower extract, Bergamot leaf extract, Bergamot leaf oil, Dulcis orange flower, Dulcis flower wax, Dulcis leaf extract.

DR. ANSELL: That's seven.

DR. HILL: Seven, yes.

DR. MARKS: What did you want defined?

DR. HILL: Data, no safety data, no composition data, no method of manufacture data. No data at all. I can drop down to the bottom and see with our generic INCI which ones of those are being informed, and the answer is not many.

DR. MARKS: When you say you need more data, is chemical composition a part?

DR. HILL: Yes, chemical composition as well as method of manufacture that gives some indication the extract somehow reflects that composition, especially when our composition is coming from generic literature data that is not necessarily ingredient.

DR. SLAGA: So, what endpoint are you worried about, is it irritation, sensitization, toxicity? If we go with formulating to be non-irritating, we eliminate that.

DR. HILL: If you formulate it to be non-sensitizing and we trust sensitization is a sentinel for any activity like carcinogenesis of some sort --

DR. MARKS: Or irritation.

DR. HILL: Or irritation is a sentinel. I'm still working on cancer biology at the level where I think I need it, and I'm learning a lot these days.

DR. SLAGA: We could ask for genotoxicity because there is no data.

DR. HILL: Run an Ames test or something else.

DR. SLAGA: The fact that there was no furocoumarins --

DR. HILL: Not those endpoints.

DR. MARKS: You would like to see genotoxic --

DR. SLAGA: We forgot that last time.

DR. HILL: I went down through each one of these and I wrote down the concentrations in tabular form, I just had maximum concentrations, and they are all small with a couple of exceptions. That is the margin of safety. In fact, a significant margin of safety.

I really was paying attention to and taking it into account. I just wanted to let people know that, so in that regard, perhaps sensitization is a sufficient sentinel in combination with irritation.

Having a little more to go on when I'm being asked to read across and say sure, fine, no problem.

DR. MARKS: It sounds like the seven ingredients Ron Hill is talking about, should we ask for those or see what comes out? I agree, if you're not concerned about an endpoint, then do we really need it.

DR. SLAGA: There has to be a reason you want it for composition. The composition among all these is not that far apart.

DR. MARKS: That's why I asked that question with Christina, how much is there a similarity.

DR. SLAGA: Based on a long time ago, we never got this level of composition before. It's kind of nice to see going through there. I didn't come up with any chemicals that I felt were --

DR. HILL: It's beautiful to have that composition and really highly valuable and important. I would not want somebody to think why bother. Again, there are at low concentrations. Cancers do start and cancers are promoters in skin, promotion is a sketchy thing, and the reality is most of the ingredients that we see in these plant substances are actually cancer suppressing.

DR. SLAGA: Anti-genotoxic.

DR. HILL: Anti-genotoxic, perhaps curative in some cases.

DR. MARKS: The list I have now is Ron Hill's seven ingredients, more data on method of manufacture, chemical composition. Do you want me to present that tomorrow and you can clarify, or at this point, no, after our discussion, we really need --

DR. HILL: If this is not the last time we are seeing this report, unless --

DR. MARKS: It is not the last time.

DR. HILL: Unless somebody asks me from across this table, I see --

DR. MARKS: Do you want me to include that tomorrow or should we see what falls out in the next one, Ron Hill?

DR. HILL: I don't care if you don't include it. If we are asked from across the table, probably better to list.

MS. BURNETT: The list that you are looking at is from the profile, so you are marking the ones that are in current use? That profile table, that is not all the ingredients, it says at the bottom --

DR. HILL: I'm looking at the bottom, and saying how many of those would actually inform the ones at the top.

MS. BURNETT: No, no. At the very bottom, not all ingredients are listed in that profile table. You are concerned about the ones that are in current use.

DR. HILL: You're talking about the ingredients that don't show up in that profile table?

MS. BURNETT: Right.

DR. ANSELL: That's what I heard.

DR. HILL: I thought in your profile tables like this, you had every ingredient, I don't think I noticed we were missing any.

MS. BURNETT: When there is a lot of ingredients, like over 10, I do not include -- if there is no data, I put that disclaimer at the bottom.

DR. HILL: Okay. I didn't see that disclaimer. I assumed these tables were always 100 percent complete and every ingredient in the report was showing up in the read across. It needs to all the time, period. If it's 400 ingredients, that needs to show up in that table, data or not.

We are going to have a list at the bottom of the ones that have no data at all, no uses and no data, put them at the bottom. Why would you not? You can capture them straight out of the conclusion or the introduction, and then put the whole list there, and erase the ones that are already in the table.

DR. MARKS: I'd go to the introduction and look at the list of ingredients.

DR. HILL: But then you don't see the read across, so you don't see the concentrations, now in my head I have to put together the table that has the use concentrations, the table where I have safety data profile for read across with that listing in the introduction and eventually in the conclusion.

I can do that work, but we're talking hours and hours, and you have given me three weeks to prepare. Pretty much weekends because I work. (Laughter)

DR. HELDRETH: Table 10 that lists those ingredients not recorded to be in use, beginning on page 33.

DR. HILL: See, that comes to that statement which again, the statement where we say in our conclusion after it, for ingredients that are not in current use to be used, it would be consistent with the table, is that consistent with the six percent or is that consistent with.00005 percent, in some of the ingredients.

So, I'm assuming somebody would look at all the in's and out's of different ingredients that we did assess the safety and come to a conclusion about what they really need to do and what those limits really are based on similarity to the other ingredients that they reviewed.

If that happens a lot, I don't want to name a specific company, I would have very great confidence they did it right. If it happens with mom and pop somewhere, they might have also done it right because maybe they are consulting with high power people who are consultants in this industry, so we had an assessment, we say all is well, wherein ingredients that are not being used or used in a similar fashion and then what do I mean by similar fashion. It's a very vague statement at that point. That is my concern.

On Table 10, you say, not being used?

DR. MARKS: Let's get back to -- you can look at those in more detail, Ron Hill, a bit later.

DR. HILL: For some of those, those are the ones where we have generic data -- sorry to interrupt -- we have generic data which actually informs some of these, even though they are not in current use per our VCRP and survey data. They are not used in the United States but they are in Japan or in India, wherever it happens to be.

DR. MARKS: So, we want clarification, is it just GRAS on these ingredients?

DR. ANSELL: Food use.

DR. MARKS: And food additive use? Just say food use or both? I hear GRAS in one instance and food additive in another.

DR. ANSELL: Right, different --

DR. MARKS: I can say clarification of GRAS and food additive status or use.

DR. LORETZ: If we said food use, that would get even outside the U.S., too. That would be relevant. If we just said "food," that would also get outside the U.S.

DR. ANSELL: That list wouldn't pull up --

DR. HELDRETH: To help Christina out here, where is that information coming from? It's not like there is a clear cut database that tells you one of these specific genus and species is used as a food in Japan for the past 50 years or used in Sri Lanka for the last few years as a food.

MS. BURNETT: I get recipes from Food Network. I know one of them is used. It is not specifically listed anywhere. They use that in cooking all the time now, but --

DR. ANSELL: Kale is losing its popularity.

DR. HILL: Sometimes the Code of Federal Regulations does have genus species listed in there and it says for direct food addictive use. In one of the other reports today, where it has a specific listing, and it has direct and indirect.

DR. MARKS: Ron Shank, are you happy that Christina can find out what she can find out in terms of this, and let's just see what we get back with that?

DR. ANSELL: The CIR Science and Support Committee would promise to help with perhaps some searchable databases, the Expert Committee on Food Additives run by the World Health Organization, as an example.

MS. BURNETT: That would be wonderful.

DR. HILL: It would be informative, in some of these cases like this because I don't like to be making something out of nothing. I'd rather make nothing out of nothing.

DR. MARKS: After all this discussion, I'm trying to solidify what our team really would like to see, second was just genotoxicity, any genotoxicity at this point, we have none, right?

MS. BURNETT: Correct.

DR. MARKS: Third --

DR. SLAGA: I don't have a concern but it would be nice to see if there was any data.

DR. MARKS: That will obviously be in the minutes that you don't have a concern. I guess the question is if we don't get any genotoxicity, will that then be a reason to say it's insufficient.

DR. SLAGA: I'll drop it.

DR. HILL: I won't, at least not right now.

DR. SHANK: If the compounds are approved as food, food additives, and generally used, then you would not need --

MS. BURNETT: A caveat, if it is not approved food use, then genotoxicity data?

DR. SHANK: Yes, that's the way to go.

DR. SLAGA: Furocoumarins, too, that are not being present.

DR. HILL: Or enough details in the method of manufacture and composition that we can use that for the read across.

DR. MARKS: So, we have one clarification, GRAS food use to genotoxicity of not approved for food use, so that will drop out, presumably, and then three, I wanted to see the orange flower extract at 6 percent in HRIPT or some sensitization, despite our conclusion that says formulated to be non-sensitizing, because when you look at the concentrations of use, the citrus aurantium dulcis, the orange flower extract, has 70 uses, and the highest concentration is 6 percent, nothing in the other ingredients where we have concentration that even comes close to 1 percent. So, it is really a lot higher concentration. That is in an eye shadow.

DR. HILL: But I wanted to point out on the flower wax that we have five uses showing up in the VCRP but we don't have any concentration data.

DR. MARKS: Yes.

DR. HILL: There is another one, flower water, but I'm not so worried about flower water honestly, because knowing what those waters are like and when they are typically used. That would be a low concentration.

DR. MARKS: That was the only need from sensitization, again, I find it somewhat contradictory to ask for HRIPTs when presumably we are going to say -- it is going to be second a motion with a tentative report, insufficient conclusion, and those three data needs at this point. Does that sound good, team?

DR. SHANK: Yes.

Dr. Belsito's Team

DR. BELSITO: So moving on to the next group of interesting botanicals. Citrus flower and leaf-derived ingredients. So we had split these up at the December 2015 or even before. Actually I guess before we split up how we're going to look at the citrus-derived ingredients. And at the December 2015, we went insufficient for the 32 ingredients including method of manufacture, composition, and some HRIPT data. We got a lot of the requested data on method of manufacture and composition that have been added. We got irritation and sensitization on the bitter orange flower extract, but not the requested HRIPT. Of note however, some of the ones that we had asked for, HRIPT sensitization data, based upon the reported concentration of use when we last looked at them, we now find are used at much lower concentrations of use. So a lot of, I think, those data needs have probably disappeared but maybe not. So as soon as my report opens.

So, I thought that we're still having some issues on sensitization and irritation. Obviously, in the summary we're getting rid of the methoxypsoralen issues, right, because those are peel only, so we're not dealing with them with -- and you mentioned that. But on PDF page 20 of the summary, you still have -- you've still brought up the psoralen issues. That needs to be deleted.

So for the dulcis flower extract, it's used at six percent and we have no sensitization at that level. What we have is a study, a new study, at.0225 percent. We also don't have composition for the dulcis. We have it for the sinensis. The ingredient --

DR. EISENMANN: Sinensis is another name for --

DR. BELSITO: Dulcis.

DR. EISENMANN: -- the orange. Yes.

DR. BELSITO: Okay, so we do have -- so we need to make that clearer because it wasn't clear to me.

MS. BURNETT: Yes, they INCI -- there's two different INCI names. But sinensis is the old botanical nomenclature if I understand it for -- or it's the other way around or --

DR. EISENMANN: I don't know if it's old or new but there --

MS. BURNETT: It's the same thing.

DR. EISENMANN: Right.

DR. BELSITO: Okay, did -- is this one of the reports where we had a table listing the various names?

MS. BURNETT: In the back.

DR. BELSITO: And is that clear? What table was that, Christina.

MS. BURNETT: It should be Table 2, I think.

DR. BELSITO: Because I --

MS. BURNETT: Two or three.

DR. BELSITO: -- obviously missed that. Okay, two not use, okay.

MS. BURNETT: Table --

DR. BELSITO: Species name, yeah. Table 3.

MS. BURNETT: Table 3.

DR. BELSITO: And where's it have sweet orange?

MS. BURNETT: Under citrus sinensis it also mentions citrus ex-aurantium. It doesn't specifically say dulcis, but.

DR. BELSITO: Could we put that in?

MS. BURNETT: Put -- no, I'm sorry, it does say that at the top.

DR. EISENMANN: It does say it.

MS. BURNETT: Sorry, the fourth line down; one, two, three, four. Citrus aurantium dulcis orange.

DR. BELSITO: Yeah, but then --

MS. BURNETT: Oh, it doesn't say.

DR. BELSITO: -- it -- there's citrus aurantium bergamia. There's citrus aurantium amara, bitter orange, so.

MS. BURNETT: Yep.

DR. BELSITO: So citrus aurantium --

MS. BURNETT: Dulcis, it's just a --

DR. BELSITO: Sinensis --

MS. BURNETT: Right.

DR. BELSITO: -- is also citrus aurantium dulcis.

MS. BURNETT: Okay.

DR. BELSITO: You need to make that clearer in the table.

MS. BURNETT: Okay.

DR. BELSITO: So basically, still, the sensitization we have for this, that's the max concentration of use of these. Six percent, is the dulcis. And we have an HRIPT or we have a study at.025 percent, 0.0225 percent.

So if we look at what the sinensis is, the constituents of concern from my standpoint, in terms of skin sensitization, are linalool at 47 percent if it's oxidized. That would be used if assuming it's used at six percent, the maximum amount of linalool in that product would be 2.8 percent. Now IFRA does not have a standard for a concentration of linalool. It has a standard for how much linalool hydroperoxides can be in linalool. And that's 20 millimole per liter is the RIFM restriction.

So I'm okay with allowing a.0225 study to pass for six percent. Is -- but then we would have to say something about -- which we always do RIFM restrictions but, you know, it's our -- I think here as opposed to restricting the methoxypsoralens as we did for peel ingredients, we probably have to look at at least mentioning the idea of linalool hydroperoxides as potential sensitizers. I didn't know which way to go.

The bottom line is we don't have a six percent study.

So we could go insufficient that we want a study at six percent, or we could, you know, discuss the composition and say something about, you know, we're not concerned that, you know, linalool could be at six percent or 2.8 percent in a product as long as the peroxides -- hydroperoxides are 20 millimole or less per their -- per IFRA standards.

DR. LIEBLER: Don, are you confident that linalool's the only problem, potential problem, in that?

DR. BELSITO: So it -- this is Table 7 which is the constituents.

DR. LIEBLER: Uh-huh.

DR. BELSITO: And so there is -- the citrus flower and leaves are really, you know, -- the sensitizers are really all pretty low.

DR. LIEBLER: Mm-hmm.

DR. BELSITO: And there was nothing there that jumped out at me. And then Table 7 for the volatiles in the citrus sinensis, or any of them for that matter. I mean, when you're looking down them, the only ones that jump out at me are the linalool. And then there -- limonene -- again, the issue is with the hydroperoxides and there are none reported or, you know, fairly low -- well, I guess. Limonene oxide trends, 3.05 in lemon. But otherwise the concentrations -- I mean, of the sensitizers, geranial, you know, citral, citranello, they're all pretty low in these.

DR. LIEBLER: So I -- I mean I'm not taking issue with the logic, but we -- I can't recall our having used this, sort of, provisionally calculation as a way around having test data at a maximum use concentration. And so I don't necessarily object. I need to think about it a little bit. But I don't necessarily object, but it seems to me the thing to do is ask for test data.

DR. BELSITO: Yeah, on the other hand we always go - - we know the fact also that there -- this could be combined with other botanicals containing linalool, and we always go when formulated to be non-sensitizing. The sensitizing capacity of that would be the hydroperoxides. So I don't know if -- I mean I'm just --

DR. LIEBLER: Yeah.

DR. BELSITO: -- you know, pointing this out because before we were asking for HRIPT data on several compounds because of their concentration of use. So now we've gotten different concentrations of use which eliminates our need for that data for certain compounds, but not for sweet orange, orange dulcis. So -- and we know that it -- the flower extract is used up to six percent and we -- the -- or whatever study it is, I have it listed here as.0225 percent.

And I didn't have -- I just wanted to raise this, you know, because the way we frame our conclusion with it being non-sensitizing, you know, would cover the fact that we don't have the data in a sense. But it also covers the fact that we realize that this could be added with other botanicals that would, in this case, potentially have linalool and limonene in them. And we shouldn't exceed those levels. I just -- you know, in this case, the ingredient or the component of concern in the mixture is not the concern for sensitization. It's the oxidation of that component to a hydroperoxide --

DR. LIEBLER: Right.

DR. BELSITO: -- that presents the concern. So it's a little bit of a twist on what we've looked at before.

DR. LIEBLER: Correct, yeah. So you're saying, with that logic we could say basically safe as used, formulated to be non-sensitizing?

DR. BELSITO: I mean, again --

DR. LIEBLER: That our data needs are met.

DR. BELSITO: Yeah, I mean I think that, you know, perhaps in the discussion we could point out that, you know, we had no sensitization at six percent, but you know, I -- again, what I said here is safe as used. We don't have repro or genotox studies. It didn't really bother me. We need the pesticide boilerplate, the inhalation boilerplate, the botanical boilerplate for non-sensitizing, and that covers the fact that we don't have the sensitization data for six percent. But I'm amenable to saying it's insufficient and we want to see that data. I don't -- you know, I'm surprised that there were reports that it said six percent, and we get one study at.0225. I could go either way here. I --

DR. SNYDER: But the six percent becomes irrelevant if it's going to be combined with other botanicals and formulations of being at a similar constituent.

DR. BELISTO: Right, --

DR. SNYDER: So it -- we --

DR. BELSITO: -- it still has to be non-sensitizing.

DR. SNYDER: So (inaudible)

DR. BELSITO: Oh, no, I agree that we -- you know, we've decided for all these botanicals that have a sensitizer or a component of concern, that we'll use that boilerplate when formulated to be non-sensitizing or, you know, when formulated to have pohon below a certain level or whatever. But, you know, I think that the conclusion will cover the fact that we don't have the data, but I'm certainly willing to say insufficient and I would like to see if there are other data out there for sensitization for the orange flower extract at six percent.

DR. LIEBLER: You know, relative to the other ingredients in this report, that six percent just stands out like a sore thumb. It's an order of magnitude --

DR. BELSITO: Right.

DR. LIEBLER: -- higher than the next highest use concentration which is the flower oil. Now I don't know if it's just one product that was driving that or what, but we'll either get the data -- if we ask for the data we'll either get the data or we'll get a clarification or we might not get the data I suppose. Then we can weigh whether or not we want to use the logic you described. I guess, you know, if you put it to me, I basically fall down -- fall on the side of let's ask for the data.

DR. BELSITO: Yeah, it's said to be is at six percent in an eye area.

DR. BERGFELD: Carol, you have a comment about that?

DR. EISENMANN: I can't remember specifically. I probably asked, but I don't know if I got a response, but I would ask again. We could always set -- I mean, what is a more reasonable limit? You could set a limit as if you wanted to move the report forward.

DR. BELSITO: Well we are setting a limit simply because of the botanical -- the way we phrase botanicals to be non-sensitizing. So that's setting a limit because we understand that a single product when formulated could contain multiple botanicals that could include linalool and limonene which would be the substances of concern for this group. So in that sense, we've covered our need. But I agree with Dan. It does sort of stick out. You have everything else. I mean, and even here in that range you're going from like 16 parts per million or per billion up to six percent which is a huge, huge range.

DR. LIEBLER: It's like selling a spice mixture that's 50 percent nutmeg. I mean, we used just a teeny bit of nutmeg. I mean these oil -- these extracts, you know, a little goes a long way. And in a way it seems like it's got to be wrong --

DR. EISENMANN: Some companies --

DR. LIEBLER: -- because it would be so wasteful.

DR. EISENMANN: -- have difficulty understanding when I ask for the context and abstract of it. I mean just the abstract part of it and not the rest of the material so that -- does it -- (inaudible) possible the six percent means -- includes the solvent also. But --

DR. BELSITO: Right.

DR. EISENMANN: -- I tend -- I try to get them to not tell me to include the solvent, but sometimes, you know, I -- they -- I don't get through to them.

DR. BELSITO: Okay.

DR. LIEBLER: Okay.

DR. BELSITO: Well the -- so then I think we need to determine tomorrow whether we're going safe as used or if we're going insufficient for clarification as to whether the dulcis flower extract is in fact used at six percent. And assuming that we're going insufficient for that, then I think we have to be saying we also want sensitization data if it is used at six percent. Is that what you're saying, Dan?

DR. LIEBLER: I completely agree with that. Yeah, that's exactly what I'm saying.

DR. BELSITO: Paul and Curt?

DR. SNYDER: That's fine.

DR. BELSITO: Okay.

DR. EISENMANN: One comment. There's a material in here called petitgrain bigarade oil, however you say the second term. It's actually a leaf twig preparation so that either the data has to be moved to the other report or the ingredient has to be moved to this report.

DR. BELSITO: Okay, and we have no repro or genotox studies, so I'm asking my other colleagues are we comfortable with that?

DR. SNYDER: Well I made a comment that in the discussion where we make this (inaudible), we've done this in two or three reports this time. We need to put a basis for why we don't think it's necessary.

DR. BELSITO: So what is that basis, Paul?

DR. SNYDER: Would be that probably the --

DR. BELSITO: GRAS status?

DR. SNYDER: GRAS and low concentration of use, et cetera. So --

DR. BELSITO: But six percent is not low, is it?

DR. EISENMANN: Well if you're not comfortable to six percent and that's what I'm trying to say. Go to the next highest concentration and say save up to whatever percent, when formulated to meet that -- to be formulated to be non- sensitizing.

MS. BURNETT: For that ingredient the next lowest is two percent in a lipstick.

DR. BELSITO: Yeah, I mean I'm not uncomfortable with it, Carol, because of the way we formulate the conclusions for these botanicals, as long as my colleagues are not uncomfortable with a lack of repro or genotox studies for these which need to be in the discussion. So I don't know that we need to -- I mean, you know, regardless of whether we say, you know, it can't be used over two percent the -- if our only concern is sensitization, we've covered whatever concentration they want to use. I mean they can add antioxidants to a BHA, BHG. I mean they can do various things to prevent the formation of hydroperoxides. And then I'm not concerned with the linalool at a potential max of six percent, you know.

Or the content of linalool when this -- the orange dulcis is used at a potential max of six percent. I would be concerned about the hydroperoxides that could be formed. And then the question is, you know, do we add that degree of information from the IFRA standards for the components of concern which would be linalool and limonene because for both of those the IFRA standards are not on concentrations of the actual material, but on concentrations of the hydroperoxides that could be there as contaminants.

But -- so we're going for insufficient sensitization at six percent or clarification that it in fact is used at six percent. And again, are we asking for repro or genotox studies or are we just going to explain why --

DR. SNYDER: I think we need to just explain why.

DR. BELSITO: Okay.

DR. LIEBLER: Yeah, we don't need it, we don't need it.

DR. SADRIEH: You just mentioned that the reason why was because it's GRAS. I just want to mention that GRAS is not for cosmetics. It's for the indications, so.

DR. BELSITO: Right.

DR. SNYDER: So there's no constituents of concern related to dermal or systemic exposure works with that.

DR. BELSITO: Okay, so I mean I think that, in all honesty, we'll probably, even if we don't get the data going sufficient. So I think when you start writing up more of the discussion when used again it's going to be the pesticide boilerplate, the inhalation boilerplate, and the botanical usual non-sensitizing, non-sensitizer formulation boilerplate. And then an explanation as to why we felt that repro and genotox studies weren't necessary for this group. Or, I guess, this is Christina, right? I'm sorry. Why it's not necessary for this group. Is that fair? But right now we're going insufficient.

Full Panel Meeting

DR. BERGFELD: Okay. Moving on to the second set reports advancing. And the first one of that set is citrus flower and leaf. Dr. Belsito.

DR. BELSITO: Right. So this is part of a continuing citrus group that we split and resplit, and so now we've decided to group the leaf and flower ingredients. After looking at this, we noted that citrus sinensis and citrus dulcis are actually the same orange. And so, the composition we had for one was the same for the other. Because we were a bit concerned the citrus dulcis/sinensis had no sensitization at six percent, which was its maximum leave on. However, given the fact that we now know the constituents and given our usual boilerplate about not combining them with other botanicals to make them sensitizing and our GRAS status, we thought we could go ahead with a safe-as-used for this group.

DR. BERGFELD: And that's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: Is there a second or a comment?

DR. MARKS: So you'd answered one of our questions of our tact was to issue a tentative report with an insufficient conclusion. Ultimately, we will get a conclusion that's safe when formulated to be nonirritating and non- sensitizing. But needs we have: One, is we wanted clarification of the GRAS food use of these ingredients, so that we could have a better understanding of potential toxicity. Two, we want a genotoxicity, if not, approved food use. And then you have answered, Don, the question about the orange flower extract as six percent. So that need could drop off for us. So we have two needs. The clarification of GRAS food use and genotoxic if not approved use. Now, with that saying, and these are clarifications, perhaps it could go on as a safe and then just clarify those two points.

DR. BELSITO: If we don't get GRAS, we also have no reproductive toxicity. And which is we cleared the (inaudible) based on GRAS status. So would you want reproductive toxicity as well?

DR. SHANK: (And no GRAS)?

DR. BELSITO: No, but if you have like part of the flower that's not GRAS, do you want repro toxicity. Because Jim just mentioned genotoxicity.

DR. SLAGA: Well, the genotoxicity was only a side because without the furocoumarins, I didn't really have a concern. But if we were asking for something, I (inaudible). So I'm not really big on that.

DR. BELSITO: So, okay. So you're going insufficient for clarification of the GRAS status and for if any of them are not GRAS for genotoxicity.

DR. SLAGA: Well, yeah.

DR. BELSITO: Dan? And you guys were the ones that cleared these based upon GRAS, what do you --

DR. LIEBLER: I'm fine with that.

DR. BELSITO: Okay. So I'll change my motion, and we'll go --

MS. SADRIEH: I just want to clarify the GRAS is not for cosmetics.

DR. BELSITO: Well, we understand that.

MS. SADRIEH: I just need to say so.

DR. BELSITO: So we'll amend it insufficient to determine the GRAS status of the ingredients and any that aren't GRAS for reproductive toxicity.

DR. MARKS: And geno if it is.

DR. BELSITO: I mean genotoxicity, I'm sorry. Ron said he -- Tom said he didn't need repro, correct? So just geno. And the only thing that obviously would go in the discussion are the usual boilerplates; inhalation pesticide, sensitizing. And I thought that in terms of the composition of these, it's really not so much the linalool and the limonene that are issues for sensitization, it's the hydroperoxides of limonene and linalool and probably a little bit of discussion about that because that's what IFRA regulates. It doesn't regulate the concentration of linalool or limonene in a product. It regulates the amount of hydroperoxides that are present.

DR. BERGFELD: Are you seconding that, Jim?

DR. MARKS: Yes, second.

DR. BERGFELD: And you feel that he's gotten all that --

DR. GILL: Yes.

DR. BERGFELD: -- that's been sent? Okay. All right then, Ron, are you raising hand to make a comment?

DR. HILL: Yes.

DR. BERGFELD: Please.

DR. HILL: I would still like to express a little bit of perturbation that we don't have -- we have five uses for the flower wax, which is a key piece because we have data on that. We don't have concentrations of use. We have the uses in VCRP, but we don't have concentrations. And, similarly, for the lime, the kaffir, the hystrix, we have 26 VCRP, 12 leave on, and 12 rinse off, I guess, and still no concentrations of use. So that missing information is bothersome because you're always making an assessment. And also, when we say in current -- state of current use, that's a key piece of information. And we don't have -- we got method of manufacturer for the dulcis flower extract that says specified eluant and doesn't provide enough information to give an idea of what sorts of things would be extracted. And since we're relying on -- I'm not suggesting it, but we're relying on that kind of information in lieu of the fact that we don't have direct-safety testing or getting some sense of what components might be present that might be of concern. So I feel like that's information that industry could readily provide, and that they didn't is bothersome.

DR. BERGFELD: Don, comment on adding that to your list of --

DR. HILL: I wasn't even saying you had to add to the list, I was suggesting it would be good if we pushed on that a little bit.

DR. BERGFELD: Well, if it's going to go insufficient, it might be added. What do you think?

DR. BELSITO: We can ask for them. I don't think we need it, but.

DR. BERGFELD: Okay. We can ask. Beth, you want to say anything? Anyone else want to make a comment? Then we're going to proceed with insufficient, and it's been -- the motion's been made and seconded. The comments have been recorded. All those in favor of insufficient. Okay. Unanimous. Okay. Thank you.

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

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

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 33 *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 that the data are insufficient to determine safety.

INTRODUCTION

According to the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), *Citrus* flower- and leaf-derived ingredients 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 33 ingredients:

Citrus Aurantifolia (Lime) Flower Extract
Citrus Aurantifolia (Lime) Leaf Oil
Citrus Aurantium Amara (Bitter Orange) Flower Extract
Citrus Aurantium Amara (Bitter Orange) Flower Oil
Citrus Aurantium Amara (Bitter Orange) Flower Water
Citrus Aurantium Amara (Bitter Orange) Flower Wax
Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract
Citrus Aurantium Bergamia (Bergamot) Leaf Extract
Citrus Aurantium Bergamia (Bergamot) Leaf Oil
Citrus Aurantium Dulcis (Orange) Flower Extract
Citrus Aurantium Dulcis (Orange) Flower Oil
Citrus Aurantium Dulcis (Orange) Flower Wax
Citrus Aurantium Dulcis (Orange) Flower
Citrus Aurantium Dulcis (Orange) Leaf Extract
Citrus Clementina Leaf Cell Extract
Citrus Depressa Flower Water
Citrus Grandis (Grapefruit) Leaf Extract
Citrus Hystrix Leaf Extract
Citrus Hystrix Leaf Oil
Citrus Junos Flower Oil
Citrus Limon (Lemon) Flower Water
Citrus Limon (Lemon) Leaf Extract
Citrus Limon (Lemon) Leaf Cell Extract
Citrus Natsudaidai Flower Water
Citrus Natsudaidai Flower Oil
Citrus Reticulata (Tangerine) Leaf Oil
Citrus Reticulata (Tangerine) Leaf Water
Citrus Sinensis (Orange) Flower Water
Citrus Tamurana Flower Extract
Citrus Unshiu Flower Extract
Citrus Unshiu Flower powder
Citrus Unshiu 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 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] *Citrus* plant- and seed-derived ingredients and *Citrus* peel-derived ingredients are being reviewed in separate reports.

Some of the *Citrus* flowers and leaves that are used to derive the ingredients described in this safety assessment are 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 from cosmetics. 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 the safety of topical exposure to the ingredients used as foods.

To avoid redundancy, CIR has the option to exclude ingredients that are known to exclusively function as fragrance ingredients, because the safety of fragrance ingredients is commonly evaluated by the Research Institute for Fragrance Materials (RIFM). According to the *Dictionary*, four of the *Citrus* flower- and leaf-derived ingredients in this report are reported to function exclusively as fragrance ingredients (see Table 2).[1] However, personal communications with RIFM in March 2015, revealed that these ingredients have neither been assessed for safety by the RIFM expert panel, nor are these ingredients on RIFM's prioritized agenda to be reviewed in the foreseeable future. Thus CIR is reviewing the safety of these ingredients as part of this current assessment.

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 *Dictionary*.[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.[4]

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 from which an ingredient is derived. 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 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 mean that fragrance is their only function.

Physical and Chemical Properties

Citrus Aurantium Amara (Bitter Orange) Flower Extract

A supplier reported that Citrus Aurantium Amara (Bitter Orange) Flower Extract in sunflower seed oil has an ultraviolet (UV) absorption wavelength <250 nm, with the maximum absorption value at 220 nm.[5]

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.

Citrus Aurantium Dulcis (Orange) Flower Wax

A supplier reported that Citrus Aurantium Dulcis (Orange) Flower Wax has a melting point of 60.0° C and a UV absorption value of 1250 at 280 nm.[7]

Method of Manufacturing

According to the *Dictionary*, essential oils and waters are prepared from leaves, stems, flowers, bark, roots, or other parts of a plant or the whole plant.[1] Essential oils are prepared by a number of processes including, but not limited to, steam or dry distillation, flash pasteurization and mechanical processes such as cold-pressing; however, the most widely used method for preparing essential oils from plants is steam distillation. The condensate from steam distillation produces two distinct fractions that contain the volatile ingredients from the plant. The water

insoluble fraction contains the "oil." The water soluble fraction contains constituents of the plant that are water soluble. The name assigned to the water insoluble fraction from steam distilled plant materials includes the term "oil" in the INCI name. The water soluble fraction from the steam distilled plant material includes the term "water" in the INCI name.

Citrus Aurantium Amara (Bitter Orange) Flower Extract

A supplier reported that Citrus Aurantium (Bitter Orange) Flower Extract is produced by macerating the flowers in hot water followed by clarification, addition of glycerin and preservative, and filtration.[8] This supplier also reported that the flowers may be extracted in sunflower seed oil before clarification and decontamination.[9]

Another supplier reported that Citrus Aurantium Amara (Bitter Orange) Flower Extract was extracted by hydrocarbons (not specified) from *Citrus aurantium amara* flowers grown in Morocco.[10] The resultant mixture was treated with ethanol, filtrated, and then concentrated and purified by distillation.

Citrus Aurantium Amara (Bitter Orange) Flower Water

As reported by a supplier, Citrus Aurantium Amara (Bitter Orange) Flower Water is produced through distillation of the flowers followed by acidification, addition of preservative, and decontamination.[11]

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 further refined.

Citrus Aurantium Dulcis (Orange) Flower Extract

According to a supplier, fresh or dried flowers of *Citrus aurantium dulcis* are 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 reported that Citrus Hystrix Leaf Extract is produced by extracting dried leaves with 80% ethanolic solution, and the extract is filtered and concentrated before the addition of 70% 1,3-butylene glycolic solution.[12] 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.[13] 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 composed of numerous constituents. Table 4 lists Citrus constituents that are established contact allergens, according the European Commission’s Scientific Committee on Consumer Safety (SCCS). Table 5 presents the cosmetic allergens certificates of analysis for Citrus Aurantium Amara (Bitter Orange) Flower ingredients. Table 6, Table 7, Table 8, Table 9, and Table 10 list the composition (%) of several *Citrus* leaf and flower ingredients and volatiles.

The International Fragrance Association (IFRA) has issued standards for limonene and linalool in natural products, stating that these constituents “should only be used when the level of peroxides is kept to the lowest practical level, for instance by adding antioxidants at the time of production.”[14,15]

Citrus Aurantium Amara (Bitter Orange) Flower Extract

A supplier reported that their raw material contains 1.5%-2.5% Citrus Aurantium (Bitter Orange) Flower Extract, 73.05%-74.05% water, >23% glycerin, <1.0% citric acid, 0.3% sodium benzoate, and 0.15% potassium sorbate.[16] This product was certified to contain 27 ppm of acetaldehyde (detection limit was 10 ppm).[17] This

product was certified to not contain the furocoumarins bergapten and 8-methoxypsoralen (detection limit was 10 ppm).[18]

Another raw material of this supplier was reported to contain 0.1%-0.5% Citrus Aurantium Amara (Bitter Orange) Flower Extract in 99.5%-99.9% sunflower seed oil.[19]

A raw material containing 0.15% Citrus Aurantium Amara (Bitter Orange) Flower Extract is reported to have 0.0016% (16 ppm) furanocoumarins with the following (calculated) break-out: 0.95 ppm psoralen, 0.3 ppm bergapten, 0.88 ppm oxypeudecanin, 0.08 ppm imperatorin, 0.18 ppm isoimperatorin, and 13.62 ppm epoxybergamottin.[10] This material also contains approximately 630 ppm linalool, 185 ppm linalyl acetate, 6 ppm β-pinene, and 2 ppm ocimene. Total polyphenolic content is approximately 29 ppm.

Citrus Aurantium Amara (Bitter Orange) Flower Water

A supplier reported that their raw material contains >98% Citrus Aurantium Amara Flower Water, <1% citric acid, 0.55% water, 0.3% sodium benzoate, and 0.15% potassium sorbate.[20] This product was certified to not contain furocoumarin, bergapten, bergaptol, bergamothine, citropten, coumarine, imperatorine, isoemperatorine, isopimpinelline, ombelliferone, or scopolettine (detection limit was 10 ppm).[21]

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).[22] 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 Aurantium Dulcis (Orange) Flower Wax

A supplier reported that Citrus Aurantium Dulcis (Orange) Flower Wax contains 35%-50% hydrocarbons (C21-C35), 12%-20% polycosanols (C24-C36), 25%-40% esters (C40-C60), and 0.5%-5.0% essential oils and bioflavoids.[7]

Citrus Hystrix Leaf Extract

A supplier reports that Citrus Hystrix Leaf Extract is composed of tannin and sugar.[12] 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 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 cosmetic ingredients in this report, with a total of 99; the majority of the uses are in leave-on skin care preparations (Table 11).[23] 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 Oil has the highest reported maximum concentration of use; it is used at up to 0.66% in a depilatory.[24] Citrus Aurantium Dulcis (Orange) Flower Wax had the second highest reported maximum concentration of use; it is used at up to 0.12% in a lipstick.

Table 12 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 Wax is used at 0.12% 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.[25-28] 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.[26,27] 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.[29-31]

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.[32]

Non-Cosmetic

The essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from the following *Citrus* plant sources are 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).

While not specifically listed as GRAS, *Citrus hystrix* (kaffir lime) leaves are recognized as a seasoning ingredient commonly used in Southeast Asian cuisine.[33]

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. Toxicokinetics data were not expected to be found because each botanical ingredient is a mixture of hundreds of constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity

Some of the *Citrus* ingredients in this assessment are found in foods, and daily exposures from food use would result in much greater systemic doses than those 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 flowers and 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 assessment focuses on the potential for irritation and sensitization from topical exposure to these *Citrus* ingredients.

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 13.[12,34-37] In rabbit studies, moderate, reversible erythema was observed with undiluted Citrus Aurantium Amara (Bitter Orange) Flower Wax. Citrus Hystrix Leaf Extract was not irritating in rabbits at up to 10%. In human subjects, no irritation was observed after topical exposure to Citrus Natsudaidai Flower Oil (1% in jojoba seed oil) or Citrus Aurantium Amara (Bitter Orange) Flower Extract (up to 0.001% in leave-on formulations).

Ocular Irritation

Citrus Auramtium Amara (Bitter Orange) Flower Water

The irritancy potential of a raw material product containing >98% Citrus Aurantium Amara (Bitter Orange) Flower Water was tested in a hen's egg test-chorioallantoic membrane (HET-CAM) assay and a cytotoxicity in vitro (CFIO) method.[36] The test material was studied diluted at 10% in saline or in Hank's balanced salt solution. While the HET-CAM assay concluded the test material was practically not irritating, the CFIO method concluded that the test material must be considered slightly irritating to the eye.

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 Statens Seruminstitut rabbit cornea (SIRC) cell model.[38] Tolerance was evaluated by measuring cytotoxicity. Negative control solutions were physiological serum or sample diluent and positive control solutions were 0.01% to 0.2% sodium dodecyl sulfate. Negligible cytotoxicity was observed.

Sensitization

Sensitization studies are presented in Table 14.[12,37,39-42] 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%, and 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 15.[37,43] Undiluted Citrus Aurantium Amara (Bitter Orange) Flower Oil (described as neroli oil) was not photosensitizing in tests with hairless mice or miniature swine. Citrus Aurantium Amara (Bitter Orange) Flower Extract at up to 0.002% in a leave-on product was not phototoxic or photosensitizing.

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 33 *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 be toxic. CIR reviewed the information available for 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 composed.

Citrus Aurantium Amara (Bitter Orange) Flower Oil has the most reported uses of the cosmetic ingredients in this report, 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 that Citrus Aurantium Dulcis (Orange) Flower Oil has the highest reported maximum concentration of use; it is used at up to 0.66% in a depilatory. Citrus Aurantium Dulcis (Orange) Flower Wax had the second highest reported maximum concentration of use; it is used at up to 0.12% in a lipstick.

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 much larger systemic exposures than those resulting from use in cosmetic products. Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from some *Citrus* sources (specifically *Citrus aurantium* (bitter orange; the flowers and leaf/twig oil) and *Citrus sinensis* (orange; the leaf and flowers)) are GRAS for their intended use in foods for human and animal consumption according to the FDA. While not specifically listed as GRAS, *Citrus hystrix* (kaffir lime) leaves are commonly used in Southeast Asian cuisine.

In rabbit studies, moderate, reversible erythema reactions were observed with undiluted Citrus Aurantium Amara (Bitter Orange) Flower Wax. Citrus Hystrix Leaf Extract was not irritating in rabbits at up to 10%. In human subjects, no irritation was observed after topical exposure to Citrus Natsudaidai Flower Oil (1% in jojoba seed oil).

A raw material product containing >98% Citrus Aurantium Amara (Bitter Orange) Flower Water was considered practically not irritating in a HET-CAM assay but was considered slightly irritating to the eyes in a CFIO test. 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%. Citrus Aurantium Dulcis (Orange) Flower Oil was not irritating or sensitizing at 0.4% in a face and neck product.

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

The *Citrus* ingredients in this assessment are found in foods, and daily exposures from the consumption of foods can be expected to yield much larger systemic exposures to these ingredients than those from use in cosmetic products. Essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some *Citrus* flowers and leaves are GRAS in foods and animal feeds. Consequently, the primary focus of this safety assessment is on the potential for irritation and sensitization from dermal exposures to the *Citrus* ingredients.

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

The Panel discussed the issue of incidental inhalation exposure from hair sprays, fragrance preparations, and face powders. There were no inhalation toxicity data available. The Panel noted that droplets/particles from spray and loose-powder cosmetic products would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

The Panel expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

The Panel found that the data are insufficient to make a conclusion upon the safety of the 33 Citrus flower- and leaf-derived ingredients found in this safety assessment. The data that are needed to properly evaluate the safety of these ingredients are:

- Clarification of the generally recognized as safe (GRAS) food status of these ingredients and/or verification of accepted food use
- Genotoxicity data if these ingredients are not GRAS foods or recognized as being an accepted food
- Concentration of use data for Citrus Aurantium Amara (Bitter Orange) Flower Wax and Citrus Hystrix Leaf Oil
- Composition and impurities data for Citrus Aurantium Dulcis (Orange) Flower Extract.

CONCLUSION

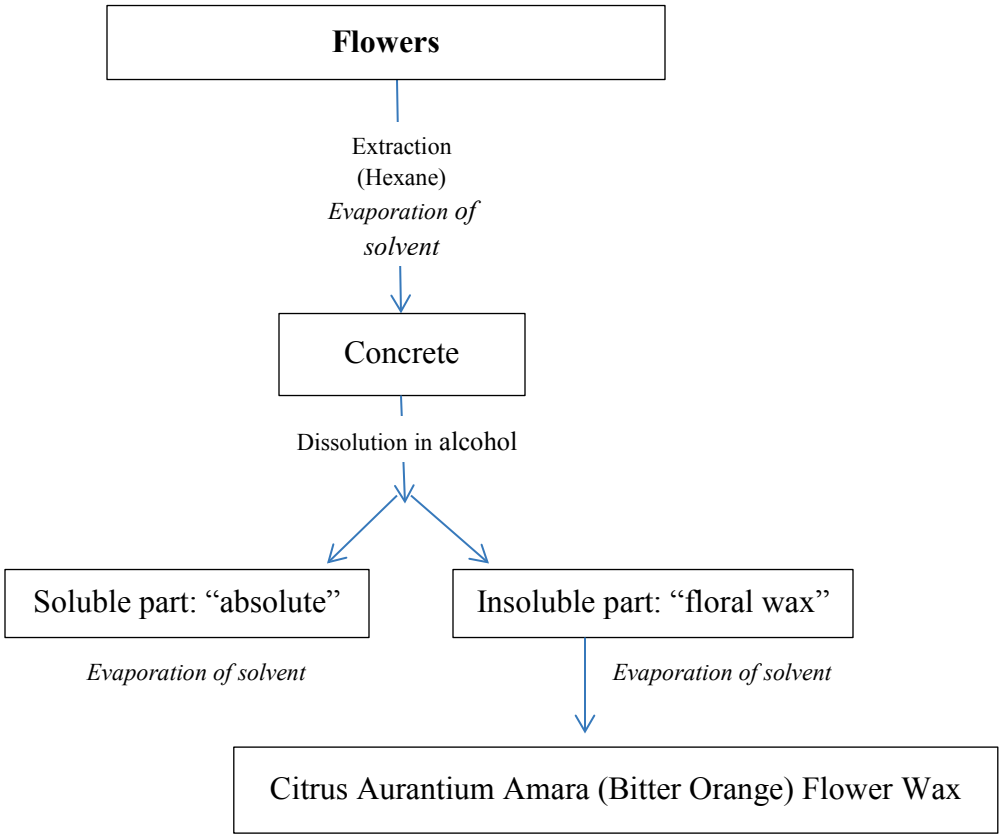
The CIR Expert Panel concluded that the available data are insufficient to make a determination that the following 33 ingredients are safe under the intended conditions of use in cosmetic formulations.

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

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

FIGURES

Figure 1. Manufacturing flow chart of Citrus Aurantium Amara (Bitter Orange) Flower Wax.[44]



TABLES

[1]

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

Ingredient	Definition	Function
Citrus Aurantifolia (Lime) Flower Extract	Citrus Aurantifolia (Lime) Flower Extract is the extract of the flowers of *Citrus aurantifolia.*	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 *Citrus aurantifolia.*	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 *Citrus aurantium amara.*	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 *Citrus aurantium amara.*	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 *Citrus aurantium amara.*	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 *Citrus aurantium amara.*	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 *Citrus aurantium bergamia.*	Antioxidants; Skin Protectants
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	Citrus Aurantium Bergamia (Bergamot) Leaf Extract is the extract of the leaves of *Citrus aurantium bergamia.*	Cosmetic Astringents
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	Citrus Aurantium Bergamia (Bergamot) Leaf Oil is the volatile oil obtained from the leaves of *Citrus aurantium bergamia.*	Cosmetic Astringents
Citrus Aurantium Dulcis (Orange) Flower	Citrus Aurantium Dulcis (Orange) Flower is the flower of *Citrus aurantium dulcis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Flower Extract	Citrus Aurantium Dulcis (Orange) Flower Extract is the extract of the flowers of *Citrus aurantium dulcis.*	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 *Citrus aurantium dulcis.*	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 *Citrus aurantium dulcis.*	Skin-Conditioning Agents - Occlusive
Citrus Aurantium Dulcis (Orange) Leaf Extract	Citrus Aurantium Dulcis (Orange) Leaf Extract is the extract of the leaves of *Citrus aurantium dulcis.*	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 *Citrus clementina.*	Antioxidants; Skin Protectants
Citrus Depressa Flower Water	Citrus Depressa Flower Water is the aqueous solution of the steam distillates obtained from the flowers of *Citrus depressa.*	Skin-Conditioning Agents - Humectant
Citrus Junos Flower Oil	Citrus Junos Flower Oil is the volatile oil obtained from the flowers of *Citrus junos.*	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 *Citrus limon* (lemon).	Skin-Conditioning Agents - Humectant
Citrus Grandis (Grapefruit) Leaf Extract	Citrus Grandis (Grapefruit) Leaf Extract is the extract of the leaves of *Citrus grandis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Hystrix Leaf Extract	Citrus Hystrix Leaf Extract is the extract of the leaves of *Citrus hystrix.*	Skin-Conditioning Agents - Miscellaneous
Citrus Hystrix Leaf Oil (or Kaffir Lime (Citrus Hystrix) Leaf Oil)	Not in *Dictionary*.	Not in *Dictionary*.
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 *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Leaf Extract	Citrus Limon (Lemon) Leaf Extract is the extract of the leaves of *Citrus limon*.	Antioxidants
Citrus Natsudaidai Flower Oil	Citrus Natsudaidai Flower Oil is the volatile oil obtained from the flowers of *Citrus natsudaidai.*	Fragrance Ingredients
Citrus Natsudaidai Flower Water	Citrus Natsudaidai Flower Water is the aqueous solution of the steam distillates obtained from the flowers of *Citrus natsudaidai.*	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 *Citrus reticulata*	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 *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Citrus Sinensis (Orange) Flower Water	Citrus Sinensis (Orange) Flower Water is an aqueous solution of the steam distillates obtained from the flowers of *Citrus sinensis.*	Skin-Conditioning Agents - Humectant
Citrus Tamurana Flower Extract	Citrus Tamurana Flower Extract is the extract of the flowers of *Citrus tamurana.*	Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu Flower Extract	Citrus Unshiu Flower Extract is the extract of the flowers of *Citrus unshiu.*	Skin Protectants; Skin-Conditioning Agents - Humectant
Citrus Unshiu Flower Powder	Citrus Unshiu Flower Powder is the powder obtained from the dried, ground flowers of *Citrus unshiu.*	Exfoliants
Citrus Unshiu Flower Water	Citrus Unshiu Flower Water is an aqueous solution of the steam distillates obtained from the flowers of *Citrus unshiu.*	Fragrance Ingredients

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

Ingredient	Definition	Function
Citrus Unshiu Leaf Extract	Citrus Unshiu Leaf Extract is the extract of the leaves of *Citrus unshiu.*	Skin Protectants; Skin-Conditioning Agents - Humectant

*Accepted or alternate scientific names for these Citrus ingredients are found in Table 3.

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

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

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

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

Table 4. Potential constituents that are established contact allergens in humans, according to the SCCS.

Constituent
β-caryophyllene
carvone
citral
citronellol
coumarin
farnesol
geraniol
linalyl acetate
α- and β-pinene
(DL)-limonene
tepineol (mixture of isomers)/α-terpineol
terpinolene

Table 5. Cosmetic allergens certificates from manufacturer of Citrus Aurantium Amara (Bitter Orange) Flower ingredients.[45-47]

Allergen	Citrus Aurantium Amara (Bitter Orange) Flower Wax	Citrus Aurantium Amara (Bitter Orange) Flower Water	Citrus Aurantium Amara (Bitter Orange) Flower Extract	Citrus Aurantium Amara (Bitter Orange) Flower Extract in sunflower seed oil‡
Amyl cinnamal	< 5 ppm	ND	ND	ND
Benzyl alcohol	< 20 ppm	ND	ND	ND
Cinnamyl alcohol	< 1 ppm	ND	ND	ND
Citral	< 10 ppm	ND	ND	ND
Eugenol	< 5 ppm	ND	ND	ND
Hydroxycitronellal	< 5 ppm	ND	ND	ND
Isoeugenol	< 5 ppm	ND	ND	ND
Amylcinnamyl alcohol	< 1 ppm	ND	ND	ND
Benzyl salicylate	< 5 ppm	ND	ND	ND
Cinnamal	< 5 ppm	ND	ND	ND
Coumarin	< 15 ppm	ND	ND	ND
Geraniol	< 5 ppm	ND	ND	ND
Hydroxyisohexyl 3-cyclo hexane carboxaldehyde	< 5 ppm	ND	ND	ND
Anise alcohol	< 30 ppm	ND	ND	ND
Benzyl cinnamate	< 15 ppm	ND	ND	ND
Farnesol	< 50 ppm	ND	ND	ND
Butylphenyl methylpropional	< 1 ppm	ND	ND	ND
Linalool	< 50 ppm	ND	ND	ND
Benyl benzoate	< 5 ppm	ND	ND	ND
Citronellol	< 5 ppm	ND	ND	ND
Hexyl cinnamal	< 1 ppm	ND	ND	ND
Limonene	< 200 ppm	ND	ND	ND
Methyl 2-octynoate	< 1 ppm	ND	ND	ND
Alpha-isomethyl ionone	< 1 ppm	ND	ND	ND
Evernia prunastri	ND	ND*	ND†	ND
Evernia furfuracea	ND	ND*	ND†	ND

Unless noted, detection limit was 2 ppm.
*Detection limit was 20 ppm
†Detection limit was 5 ppm
‡Detection limit was 1 ppm for all allergens
ND = unable to be detected by GCSM

Table 6. Chemical composition of orange flower absolute.[48]

Constituent	Percent Range
linalool	34.0-48.0
linalyl acetate	14.0-21.0
farnesol	3.6-15.4
nerolidol	4.9-8.9
indole	2.6-9.9
methyl anthranilate	1.0-4.3
α-terpineol	1.5-3.7
limonene	0-3.6
geraniol	0-2.0
geranyl acetate	0-1.3
(E)-β-ocimene	0-2.2
2-phenethyl alcohol	0-2.1
β-pinene	0-2.7
benzyl cyanide	0-1.1
nerol	0-1.1
neryl acetate	0-0.7
terpinen-4-ol + β-caryophyllene	0-0.8
myrcyne	0-0.5

Table 7. Composition (%) of *Citrus* flower and leaves. [49-51]

	Citrus Natsudaidai Flower Oil	***Citrus reticulata* leaf oil (mandarin)**	***Citrus aurantium* L. flower oil (bitter orange)**	***Citrus aurantium* 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 anthranylate	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 8. Key constituents (%) of *Citrus* flowers and leaves*[52]

	Citrus Limon (Lemon) Leaf Oil	Citrus Aurantium Amara (Bitter Orange) Flower Oil	Bitter Orange Flower Extract	Citrus Aurantium Amara (Bitter Orange) Flower Water	Bitter Orange Leaf Extract	Citrus Aurantium Amara (Bitter Orange) Leaf Oil	Citrus Reticulata (Mandarin) Leaf Oil	Citrus Hystrix Leaf Oil
β-pinene	3.5-13.6	3.5-13.0	NR	NR	NR	0.3-2.7	1.9-2.5	0.2-1.5
sabinene	NR	0.4-2.8	NR	NR	NR	NR	NR	1.6-4.8
β-myrcene	0.4-1.5	1.4-3.1	NR	NR	2.5	0-2.0	NR	0.4-1.4
p-cymene	NR	NR	NR	NR	NR	NR	3.0-4.8	NR
(+)-limonene	8.1-30.7	6.0-17.9	NR	NR	NR	0.3-8.0	7.2-11.7	NR
citronellal	1.5-2.9	NR	NR	NR	NR	NR	NR	58.9-81.5
α-pinene	0.1-2.2	0.8-1.1	NR	NR	NR	NR	1.8-2.3	NR
γ-terpinene	0.4-2.3	NR	NR	NR	NR	NR	23.9-28.5	0.1-1.1
(E)-β-ocimene	NR	4.6-7.0	NR	NR	1.2	0-2.2	NR	NR
(Z)-β-ocimene	NR	0.7-1.0	NR	NR	NR	NR	NR	NR
(+)-limonene + (Z)-β-ocimene	NR	NR	0-5.1	NR	NR	NR	NR	NR
β-caryophyllene	0.6-2.0	NR	NR	NR	NR	NR	1.2-1.4	NR
α-thujene	NR	NR	NR	NR	NR	NR	0.8-1.0	NR
linalool	1.2-1.8	31.4-54.3	30.0-32.0	NR	42.5	12.3-25.2	NR	2.9-4.7
linalool + 2-phenylethanol	NR	NR	NR	67.5	NR	NR	NR	NR
2-phenylethanol	NR	NR	4.5-35.0	NR	NR	NR	NR	NR
(Z)-linalool oxide	NR	NR	NR	1.9	NR	NR	NR	NR
(E)-linalool oxide	NR	NR	NR	1.1	NR	NR	NR	NR
nerolidol	NR	NR	0-7.6	NR	NR	NR	NR	NR
(E)-nerolidol	NR	1.3-4.0	NR	NR	NR	NR	NR	NR
farnesol	NR	NR	trace-7.7	NR	NR	NR	NR	NR
(E,E)-farnesol	NR	1.6-3.2	NR	NR	NR	NR	NR	NR
(E,Z)-farnesol	NR	0.7-1.6	NR	NR	NR	NR	NR	NR
α-terpineol	0.4-1.1	1.1-5.8	2.0-2.4	20.0	NR	2.1-6.8	NR	NR
terpinen-4-ol	NR	0.3-1.3	NR	NR	NR	NR	NR	NR
nerol	1.3-7.4	1.1-1.3	0.9-4.0	3.0	NR	0.4-1.1	NR	NR
neral	6.5-25.3	NR	NR	NR	NR	NR	NR	NR
geranial	10.9-39.0	NR	NR	NR	NR	NR	NR	NR
geraniol	0.5-15.0	0.8-3.6	< 1.5	NR	NR	1.4-3.0	NR	NR
isopulegol	NR	NR	NR	NR	NR	NR	NR	0.3-4.9
linalyl acetate	trace-6.5	0.6-10.0	7.0-16.8	NR	48.9	47.4-71.0	NR	NR
methyl anthranilate	NR	NR	3.0-15.0	3.0	NR	NR	NR	NR
dimethyl anthranilate	NR	NR	NR	NR	NR	NR	43.2-51.9	NR
geranyl acetate	trace-4.0	0.7-4.1	NR	NR	1.6	1.9-4.5	NR	NR
citronellyl acetate	NR	NR	NR	NR	NR	NR	NR	0.9-5.1
α-terpinyl acetate	trace-7.3	NR	NR	NR	NR	NR	NR	NR
neryl acetate	3.7-7.4	0.3-2.1	0.8-4.0	NR	1.0	0-3.0	NR	NR
indole	NR	NR	0.1-1.0	NR	NR	NR	NR	NR
benzyl cyanide	NR	NR	1.0	NR	NR	NR	NR	NR

NR = not reported

*Composition reported down to the level of 1%, or lower for known toxic constituents.

Table 9. *Citrus* flower volatiles composition (%), identified by headspace-solid phase microextraction gas chromatography-mass spectrometry.[53]

	Citrus reticulata **(mandarin orange)**	***Citrus unshiu***	***Citrus sinensis*** **(sweet orange)**	***Citrus limon*** **(lemon)**	***Citrus grandis*** **(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
benezene 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
p-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
(*Z*)-ocimene	trace	NR	0.1-1.71	0.1-1	0.1-1
(*E*)-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
cis-β-terpineol	1.08-1.99	0.1-1	0.1-3.60	trace-1	trace-1
cis-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, *cis*	NR	NR	NR	NR	trace-1.15
limonene oxide, *trans*	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
p-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
trans-dihydrocarvone	NR	NR	NR	0.1-1	NR
p-menth-1-en-9-al	trace-1	0.1-1	NR	0.1-1	0.1-1
cis-carveol	NR	0.1-1	trace	0.1-1	trace
cis-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
trans-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
trans-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
bicyclosesquiphellandrene	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
α-muurolene	0.1-1	NR	NR	NR	trace-1

Table 9. *Citrus* flower volatiles composition (%), identified by headspace-solid phase microextraction gas chromatography-mass spectrometry.[53]

	Citrus reticulata **(mandarin orange)**	***Citrus unshiu***	***Citrus sinensis*** **(sweet orange)**	***Citrus limon*** **(lemon)**	***Citrus grandis*** **(pomelo)**
α-bulnesene	trace-1	NR	trace	0.1-1	trace
(Z,E)-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
p-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 10. Volatile organic compounds (%) in *Citrus* leaves, identified by gas chromatography-mass spectroscopy.[54]

	Citrus aurantium **(bitter orange)**	***Citrus sinensis*** **(sweet orange)**	***Citrus grandis*** **(pomelo)**	***Citrus paradisi*** **(grapefruit)**	***Citrus depressa***	***Citrus reticulata*** **(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 11. Frequency and concentration of use according to duration and type of exposure for *Citrus* flower- and leaf-derived ingredients.[23,55]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Citrus Aurantifolia (Lime) Flower Extract[d]		**Citrus Aurantium Amara (Bitter Orange) Flower Extract[e]**		**Citrus Aurantium Amara (Bitter Orange) Flower Oil[e]**		**Citrus Aurantium Amara (Bitter Orange) Flower Water[e]**	
Totals[†]	**10**	**0.00001-0.005**	**45**	**0.000000072-0.032**	**99**	**0.00098-0.049**	**31**	**0.000033-0.05**
Duration of Use								
Leave-On	5	0.00001-0.0005	36	0.000000072-0.032	83	0.00098-0.049	23	0.00016-0.0023
Rinse Off	2	0.0005-0.005	9	0.00028-0.001	13	0.001-0.019	8	0.00005-0.05
Diluted for (Bath) Use	3	0.0005	NR	NR	3	NR	NR	0.000033
Exposure Type								
Eye Area	NR	NR	6	NR	4	NR	8	0.0017-0.0023
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]	0.00001-0.0005; 0.00001[b]	1; 6[b]; 19[a]	0.000000072-0.001; 0.032[b]	2; 34[b]; 32[a]	0.0024; 0.049[b]	1; 10[b]; 3[a]	NR
Incidental Inhalation-Powder	1[a]	0.0005[c]	19[a]	0.001-0.023[c]	2[c]; 32[a]	0.01; 0.00098-0.005[c]	3[a]	0.00021[c]
Dermal Contact	9	0.0005	43	0.00001-0.023	95	0.00098-0.019	31	0.000033-0.05
Deodorant (underarm)	NR	NR	NR	0.00001-0.0099	NR	NR	NR	NR
Hair - Non-Coloring	1	0.00001-0.005	1	0.000000072-0.032	4	0.001-0.049	NR	0.00005-0.00014
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	NR	NR	NR	NR
Mucous Membrane	4	0.0005	3	0.00028-0.001	8	0.019	1	0.000033-0.05
Baby Products	NR	NR	NR	NR	3	NR	NR	NR

	Citrus Aurantium Amara (Bitter Orange) Flower Wax[e]		**Citrus Aurantium Bergamia (Bergamot) Leaf Extract**		**Citrus Aurantium Bergamia (Bergamot) Leaf Oil[f]**		**Citrus Aurantium Dulcis (Orange) Flower[g]**	
Totals[†]	**5**	**NR**	**NR**	**0.002**	**2**	**0.002**	**6**	**0.00008-0.005**
Duration of Use								
Leave-On	5	NR	NR	0.002	2	0.002	5	NR
Rinse Off	NR	NR	NR	0.002	NR	0.002	NR	0.00008-0.005
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	1	NR
Exposure Type								
Eye Area	1	NR	NR	NR	NR	NR	1	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[b]; 2[a]	NR	NR	NR	2[a]	NR	3[b]; 1[a]	NR
Incidental Inhalation-Powder	2[a]	NR	NR	0.002[c]	2[a]	0.002[c]	1[a]	NR
Dermal Contact	4	NR	NR	0.002	2	0.002	6	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.002	NR	0.002	NR	0.00008-0.005
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 11. Frequency and concentration of use according to duration and type of exposure for *Citrus* flower- and leaf-derived ingredients.[23,55]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Citrus Aurantium Dulcis (Orange) Flower Extract[h]		**Citrus Aurantium Dulcis (Orange) Flower Oil[i]**		**Citrus Aurantium Dulcis (Orange) Flower Water**		**Citrus Aurantium Dulcis (Orange) Flower Wax[j]**	
Totals[†]	**70**	**0.0000016-0.1**	**67**	**0.000011-0.66**	**16**	**NR**	**4**	**0.12**
Duration of Use								
Leave-On	36	0.00003-0.056	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
Exposure Type								
Eye Area	NR	0.01	1	NR	2	NR	NR	NR
Incidental Ingestion	NR	NR	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]	0.002-0.056[c]	15[a]	0.04-0.21[c]	1[a]	NR	NR	NR
Dermal Contact	70	0.0000016-0.1	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	0.01-0.1	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**
Duration of Use						
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
Exposure Type						
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 12. Ingredients that are not reported to be in use.

Citrus Aurantifolia (Lime) Leaf Oil
Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract
Citrus Clementina Leaf Cell Extract
Citrus Depressa Flower Water
Citrus Grandis (Grapefruit) Leaf Extract
Citrus Hystrix Leaf Extract
Citrus Junos Flower Oil
Citrus Limon (Lemon) Flower Water
Citrus Limon (Lemon) Leaf Extract
Citrus Limon (Lemon) Leaf Cell Extract
Citrus Natsudaidai Flower Water
Citrus Natsudaidai Flower Oil
Citrus Reticulata (Tangerine) Leaf Water
Citrus Tamurana Flower Extract
Citrus Unshiu Flower Extract
Citrus Unshiu Flower Powder
Citrus Unshiu Flower Water
Citrus Unshiu Leaf Extract

Table 13. 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	[34]
Citrus Hystrix Leaf Extract	10%	3 rabbits	primary skin irritation test, details not provided	no irritation	[12]
Citrus Hystrix Leaf Extract	10%	Details not provided	cumulative application test, details not provided	no irritation	[12]
HUMAN					
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0001% in a leave-on product	26 subjects	Cumulative irritation patch; occluded; 100 µl applied on a total of 12 patches	not irritating	[37]
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0005% to 0.001% in a leave-on product	140 subjects	Cumulative irritation patch; occluded; 20 µl applied on a total of 12 patches	not irritating	[37]
98% Citrus Aurantium Amara (Bitter Orange) Flower Water	10% diluted in distilled water	11 subjects	24 h occlusive cutaneous patch test; patch area 50 mm on upper back	No skin reaction in 9 subjects, very slight erythema in 2 subjects; irritation index = 0.04; not irritating	[36]
Citrus Natsudaidai 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	[35]

Table 14. 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	[12]
			HUMAN		
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0001% in a leave-on product	207 subjects	HRIPT; 50 µl; occlusive patch	not sensitizing	[37]
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.00001% in a rinse-off product	207 subjects	HRIPT; 50 µl; occlusive patch	not sensitizing	[37]
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0225% in a cream	108 subjects	HRIPT; 0.2 g; occlusive patch	as many as 17 subjects had faint, minimal erythema reactions during induction (7th patch); as many as7 subjects had a erythema reaction (4th patch) during induction; as many as 3 subjects had a erythema with edema reactions (3rd patch) during induction; during challenge as many as 14 subjects had faint, minimal erythema reactions (2nd challenge reading) and as many as 6 subjects had erythema reactions (1st challenge reading); study authors concluded test material was non-sensitizing	[40]
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0225% in a body cream	106 subjects	HRIPT; 0.2 g; semi-occlusive patch	one subject had a faint, minimal erythema reaction on the 1st challenge reading; study authors concluded test material was non-sensitizing	[39]
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	[41]
Citrus Aurantium Dulcis (Orange) Flower Oil	0.4% in a face and neck product	104 subjects	modified HRIPT; semi-occlusive patch; 150 µl over 2 cm^2	not irritating, not sensitizing	[42]

Table 15. Photosensitization studies.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
Citrus Aurantium Amara (Bitter Orange) Flower Oil (described as "oil neroli bigarde petale")	undiluted	hairless mutant mice (6/light source; 12 total) and miniature swine (1/light source; 2 total)	20 µl test material was applied to 2 cm^2 back skin, and the test sites were irradiated with UVA irradiation by blacklight or 6 kW long-arc xenon lamp; exposure was 40 min at a distance of 1 m	barely perceptible erythema; not photosensitizing	[43]
Citrus Aurantium Amara (Bitter Orange) Flower Oil (described as "oil neroli Tunisian")	undiluted	hairless mutant mice (6/light source; 12 total) and miniature swine (1/light source; 2 total)	20 µl test material was applied to 2 cm^2 back skin, and the test sites were irradiated with UVA irradiation by blacklight or 6 kW long-arc xenon lamp; exposure was 40 min at a distance of 1 m	barely perceptible erythema; not photosensitizing	[43]
			HUMAN		
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0001% to 0.002% in a leave-on product	92 subjects	phototoxicity test; 20µl test material; occluded; 17 min exposure to UVA	not phototoxic	[37]
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0001% to 0.002% in a leave-on product	247 subjects	photoallergy test; 0.2 g test material; occluded; 17 min exposure to UVA	not photoallergenic	[37]

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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

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Memorandum

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

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

DATE: June 21, 2016

SUBJECT: Information on Orange Flower Wax

Anonymous. 2016. Flower waxes (composition and properties of flower waxes including Citrus Aurantium Dulcis (Orange) Flower Wax).

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Flower Waxes

Flower Waxes are the concentrated high molecular essence that remain after the manufacture of essential oils which are typically used in perfumes. Flower Waxes have a unique chemical composition not found in any other natural or synthetic waxes. Polycosanols are high molecular weight fatty alcohols that possess anti-inflammatory properties. While, Bioflavonids (polyphenols) have been attributed to a wide variety of biologically activity at low usage levels.

COMPOSITION:

Flower Wax Type	Hydrocarbons <%> [C-21 – C-35]	Polycosanols <%> [C-24 – C-36]	Esters <%> [C-40 – C-60]	Essential Oils & Bioflavonids <%>
Acacia	50 - 70	10 – 15	25 - 40	0.5 – 5.0
Jasmine	45 - 65	18 – 25	20 - 30	0.5 – 5.0
Mimosa	25 - 35	30 – 35	25 - 35	0.5 – 5.0
Narcissus	65 - 75	3 – 7	15 - 30	0.5 – 5.0
Orange	35 - 50	12 – 20	25 - 40	0.5 – 5.0
Rose	70 - 80	7 – 12	7 - 15	0.5 – 5.0
Tuberose	55 - 70	15 – 23	20 - 30	0.5 – 5.0

CHEMICAL PROPERTIES:

Flower Wax Type	Melting Point °C	Acid Value	Saponification Value	Iodine Value	Ultra Violet Absorption @280nm
Acacia	59.3	< 5	40 – 60	20 - 30	340
Jasmine	60.0	< 5	30 – 50	30 - 50	470
Mimosa	60.0	< 15	50 – 80	10 - 35	2000
Narcissus	61.0	< 10	40 – 50	20 - 40	900
Orange	60.0	< 5	50 – 70	30 - 50	1250
Rose	55.0	< 10	20 – 40	10 - 40	260
Tuberose	66.5	< 10	30 – 50	20 - 40	540

USES:

Creams O/W & W/O, Lotions, Baby Care, Sunscreens, Hair Conditioners, Shampoos, Lipsticks, Makeup, Treatment Products, Slimming & Massage Products and Ointments

FORMULATING ADVANTAGES:

The polycosanol and bioflavonid fraction of flower waxes possesses properties that protect the skin from a variety of external factors. By incorporating Flower Waxes into your formulation benefits will be seen, such as; sunscreen enhancer, anti-inflammatory, moisturizing, emollient and wound healing properties.

REGULATORY INFORMATION:

CLASSIFICATION:

CTFA/INCI NAME:		
	Acacia Farnesiana Flower Wax	Botanical
	Jasminum Sambac (Jasmine) Flower Wax	Botanical
	Acacia Dealbata Flower Wax	Botanical
	Narcissum Poeticus Flower Wax	Botanical
	Citrus Aurantium Dulcis (Orange) Flower Wax	Botanical
	Rose Centifolia Flower Wax	Botanical
	Polianthes Tuberosa Flower Wax	Botanical

June 2016

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: July 6, 2016

SUBJECT: Information on *Citrus hystrix* Leaves

Although not listed as GRAS *Citrus hystrix* leaves (Kaffir lime leaves) are listed as an edible spice (see: http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx). The leaves of *Citrus hystrix* are a common ingredient in Southeast Asian cuisine.

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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: July 26, 2016

SUBJECT: Information on Citrus Aurantium Amara (Bitter Orange) Flower Water and Citrus Aurantium Amara (Bitter Orange) Flower Extract

Greentech. 2012. Regulatory data sheet Orange tree flower organic distillate 1:20 (Citrus Aurantium Amara (Bitter Orange) Flower Water).

Greentech. 2014. Manufacturing process Orange tree flower organic distillate 1:20 (Citrus Aurantium Amara (Bitter Orange) Flower Water).

ExperTox. 2014. Substance safety report: Orange tree flower organic distillate 1:20 (Citrus Aurantium Amara (Bitter) Orange) Flower Water).

Greentech. 2012. 26 Allergens listed: Orange tree flower organic distillate 1:20 (Citrus Aurantium Amara (Bitter Orange) Flower Water).

Greentech. 2014. Attestation (furocoumarin analysis) Orange tree flower organic distillate 1:20 (Citrus Aurantium Amara (Bitter Orange) Flower Water).

Greentech. 2016. Toxicological tests on Orange tree flower organic distillate 1:20 (Citrus Aurantium Amara (Bitter Orange) Flower Water) (summaries).

Greentech. 2015. Regulatory data sheet Orange tree flower from Morocco Biogreen (Citrus Aurantium Amara (Bitter Orange) Flower Extract).

Greentech. 2013. Manufacturing process Orange tree flower from Morocco Biogreen (Citrus Aurantium Amara (Bitter Orange) Flower Extract).

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Greentech. 2016. CMR certificate Orange tree flower from Morocco Biogreen (Citrus Aurantium Amara (Bitter Orange) Flower Extract).

Greentech. 2016. 26 Allergens listed Orange tree flower from Morocco Biogreen (Citrus Aurantium Amara (Bitter Orange) Flower Extract).

Greentech. 2014. Attestation (furocoumarin analysis) Orange tree flower from Morocco Biogreen (Citrus Aurantium Amara (Bitter Orange) Flower Extract).

Greentech. 2013. Regulatory data sheet Orange tree flower organic oily extract (sunflower) (Citrus Aurantium Amara Flower Extract).

Greentech. 2015. Manufacturing process Orange tree flower organic oily extract (sunflower) (Citrus Aurantium Amara Flower Extract).

Greentech. 2012. 26 Allergens listed Orange tree flower organic oily extract (sunflower) (Citrus Aurantium Amara Flower Extract).

Anonymous. 2015. Scan analysis report (UV-Vis) Orange tree flower organic oily extract (sunflower) (Citrus Aurantium Amara Flower Extract).

GREENTECH naturally

Biopôle Clermont-Limagne
63 360 Saint-Beauzire
Tel : 33 04 73 33 99 00
Fax : 33 04 73 33 91 32
e-mail : greentech@greentech.fr

FICHE REGLEMENTAIRE
REGULATORY DATA SHEET

ORANGER FLEUR DISTILLAT BIO 1:20 (SB)* / ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB)*

Référence produit / Product reference : 721032

* Matière première certifiée par ECOCERT Greenlife selon le référentiel ECOCERT des Cosmétiques Ecologiques et Biologiques disponible sur http://cosmetiques.ecocert.com / * Raw material certified by ECOCERT Greenlife according to the ECOCERT Standards for Natural and Organic Cosmetics available at http://cosmetics.ecocert.com

99,55% du total des ingrédients sont d'origine naturelle *98% du total des ingrédients sont issus de l'agriculture Biologique / 99,55% of the total of ingredients are of natural origin *98% of the total of ingredients proceed from Organic farming

Nom INCI CTFA / CTFA INCI name	Citrus Aurantium Amara (Bitter Orange) Flower Water
Nom INCI EU / EU INCI name	Citrus Aurantium Amara Flower Water
N° CAS / CAS number	72968-50-4
N° EINECS / EINECS number	277-143-2

COMPOSITION CENTESIMALE FINALE / FINAL CENTESIMAL COMPOSITION

Citrus Aurantium Amara Flower Water	>98%
Citric acid	<1%
Water	0.55%
Sodium benzoate	0.3%
Potassium sorbate	0.15%

REGLEMENTATION COSMETIQUE / COSMETIC REGULATION

REACH

Distillat de Fleurs d'Oranger exempté annexe V/nouvellement annexe II point 8 / Orange Tree Flower distillate exempted annex V/new annex II point 8

Sodium Benzoate et Potassium Sorbate pré-enregistrés REACH par le fournisseur/ Sodium Benzoate and Potassium Sorbate pre registered REACH by the supplier

Acide citrique enregistré par le fournisseur N°01-2119457026-42 / Citric acid registrated by the supplier N°01-2119457026-42

USA	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name
Canada	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name
Japan	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name
Australia	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name

DONNEES TOXICOLOGIQUES / TOXICOLOGICAL DATA

Irritation cutanée / Skin irritation	Non irritant / Not irritant	Produit testé à 10% / Product tested at 10%	Patch Test
Irritation occulaire / Eye irritation	Légèrement irritant / Slightly irritant	Produit testé à 10% / Product tested at 10%	Het cam CFIO Test

Jean-Yves BERTHON
PDG / CEO

Po / For and on behalf

Sabrina BOUTREUX
Chargée réglementaire

Version 2 (04/04/2014)

GREENTECH Biotechnologies

PROCEDE D'OBTENTION / MANUFACTURING PROCESS

Nom Commercial / Trade Name : Oranger Fleur Distillat Bio 1:20 (SB) (721032) / Orange Tree Flower Organic Distillate 1:20 (SB) (721032)

Distillation des fleurs d'Oranger / Orange Tree Flower Distillation

↓

Acidification et ajout du conservateur / Acidification anda dd of preservative

↓

Décontamination / Decontamination

Jean-Yves BERTHON
PDG / CEO

Po / For and on behalf

Carine BRYLAK
Chargée réglementaire

GREENTECH
Biopôle Clermont-Limagne - 63360 Saint-Beauzire - France
Tél : 04 73 33 99 00 - Fax : 04 73 33 91 32
E-mail : greentech@greentech.fr – web site : www.greentech.fr

EXPERTOX
TOXICOLOGICAL EXPERTISE AGENCY

SUBSTANCE SAFETY REPORT
« SAFETY ASSESSMENT »
GREE 13-06-2014 D7938

SAFETY ASSESSMENT ESTABLISHED BY THE EXPERT TOXICOLOGIST :
DR STEPHANE PIRNAY

BASED ON THE REGULATION (CE) N° 1223/2009 OF THE EUROPEAN PARLEMENT AND OF THE COUNCIL OF NOVEMBER 30TH 2009 AND IN ACCORDANCE WITH THE FORMALIZED QUALITY PROCESS BASED ON THE RECOMMANDATIONS OF THE SCCS'S (SCIENTIFIC COMMITTEE ON CONSUMER SAFETY) NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION 8TH EDITION DECEMBER 11TH 2012.

RAW MATERIAL :

ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)

LABORATORY : GREENTECH
Biopôle Clermont Limagne
63360 Saint Beauzire

DATE : 13/06/2014

Table

GREE 13-06-2014 D7938

➢ I – IDENTIFICATION OF THE RAW MATERIAL

➢ ADRESS OF THE FURNISHER

GREENTECH
Biopôle Clermont Limagne
63360 Saint Beauzire

➢ QUALI-QUANTITATIVE COMPOSITION

The qualitative-quantitative composition of the raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» is as follows:

CAS number	INCI name	CONCENTRATION	FUNCTION	CHEMICAL NAME	n° EINECS/ELINCS (Ec No.)	COMMERCIAL NAME
68916-04-1	Citrus aurantium amara flower water	98	/	/	/	/
77-92-9	Citric acid	1	/	/	201-069-1	/
7732-18-5	Water	0,55	/	/	231-791-2	/
532-32-1	Sodium benzoate	0,3			208-534-8	
24634-61-5	Potassium sorbate	0,15			246-376-1	

SEE ANNEX 1.

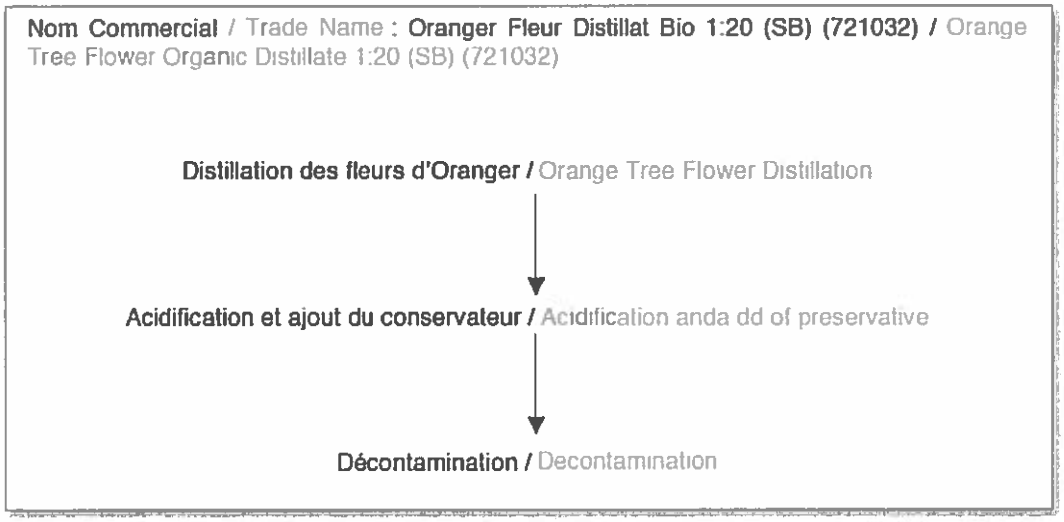
➢ PHYSICOCHEMICAL AND ORGANOLEPTIC CARACTERISTICS

Name	Liquid
Color	Colorless to yellow
Odor	Characteristic
Solubility 10% in water	Soluble
Solubility 10% in ethanol	Soluble
pH	3.4 - 4.0
Refraction index	1.330 - 1.380

➢ FUNCTION

PERFUMING

➢ PROCESS OF FABRICATION



➢ ORIGIN

GREENTECH certifies that the raw material «Orange Tree Flower Organic Distillate 1:20 (SB) (721032) » was vegetable origin (Organic Orange Tree flowers and citric acid) and synthetic origin (Sodium benzoate and potassium Sorbate).

Reference: Certificate GREENTECH, December 19th, 2013, Sabrina Boutreux.

➢ CHEMICAL COMPOSITION

We do not have information regarding the chemical composition of the raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)».

The supplier must provide evidence of compliance with the European Regulation 1223/2009 in force.

➢ PROFILE OF IMPURITIES (heavy metals, pesticides ...)

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» contains no VOCs (Volatile Organic Compounds).
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» does not contain CMR substances according to the Cosmetic Regulation EC1223/2009 and to the Proposition 65 of California.
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» is in accordance with restrictions on Glycol Ethers published in the Official Journal of November 23, 2005, decisions of 24 August 1999 of 5 May 2003 and 17 September 2004 and Directive 2009/6/EC.
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» does not contain formaldehyde or formaldehyde liberator.
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» does not contain nanoparticles (from nanotechnology) according to the EC Regulation 1223/2009.
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» is without GMO.
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» does not contain phthalates.
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» does not contain residual solvents.
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

GREE 13-06-2014 D7938

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» does not involve substances classified as SVHC "Substances of Very High Concern» according to REACH.
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» was not tested on animals.
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» is not part of the monograph of the European Pharmacopoeia 3rd reprint. Addendum 2001 "Minimizing the risk of transmission of infectious agents of animal spongiform encephalopathy in medical products."
The origin of our raw material is vegetable. The method of obtaining (extracting) does not involve products with a BSE risk.
Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

Allergen content

Nom Commercial / Trade Name : **ORANGER FLEUR DISTILLAT BIO 1:20 (SB) (721032) /**
ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)

***Détermination par CPG couplé MS** / Determination by CPG- MS*
***Température de l'injecteur 280** / Injecteur temperature 280*
Détection Mode scan 33-500 / Mode scan Detection 33-500

CONTROLE CONTENU	RESULTS
Allergènes par GC-MS selon Directive 2003/15/CE / Allergens by GC-MS (Directive 2003/15/CE)	
Amylcinnamal (n° CAS 122-40-7)	Non détecté / Not detected
Benzyl alcool (n° CAS 100-51-6)	Non détecté / Not detected
Cinnalylic alcool (n° CAS 104-54-1)	Non détecté / Not detected
Citral (n° CAS 5392-40-5)	Non détecté / Not detected
Eugénol (n° CAS 97-53-0)	Non détecté / Not detected
Hydroxycitronellal (n° CAS 107-75-5)	Non détecté / Not detected
Isoeugénol (n° CAS 97-54-1)	Non détecté / Not detected
Amylcinnamyl alcool (n° CAS 101-85-9)	Non détecté / Not detected
Benzyl salicylate (n° CAS 118-58-1)	Non détecté / Not detected
Cinnamal (n° CAS 104-55-2)	Non détecté / Not detected
Coumarin (n° CAS 91-64-5)	Non détecté / Not detected
Géraniol (n° CAS 106-24-1)	Non détecté / Not detected
Lyral (n° CAS 31906-04-4)	Non détecté / Not detected
Anise alcool (CAS 105-13-5)	Non détecté / Not detected
Benzyl cinnamate (n° CAS 103-41-3)	Non détecté / Not detected
Farnésol (n° CAS 4602-84-0)	Non détecté / Not detected
Lilial (n° CAS 80-54-6)	Non détecté / Not detected
Linalool (n° CAS 78-70-6)	Non détecté / Not detected
Benzyl benzoate (n° CAS 120-51-4)	Non détecté / Not detected
Citronellol (n° CAS 106-22-9)	Non détecté / Not detected
Hexylcinnamal (n° CAS 101-86-0)	Non détecté / Not detected
D-Limonène (n° CAS 5989-27-5)	Non détecté / Not detected
Oct-2-ynoate de méthyle (n° CAS 111-12-6)	Non détecté / Not detected
Alpha-isométhylionone (n° CAS 127-51-5)	Non détecté / Not detected
Evernia prunastri (n° CAS 90028-68-5)	Non détecté / Not detected
Evernia furfuracéa (n° CAS 90028-67-4)	

La limite de detection est de 2 ppm sauf pour Evernia prunastri et furfuracéa où la limite est de 20ppm / the detection limit is 2 ppm except for Evernia prunastri et furfuracéa, the detection limit is 20ppm

Pesticide content

GREENTECH certifies that the raw material «Orange Tree Flower Organic Distillate 1:20 SB (721032) » does not contain pesticides* (organo chlorus, phosphorus and organo sulfur pesticides). The Orange tree flower for this distillate are resulting from the Organic Farming.

Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

➢ TOXICOLOGICAL DATA

- CITRUS AURANTIUM AMARA FLOWER WATER :

*** Additional informations :** this substance is part of the GRAS list [http://www.libertynatural.com/info/eoinfo/FDA_EO_GRAS.htm 8/12/2011].

- CITRIC ACID :

*** NOAEL :**30 mg/kg/day

*** Ref. NOAEL :**1% DL50

*** Irritation of the digestive tractus :** May cause gastrointestinal tract irritation with nausea, vomiting, diarrhea. Excessive intake may cause erosion of teeth and hypocalcemia (calcium deficiency in blood). May affect behavior/central nervous system (tremor, convulsions, muscle contraction or spasticity) [Sciencelab.com 10/09/2005].

*** Cutaneous irritation :** Slightly hazardous in case of skin contact (irritant, sensitizer) [Sciencelab.com 10/09/2005].

*** Ocular irritation :** Causes moderate to severe eye irritations and possible injury [Sciencelab.com 10/09/2005].

*** Additional informations :** this substance is part of the GRAS list [FDA http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=184.1033&SearchTerm=citric%20acid (03/08/2011)].

*** Toxicity on the pulmonary system :** Hazardous in case of inhalation (lung irritant) [Sciencelab.com 10/09/2005].

*** Acute toxicity in animals :** LD50, lethal dose, rodent-rats : 3000 mg/kg [Sciencelab.com 10/09/2005].

- SODIUM BENZOATE :

*** NOAEL :**500 mg/kg/day

*** Ref. NOAEL :**[European commission, scientific committee on food, Opinion of the Scientific Committee on Food on Benzoic acid and its salts (expressed on 24 September 2002), 15/03/2011].

*** Population at risk :** The infants with a low body weight, have immature livers that are unable to metabolize benzoate and hippurate. The combination of sodium benzoate and sodium phenylacetate should be administered to infants with low body weight, provided that the benefits of treatment outweigh the risks [The United States Pharmacopeial Convention; the United States Pharmacopeia Distribution d' Informations (USP DI); Give drugs to Information for the Professional of medical Services the 12th writer, V.1 p. 2475 (1992)].

*** Reprotoxicity :** TDLo - Lowest published toxic dose by oral on rodent, rat : 44 mg/kg, female 1-22 day(s) after conception. Specific developmental abnormalities - homeostasis - eye/ear - musculoskeletal system. [Eisei Shikenjo Hokoku. Bulletin of the Institute of Hygienic Sciences. (Kokuritsu Eisei Shikenjo Kagaku, 18-1 Bushitsu Johobu, Setagaya-ku, Tokyo 158, Japan) V.1- 1886- : (96),47,1978].

*** Cutaneous irritation :** Test: irritation, skin not covered, administration on human skin 10%/1h [Dermatologica. (S. Karger Pub., Inc., 79 Fifth Ave., New York, NY 10003) V.79- 1939 - : 26,734,1984].

*** Additional informations :** Maximum concentration in ready for use preparation : 2,5 % for rince-off products, except oral care products ; 1,7 % for oral care products ; 0,5 % for leave-on products. [Annex 5 of the european legislation of cosmetic products : list of preservatives allowed in cosmetic products].

*** Subacute and Chronic toxicity :** TDLo - Lowest published toxic dose, oral, rodent - rat : 35200 mg/kg/22days (intermittent). Behavioral - food intake. Nutritional and Gross Metabolic - weight loss or decreased weight gain, related to Chronic Data - death [U.S. Environmental Protection Agency; High Production Volume (HPV) Challenge; Benzyl Derivatives.pdf (http://www.epa.gov/HPV/pubs/summaries/viewsrch.htm) : 2001].

*** CIR conclusion :** Considered as safe of use in all cosmetic formulations up to 5%; insufficient data to support safety in products which are inhaled [IJT 20(S3):23-50, 2001].

*** Genotoxicity :** Sister chromatid exchange human lymphocyte : 8 mmol/L/72h [Food and Chemical Toxicology (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.20- 1982 - 46,2390,2008].

*** Acute toxicity in animals :** LD50 - Lethal dose, 50 percent kill, by oral, on rodent - rat : 4070 mg/kg. Details of toxic effects other than the lethal dose value have not been reported yet [Journal of Industrial Hygiene and Toxicology. (Cambridge, MA) V.18-31, 1936-49. For publisher information, see AEHLAU. 30,63,1948].

- POTASSIUM SORBATE :

*** NOAEL :**66 mg/kg/day

*** Ref. NOAEL :**1% DL50

*** Packaging :** Migrate towards material food of packing [N.I. Dangerous properties of industrial materials. 4th ED. New York: Van Nostrand Reinhold, 1975. , P. 1054].

*** Additional informations :** this substance is part of the GRAS list [FDA http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.3640&SearchTerm=potassium%20sorbate (03/08/2011)].

*** Acute toxicity in animals :** LD50 - lethal dose, 50% kill, oral, rodent-rat : 6650 mg/kg / LD50 - lethal dose, 50% kill, dermal, rodent-rabbit : 7940 mg/kg [Eastman Product Safety and Stewardship, MSDS, 01/23/1998, 8p (07/11/2011)].

*** Toxicity on the pulmonary system :** Low hazard [Eastman Product Safety and Stewardship, MSDS, 01/23/1998, 8p (07/11/2011)].

*** Cutaneous irritation :** Prolonged or repeated contact may cause irritation [Eastman Product Safety and Stewardship, MSDS, 01/23/1998, 8p (07/11/2011)].

*** Ocular irritation :** Can cause an irritation of the eyes [Furia, T.E. (ED.). Additive CRC Handbook of Food. 2nd ED. Cleveland: The Chemical Rubber Co., 1972, p. 137].

*** Irritation of the digestive tractus :** Expected to be a low ingestion hazard [Eastman Product Safety and Stewardship, MSDS, 01/23/1998, 8p (07/11/2011)].

*** CIR conclusion :** Considered as safe of use up to 7 %. [JACT 7(6):837-80, 1988 confirmed 04/06].

*** Subacute and Chronic toxicity :** TDLo - lower toxic amount published by dose oral on rodent - rat : 683 g/kg/13weeks (continuous). Behavior - food supply (animals) Kidney/ureter/bladder - modifications of weight, bladder. [Nutrition Meeting Carryforward Series. (Rome, Italy) No. - 57, 1948-77. Discontinued : 40,1,1967].

➢ REGULATORY INFORMATION IN TERMS OF CLASSIFICATION

The raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» is in compliance with the appendices of the Cosmetic Directive 76 / 768 / EEC modified and the appendices of the cosmetic Regulation EC 1223/2009 in force.

Reference: Certificate GREENTECH, July 11th, 2013, Noémie Moretton.

➢ STABILITY TESTS

We do not have information regarding the stability of raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)».

The supplier shall demonstrate the stability of the product.

➢ MICROBIOLOGICAL QUALITY OF COSMETIC INGREDIENT

Germes aérobies totaux / Total germs (ufc/mL - cfu/mL)	GT100	<100
Levures et moisissures / Yeasts and moulds (ufc/mL - cfu/mL)	GT101	<100
Enterobactéries / Enterobacteria (ufc/mL - cfu/mL)	GT102	Absence

Reference: Specification sheet GREENTECH, Doc 06-I Ind I, product reference 721032.

➢ TOXICOLOGICAL TESTS

* Assessment of the skin irritant potential of the product ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032) by the use of a PATCH test under the conditions of an occlusive patch test procedure, 24h of application, conducted in 11 subjects. Under the experimental condotions adopted, the product ORANGER FLEURS DISTILLAT BIO 1:20 SB 10% diluted appeared **NOT IRRITANT** to skin.

* Assessment of the ocular irritant potential of the product ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032) by HET CAM and CFIO tests. With regard to the results obtained during both assay, and in compliance with the classification criteria retained, the test product ORANGER FLEURS DISTILLAT BIO 1:20 SB must be considered as **SLIGHTLY IRRITANT TO EYE.**

Reference: toxicological tests ORANGER FLEURS DISTILLAT BIO 1:20 SB Test done by BIOHC In December 2007, GREENTECH oranger I-20 DIS Bio IOC.

➢ II – EVALUATION OF THE RAW MATERIAL

➢ DATA OF HUMAN EXPOSITION

Quantity of product used by application (Q)	18670 mg
Percentage of raw material in formula	0,2%
Frequency of application	Once a day
Parts of the exposed body	Body
Concerned population	Adults, children over 3 years old
Possible rinsing	Yes
Time of application	few seconds

SEE ANNEX 2.

➢ CALCULATION OF MARGINS OF SECURITY

In order to exclude a possibility of systemic toxicity, the security margin of each ingredient should be **higher than 100 in adults, higher than 150 in children and higher than 230 in babies.** The security margin is defined as the ratio between the maximal tolerated dose without side effects (NOAEL) and the daily dose of systemic exposition, both expressed in mg/Kg of weight. The absorbed dose (in mg/Kg of weight) is divided by a mean weight of 60 kgs (adults), 50kgs (children) or 5 kgs (babies).

In accordance with the IKW proposals, the NOAEL used for the calculation of the margin security is refered to the results of sub acute or chronic toxicological tests when those data exist.

MS (margin of security) = NOAEL/SED

SEE ANNEX 3.

For ingredients for which only general toxicological data are known (as plant extracts) and for which no sub acute or chronic toxicity data are reported, a NOAEL of 20mg/Kg was taken into account *(A. Bulgheroni et coll. Estimation of acute oral toxicity using the No Observed Adverse Effect Level (NOAEL) from the 28 day repeated dose toxicity studies in rats. Regulatory Toxicology and Pharmacology. 53 (1); 2009: 16-19).*

➢ CONCLUSION

Considering :

- Lack of skin irritation potential,
- The safety margins,

Given the margin of safety and the assumption that adults, children over three years old use maximum 18670 mg per day of product: the use of raw material «ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)» should not pose problems of toxicity for a maximum of 100%/day in adults and in children over 3 years old for body rinse-off products.

If this product proves thereafter at the origin of significant undesirable reactions, the undersigned will be informed in order to consider a possible revaluation.

The present certificate is valid only for use in conformity with the recommendations of the manufacturer, and for the examined formula, any other use or modification of the formulation makes null and void the present certificate

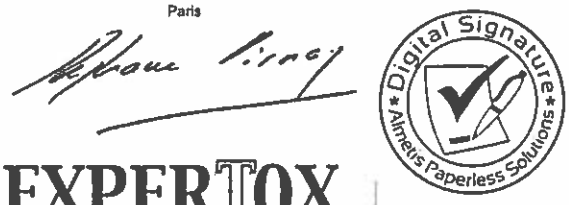
Qualifications of the toxicologist:

Stephane PIRNAY, Pharm.D., Ph.D. in Toxicology, EUROTOX registered, Recipient of the Award from the national Academy of Pharmacy, Recipient of the Award from the University René Descartes Paris V, Former Assistant Professor of the University of Paris V in Toxicology, Former Fellow at NIH, USA, Expert at the Court of Appeal of Paris, Expert Toxicologist of the agency EXPERTOX.

June 13th 2014

S. PIRNAY

Paris



EXPERTOX
CABINET D'EXPERTISES TOXICOLOGIQUES

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ANNEX 1 –QUALI-QUANTITATIVE COMPOSITION

CAS No	INCI name	Concentration	Function	Chemical name	EINECS/ELINCS No	Commercial name
68916-04-1	CITRUS AURANTIUM AMARA FLOWER WATER	98	/	/	/	/
77-92-9	CITRIC ACID	1	/	/	201-069-1	/
7732-18-5	WATER	0,55	/	/	231-791-2	/
532-32-1	SODIUM BENZOATE	0,3	/	/	208-534-8	/
24634-61-5	POTASSIUM SORBATE	0,15	/	/	246-376-1	/

ANNEX 2 – HUMAN EXPOSITION DATA

Commercial Name	C (%)	Q (mg)	F (jour^{-1})	R (%)	PT (%)	DES (mg/jr)	DES in adults (mg/kg/jr)	DES in children (mg/kg/jr)
CITRUS AURANTIUM AMARA FLOWER WATER	98	18670	1	0,02	100	3,6593	0,060988667	0,182966
CITRIC ACID	1	18670	1	0,02	10	0,0037	6,22333E-05	0,0001867
WATER	0,55	18670	1	0,02	100	0,0205	0,000342283	0,00102685
SODIUM BENZOATE	0,3	18670	1	0,02	10	0,0011	0,00001867	0,00005601
POTASSIUM SORBATE	0,15	18670	1	0,02	10	0,0006	0,000009335	0,000028005

ANNEX 3 – CALCULATION OF MARGINS OF SECURITY

Commercial Name	DES in adults (mg/kg/jr)	DES in children (mg/kg/j	NOAEL	MS in adults	MS in children
CITRUS AURANTIUM AMARA FLOWER WATER	0,060988667	0,182966	GRAS	-	-
CITRIC ACID	6,22333E-05	0,0001867	30	482057	160686
WATER	0,000342283	0,00102685	GRAS	-	-
SODIUM BENZOATE	0,00001867	0,00005601	500	26780932	8926977
POTASSIUM SORBATE	0,000009335	0,000028005	66	7070166	2356722

GREENTECH naturally

DOSAGE DES 26 ALLERGENES / 26th ALLERGENS LISTED

Nom Commercial / Trade Name : ORANGER FLEUR DISTILLAT BIO 1:20 (SB) (721032) / ORANGE TREE FLOWER ORGANIC DISTILLATE 1:20 (SB) (721032)

Determination par CPG couplé MS / Determination by CPG- MS
Température de l'injecteur 280 / Injecteur temperature 280
Détection Mode scan 33-500 / Mode scan Detection 33-500

CONTROLE CONTENU	RESULTS
Allergènes par GC-MS selon Directive 2003/15/CE / Allergens by GC-MS (Directive 2003/15/CE)	
Amylcinnamal (n° CAS 122-40-7)	Non détecté / Not detected
Benzyl alcool (n° CAS 100-51-6)	Non détecté / Not detected
Cinnalylic alcool (n° CAS 104-54-1)	Non détecté / Not detected
Citral (n° CAS 5392-40-5)	Non détecté / Not detected
Eugénol (n° CAS 97-53-0)	Non détecté / Not detected
Hydroxycitronellal (n° CAS 107-75-5)	Non détecté / Not detected
Isoeugénol (n° CAS 97-54-1)	Non détecté / Not detected
Amylcinnamyl alcool (n° CAS 101-85-9)	Non détecté / Not detected
Benzyl salicylate (n° CAS 118-58-1)	Non détecté / Not detected
Cinnamal (n° CAS 104-55-2)	Non détecté / Not detected
Coumarin (n° CAS 91-64-5)	Non détecté / Not detected
Géraniol (n° CAS 106-24-1)	Non détecté / Not detected
Lyral (n° CAS 31906-04-4)	Non détecté / Not detected
Anise alcool (CAS 105-13-5)	Non détecté / Not detected
Benzyl cinnamate (n° CAS 103-41-3)	Non détecté / Not detected
Farnésol (n° CAS 4602-84-0)	Non détecté / Not detected
Lilial (n° CAS 80-54-6)	Non détecté / Not detected
Linalool (n° CAS 78-70-6)	Non détecté / Not detected
Benzyl benzoate (n° CAS 120-51-4)	Non détecté / Not detected
Citronellol (n° CAS 106-22-9)	Non détecté / Not detected
Hexylcinnamal (n° CAS 101-86-0)	Non détecté / Not detected
D-Limonène (n° CAS 5989-27-5)	Non détecté / Not detected
Oct-2-ynoate de méthyle (n° CAS 111-12-6)	Non détecté / Not detected
Alpha-isométhylionone (n° CAS 127-51-5)	Non détecté / Not detected
Evernia prunastri (n° CAS 90028-68-5)	Non détecté / Not detected
Evernia furfuracéa (n° CAS 90028-67-4)	

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La limite de detection est de 2 ppm sauf pour Evernia prunastri et furfuracéa où la limite est de 20ppm / the detection limit is 2 ppm except for Evernia prunastri et furfuracéa, the detection limit is 20ppm.

Jean-Yves BERTHON
PDG / CEO

Po / For and on behalf

Sabrina BOUTREUX
Chargée réglementaire

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Version 1 (30/06/2014)

ATTESTATION

Je soussigné, Jean-Yves BERTHON, PDG de la S.A. GREENTECH certifie que la matière première « ORANGER FLEUR DISTILLAT BIO 1 :20 (SB) (721032) » ne contient pas de furocoumarine : bergapten, bergaptol, bergamothine, citropten, coumarine, imperatorine, isoemperatorine, isopimpinelline, ombelliferone, scopolettine (limite de détection : 10ppm).

Mr. Jean-Yves BERTHON, CEO of S.A. GREENTECH certifies that the raw material « ORANGER TREE FLOWER ORGANIC DISTILLATE 1 :20 (SB) (721032)» does not contain furocoumarin : bergapten, bergaptol, bergamothine, citropten, coumarine, imperatorine, isoemperatorine, isopimpinelline, ombelliferone, scopolettine (detection limit: 10ppm).

Saint-Beauzire,

Le 30 Juin 2014 / June 30th, 2014

Jean-Yves BERTHON
PDG / CEO

Po / For and on behalf

Carine BRYLAK
Chargée réglementaire

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TOXICOLOGICAL TESTS

ORANGER FLEURS DISTILLAT BIO 1:20 SB

Test done by BIOHC
In December 2007

GREENTECH S.A.

TOXICOLOGICAL TESTS BY ALTERNATIVE METHODS

ORANGER FLEURS DISTILLAT BIO 1:20 SB

Citrus Aurantium Amara (Bitter Orange) Flower water > 98 %
citric Acid, Water, sodium Benzoate, Potassium Sorbate

Evaluation of cutaneous irritation (patch test)

The study was performed according to the protocol referenced HICV of 31/07/2000.

12 volunteers (9 females and 3 males), from 25 to 64 years old were enrolled.

The product was applied 10% diluted in distilled water, on the upper back of the volunteers during 24 hours.

The area to be patched is examined prior to the application in order to verify the absence of dermatological disease. The occlusive epicutaneous test technique involves the use of aluminium cups of 8mm in diameter and 20 microliters in volume. Each cup covers about a 50mm area. They are affixed by two on an adhesive tape.
The patch is applied on the upper back of every subject and then covered with an adhesive tape. The product is left in contact with the skin during 24 hours.
Two control cups are applied in parallel. One receives a 1 % solution of sodium lauryl sulfate, the other receives distilled water.
The test product is generally applied as supplied.

After 30 minutes to 1 hour after patch removal, the panelist are subjected to a cutaneous examination. The aim of this examination is to point out any objective signs of irritation.

Six parameters (Erythema, Edema, Vesicles, Cutaneous Dryness, Wrinkling, Glazing) will be researched and scored according to a 5 level score scale (0 through 4).

Depending on the index obtained, the product will be classed according to the following table

Index HICV	CLASSIFICATION
below 0.1	No irritant
From 0.1 to less than 0.3	Slightly irritant
From 0.3 to less than 0.5	Moderately irritant
Higher than 0.5	Irritant

A reading was performed 30 minutes after patch removal and 24 hours later in order to assess possible delayed reactions.

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One subject developed a very slight erythema to negative control so he was excluded from the interpretation of results.

The irritation index was calculated from the 11 subjects who were retained.

On test product site, no skin reaction was found on 9 subjects and very slight not lasting erythema was found on 2 subjects.

The score attributed allow to obtain an irritation index of: 0,04 which would class the test product as not irritant.

To conclude, under the experimental condotions adopted, the product ORANGER FLEURS DISTILLAT BIO 1:20 SB 10% diluted appeared not irritant to skin.

Evaluation of ocular irritation (HET-CAM / CFIO tests)

The studies were performed according to the experimental protocol referenced IOP of 11/23/2005.

The potential irritancy of a cosmetic compound is detected, on the one hand, by observing adverse changes which occur in the chorionallantoic membrane of the egg after exposure to test product (HET CAM assay) and, on the other hand by recording cytotoxicity obtained after contact with cornea fibroblasts (CFIO assay). This assay is proposed as an alternative test to the Draize Rabbit Eye test to assess the occular irritancy potential of cosmetics and toiletries.

The results of a previous study on 107 cosmetics and toiletries have shown a good correlation between both alternative methods and the Draize test and the simultaneous use of both methods CFIO and HET CAM gave a satisfactory assessment of the ocular irritation potential of the cosmetics and toiletries. As there were no false negatives common to both methods, the risk of underestimating the occular irritation potential was avoided.

Chorion-allantoic membrane assay

The ocular irritating potential is determined on embryonar eggs of White Leghorn of chicken. The product is put on the chorioallantoic membrane.

0,3 ml of the test product was applied on the CAM and eliminated by irrigation with 5 ml of saline solution, after 20 seconds.

The CAM is observed through a magnifying glass 30 seconds, then 2 and 5 minutes after application. This macroscopic examination consists in monitoring the appearance of the following phenomena : hyperaemia, haemorrhage, coagulation.

The observations are scored as fllows depending on the time for each reaction to occur :

APPARITION TIMES	HYPERAEMIA	HAEMORRHAGE	COAGULATION
30 secondes	5	7	9
2 minutes	3	5	7
5 minutes	1	3	5

The score obtaines for the 3 parameters are summed to give the irritation index for each egg. The mean score is calculated to obtain the primary irritancy index (IP-CAM).

The table below allows to classify the product depending on the index obtained :

Medium score	Classification
0 to ≤ 0.9	Pratically not irritant
1 to ≤ 4.9	Slightly irritant
5 to ≤ 8.9	Moderately irritant
9 to ≤ 21	Very irritant

The results obtained with « Oranger fleurs Distillat Bio 1:20 SB» are referenced in the following table:

Assay	Concentration	Score/egg	IP-CAM	Classification
Oranger fleurs DIS Bio1:20 SB	10% (in saline)	0/0/0/0	0,00	Practically not irritant

The positive control (3% SLS) tested in parallel induced clear irritating phenomena on every membrane and confirmed the good reactivity of eggs.

The results of the chorio-allantoic membrane assay allowed to obtain an IP-CAM of 0,00 which should class the tested product as **practically not irritant.**

CFIO test

(in Hank's Balanced Salt solution)

The product was studied 10% diluted. Cell viability was assessed at the end of the study by a MTT test.

After three contact times, cell viability intreated and control plates is evaluated by a colorimetric method, either MTT or neutral Red test.

After an incubation period of 2 to 3 hours with MTT or NR solution, the absorbance of the resulting coloured solution is measured at 570 nm(MTT) or 540nm (NR) using a microplate reader (Dynatech MR 5000).

From the optical densities (OD) measured for each contact time, a cytotoxicity percentage is calculated according to the formula :

$$\%(t)= ((OD_{CO}-OD_{TR})/OD_{CO})x100$$

where

OD_{CO}= mean « control » OD
OD_{TR}= mean « treated » OD

A mean cytotoxicity Index (MCI) is calculated according to the formula :

$$MCI= (\%(30mn)+0.5x\%(1h)+0.125x\%(4h))/3$$

From the value of MCI, an equivalent ocular irritation index (IO eq) is calculating according to the equations established from results obtained from in vivo/in vitro correlations studies.

$$OIeq = 0,922 \times MCI + 2,787$$

The IOeq index obtained allows to classify the test product according to the classification proposed by the « Journal de la République Française » dated July the 10th, 1992, for assessmnt of primary ocular irritation

IOeq	CLASSIFICATION
IOeq ≤15	Slightly Irritant
15< IOeq≤30	Moderately Irritant
30< IOeq ≤50	Irritant
50< IOeq	Very Irritant

The results obtained with « Oranger fleurs Distillat Bio 1:20 SB » are referenced in the following table

	Control	Contact 30min	Contact 1hour	Contact 4 hour
D.O.1 (O.D.1)	0,533	0,583	0,629	0,650
D.O.2 (O.D.2)	0,578	0,554	0,629	0,621
D.O.3 (O.D.3)	0,548	0,554	0,610	0,621
Mean	**0,553**	**0,564**	**0,623**	**0,631**
Viability (%)	**100**	**102**	**113**	**114**
Cytotoxicity (%)	**0**	**0**	**0**	**0**
Mean cytotoxicity index (IMC-c)	**0,0**			

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Ocular irritation index (IOeq)	**2,8 Slightly irritant**

The calculated scores MCI = 0,0 and IOeq = 2,8 would class the product as slightly irritant.

Taking into account the complementary results of these two In Vitro methos, the occular irritation potential of the test product is calculated according to the following table :

	Oleq		
IP-CAM	*0 to 15*	*15 to 30*	*>30*
0 to 4,9	Slightly irritant	Moderately iritant	Irritant / very irritant
5 to 8,9	Moderately irritant	Moerately irritant	Irritant / very irritant
9 to 21	Irritant / very irritant	Irritant / very irritant	Irritant / very irritant

With regard to the results obtained during both assay, and in compliance with the classification criteria retained, the test product « ORANGER FLEURS DISTILLAT BIO 1:20 SB » must be considered as slightly irritant to eye.

GREENTECH Biotechnologies

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FICHE REGLEMENTAIRE
REGULATORY DATA SHEET

ORANGER FLEUR DU MAROC BIOGREEN (SB) / ORANGE TREE FLOWER FROM MOROCCO BIOGREEN (SB)

Référence produit / Product reference : 400283

Nom INCI CTFA / CTFA INCI name	Water, Glycerin, Citrus Aurantium Amara (Bitter Orange) Flower Extract
Nom INCI EU / EU INCI name	Aqua, Glycerin, Citrus Aurantium Amara Flower Extract
N° CAS / CAS number	7732-18-5, 56-81-5, 72968-50-4
N° EINECS / EINECS number	231-791-2, 200-289-5, 277-143-2

COMPOSITION CENTESIMALE FINALE / FINAL CENTESIMAL COMPOSITION

Water	73.05-74.05%
Glycerin	>23%
Citrus Aurantium Amara Flower Extract	1.5-2.5%
Citric Acid	<1.0%
Sodium Benzoate	0.3%
Potassium sorbate	0.15%

REGLEMENTATION COSMETIQUE / COSMETIC REGULATION

REACH	Extrait d'Oranger exempté annexe V/nouvellement annexe II point 8 / Orange tree extract exempted annex V/new annex II point 8
	Glycérine exemptée annexe V/nouvellement annexe II point 9 / Glycerin exempted annexe V/new annex II point 9
	Acide citrique enregistré REACH n° 01-2119457026-42/ Citric Acid registered REACH n° 01-2119457026-42
	Sodium Benzoate et Potassium Sorbate pré-enregistrés REACH par le fournisseur/ Sodium Benzoate and Potassium Sorbate pre registered REACH by the supplier
USA	Autorisé en cosmétique avec le nom INCI CTFA et le n° CAS / Approved for use in cosmetic with INCI CTFA name and CAS number
Canada	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name

Japan	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name
Australia	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name
China	Autorisé pour un usage cosmétique avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name

Jean-Yves BERTHON
PDG / CEO

Po / For and on behalf

Noémie MORETTON
Chargée réglementaire

Version 3 (10/10/13)

GREENTECH naturally

PROCEDE D'OBTENTION / MANUFACTURING PROCESS

Nom Commercial / Trade Name : **Oranger Fleur Du Maroc Biogreen SB** / Orange Tree Flower From Morocco Biogreen SB

Macération dans l'eau chaude des Fleurs d'Oranger / Maceration into hot water of Oranger Tree Flowers

↓

Clarification / Clarification

↓

Ajout de la glycérine et des conservateurs / Add of glycerin and preservative

↓

Filtration / Filtration

Jean-Yves BERTHON
PDG / CEO

Po / For and on behalf

Carine BRYLAK
Réglementaire Greentech

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BIOTECHNOLOGIES
GREENTECH

CERTIFICAT CMR / CMR CERTIFICATE

Nom Commercial / Trade Name : ORANGER FLEUR DU MAROC BIOGREEN (SB) (400283) / ORANGE TREE FLOWER FROM MOROCCO BIOGREEN (SB) (400283)

Substances CMR / CMR Substances	CAS	RESULTATS / RESULTS	Limite de quantification / quantification limit
Acétaldehyde*	75-07-0	27 ppm	10 ppm

*Trace techniquement inévitable selon les BPF / Technically unavoidable trace according GMP

Analyse réalisée sur le lot CIA1409L1-BG / Analysis done on the batch CIA1409L1-BG

Jean-Yves BERTHON
PDG / CEO

Po / For and on behalf

Noémie MORETTON
Chargée réglementaire / Regulatory Department

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BIOTECHNOLOGIES
GREENTECH

DOSAGE DES 26 ALLERGENES / 26th ALLERGENS LISTED

Nom Commercial / Trade Name : **ORANGER FLEUR DU MAROC BIOGREEN (SB) (400283) / ORANGE TREE FLOWER FROM MOROCCO BIOGREEN (SB) (400283)**

Analyse effectuée sur le lot / Analysis done on the batch : **CIA1409L1-BG**
Determination par CPG couplé MS / Determination by CPG- MS
Température de l'injecteur 280 / Injecteur temperature 280
Détection Mode scan 33-500 / Mode scan Detection 33-500

CONTROLE CONTENU	RESULTS
Allergènes par GC-MS selon Directive 2003/15/CE / Allergens by GC-MS (Directive 2003/15/CE)	
Amylcinnamal (n° CAS 122-40-7)	Non détecté / Not detected
Benzyl alcool (n° CAS 100-51-6)	Non détecté / Not detected
Cinnalylic alcool (n° CAS 104-54-1)	Non détecté / Not detected
Citral (n° CAS 5392-40-5)	Non détecté / Not detected
Eugénol (n° CAS 97-53-0)	Non détecté / Not detected
Hydroxycitronellal (n° CAS 107-75-5)	Non détecté / Not detected
Isoeugénol (n° CAS 97-54-1)	Non détecté / Not detected
Amylcinnamyl alcool (n° CAS 101-85-9)	Non détecté / Not detected
Benzyl salicylate (n° CAS 118-58-1)	Non détecté / Not detected
Cinnamal (n° CAS 104-55-2)	Non détecté / Not detected
Coumarin (n° CAS 91-64-5)	Non détecté / Not detected
Géraniol (n° CAS 106-24-1)	Non détecté / Not detected
Lyral (n° CAS 31906-04-4)	Non détecté / Not detected
Anise alcool (CAS 105-13-5)	Non détecté / Not detected
Benzyl cinnamate (n° CAS 103-41-3)	Non détecté / Not detected
Farnésol (n° CAS 4602-84-0)	Non détecté / Not detected
Lilial (n° CAS 80-54-6)	Non détecté / Not detected
Linalool (n° CAS 78-70-6)	Non détecté / Not detected
Benzyl benzoate (n° CAS 120-51-4)	Non détecté / Not detected
Citronellol (n° CAS 106-22-9)	Non détecté / Not detected
Hexylcinnamal (n° CAS 101-86-0)	Non détecté / Not detected
D-Limonène (n° CAS 5989-27-5)	Non détecté / Not detected
Oct-2-ynoate de méthyle (n° CAS 111-12-6)	Non détecté / Not detected
Alpha-isométhylionone (n° CAS 127-51-5)	Non détecté / Not detected
Evernia prunastri (n° CAS 90028-68-5)	Non détecté / Not detected
Evernia furfuracéa (n° CAS 90028-67-4)	

La limite de detection est de 2 ppm sauf pour Evernia prunastri et furfuracéa où la limite est de 5ppm / the detection limit is 2 ppm except for Evernia prunastri et furfuracéa, the detection limit is 5ppm.

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Jean-Yves BERTHON
PDG / CEO
Po / For and on behalf

Noémie MORETTON
Chargée réglementaire / Regulatory affairs

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Version 3 (18/02/2014)

ATTESTATION

Je soussigné, Jean-Yves BERTHON, PDG de la S.A. GREENTECH certifie que la matière première « ORANGER FLEUR EXTRAIT HUILEUX BIO (TOURNESOL) (510033) » ne contient pas de furocoumarines : Bergapten et 8-Methoxypsoralen (limite de détection :10ppm).

Mr. Jean-Yves BERTHON, CEO of S.A. GREENTECH certifies that the raw material « ORANGE TREE FLOWER ORGANIC OILY EXTRACT (SUNFLOWER) (510033) » does not contain furocoumarines : Bergapten and 8-Methoxypsoralen (limit of detection : 10ppm).

Saint-Beauzire,

Le 18 Février 2014 / February 18th, 2014

Jean-Yves BERTHON
PDG / CEOscopoletine

Po / For and on behalf

Carine BRYLAK
Chargée réglementaire

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FICHE REGLEMENTAIRE
REGULATORY DATA SHEET

ORANGER FLEUR EXTAIT HUILEUX BIO (TOURNESOL) / ORANGE TREE FLOWER ORGANIC OILY EXTRACT (SUNFLOWER)

Référence produit / Product reference : 510033

* Matière première certifiée par ECOCERT Greenlife selon le référentiel ECOCERT des Cosmétiques Ecologiques et Biologiques disponible sur http://cosmetiques.ecocert.com / * Raw material certified by ECOCERT Greenlife according to the ECOCERT Standards for Natural and Organic Cosmetics available at http://cosmetics.ecocert.com

100% du total des ingrédients sont d'origine naturelle *100% du total des ingrédients sont issus de l'agriculture Biologique / 100% of the total of ingredients are of natural origin *100% of the total of ingredients proceed from Organic farming

Nom INCI CTFA / CTFA INCI name	Helianthus Annuus (Sunflower) Seed Oil, Citrus Aurantium Amara (Bitter Orange) Flower Extract
Nom INCI EU / EU INCI name	Helianthus Annuus Seed Oil, Citrus Aurantium Amara Flower Extract
N° CAS / CAS number	8001-21-6, 72968-50-4
N° EINECS / EINECS number	232-273-9, 277-143-2

COMPOSITION CENTESIMALE FINALE / FINAL CENTESIMAL COMPOSITION

Helianthus Annuus Seed Oil	99.5-99.9%
Citrus Aurantium Amara Flower Extract	0.1-0.5%

REGLEMENTATION COSMETIQUE / COSMETIC REGULATION

REACH	Extrait de fleurs d'oranger non concernée quantité produite par an inférieure à 1 tonne (matière sèche) / Orange tree flower extract not concerned quantity produced per year lower than 1 ton (dry matter)
	Huile de tournesol exemptée annexe V/nouvellement annexe II point 9 / Sunflower oil exempted annexe V/new annex II point 9
USA	Autorisé en cosmétique avec le nom INCI CTFA et le n° CAS / Approved for use in cosmetic with INCI CTFA name and CAS number
Canada	Autorisé pour un usage cosmétique avec le nom INCI CTFA avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name
Japan	Autorisé pour un usage cosmétique avec le nom INCI CTFA avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name

Australia	Autorisé pour un usage cosmétique avec le nom INCI CTFA avec le nom INCI CTFA / Approved for use in cosmetic with INCI CTFA name

Jean-Yves BERTHON
PDG / CEO

Po / For and on behalf

Sabrina BOUTREUX
Chargée réglementaire

Version 3 (03/07/2015)

BIOTECHNOLOGIES
GREENTECH

PROCEDE D'OBTENTION / MANUFACTURING PROCESS

Nom Commercial / Trade Name : ORANGER FLEUR EXTRAIT HUILEUX BIO (TOURNESOL) (510033) / ORANGE TREE FLOWER ORGANIC OILY EXTRACT (SUNFLOWER) (510033)

Extraction des Fleurs d'Oranger Bio dans l'huile de Tournesol Bio /
Extraction of Organic Orange Tree Flower into the Organic Sunflower Oil

↓

Clarification / Clarification

↓

Décontamination / Decontamination

Jean-Yves BERTHON
PDG / CEO

Po / For and on behalf

Carine BRYLAK
Chargée réglementaire

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GREENTECH naturally

DOSAGE DES 26 ALLERGENES / 26th ALLERGENS LISTED

Nom Commercial / Trade Name : Oranger Fleur Extrait Huileux Bio (Tournesol) / Orange Tree Flower Organic Oily Extract (Sunflower)

Determination par CPG couplé MS / Determination by CPG- MS
Température de l'injecteur 280 / Injecteur temperature 280
Détection Mode scan 33-500 / Mode scan Detection 33-500

CONTROLE CONTENU	RESULTS
Allergènes par GC-MS selon Directive 2003/15/CE / Allergens by GC-MS (Directive 2003/15/CE)	
Amylcinnamal (n° CAS 122-40-7)	Non détecté / Not detected
Benzyl alcool (n° CAS 100-51-6)	Non détecté / Not detected
Cinnalylic alcool (n° CAS 104-54-1)	Non détecté / Not detected
Citral (n° CAS 5392-40-5)	Non détecté / Not detected
Eugénol (n° CAS 97-53-0)	Non détecté / Not detected
Hydroxycitronellal (n° CAS 107-75-5)	Non détecté / Not detected
Isoeugénol (n° CAS 97-54-1)	Non détecté / Not detected
Amylcinnamyl alcool (n° CAS 101-85-9)	Non détecté / Not detected
Benzyl salicylate (n° CAS 118-58-1)	Non détecté / Not detected
Cinnamal (n° CAS 104-55-2)	Non détecté / Not detected
Coumarin (n° CAS 91-64-5)	Non détecté / Not detected
Géraniol (n° CAS 106-24-1)	Non détecté / Not detected
Lyral (n° CAS 31906-04-4)	Non détecté / Not detected
Anise alcool (CAS 105-13-5)	Non détecté / Not detected
Benzyl cinnamate (n° CAS 103-41-3)	Non détecté / Not detected
Farnésol (n° CAS 4602-84-0)	Non détecté / Not detected
Lilial (n° CAS 80-54-6)	Non détecté / Not detected
Linalool (n° CAS 78-70-6)	Non détecté / Not detected
Benzyl benzoate (n° CAS 120-51-4)	Non détecté / Not detected
Citronellol (n° CAS 106-22-9)	Non détecté / Not detected
Hexylcinnamal (n° CAS 101-86-0)	Non détecté / Not detected
D-Limonène (n° CAS 5989-27-5)	Non détecté / Not detected
Oct-2-ynoate de méthyle (n° CAS 111-12-6)	Non détecté / Not detected
Alpha-isométhylionone (n° CAS 127-51-5)	Non détecté / Not detected
Evernia prunastri (n° CAS 90028-68-5)	Non détecté / Not detected
Evernia furfuracéa (n° CAS 90028-67-4)	

La limite de detection est de 1 ppm. / the detection limit is 1ppm.

GREENTECH
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Jean-Yves BERTHON
PDG / CEO

Po / For and on behalf

Sabrina BOUTREUX
Chargée réglementaire

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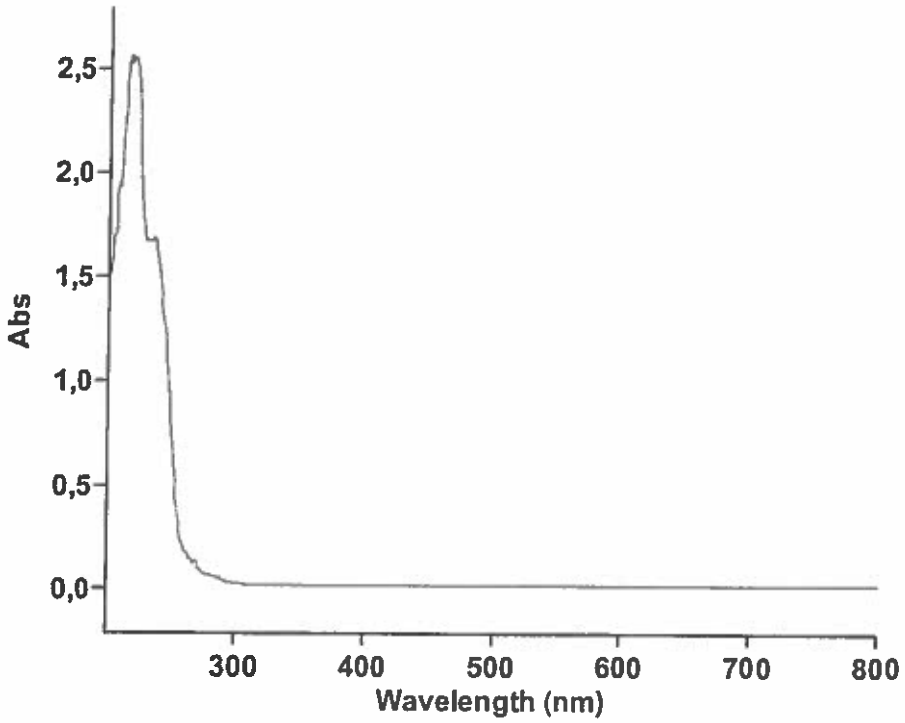

Scan Analysis Report

Report Time :	mer. 15 juil. 12:34:37 PM 2015
Method	D:\methodes\SPECTRE UV\141027 Spectre.MSW
Batch:	D:\Résultats analyses\2015\Oranger fleur ext huileux BIO tournesol (510033)\150715 CIAT1407L1-HBIO 0.1% cyclohexane.BSW
Software version:	5.0.0.999
Operator:	AS

Instrument Parameters

Instrument	Cary 60
Instrument Version	2,00
Start (nm)	800,0
Stop (nm)	200,0
X Mode	Nanometers
Y Mode	Abs
UV-Vis Scan Rate (nm/min)	600,000
UV-Vis Data Interval (nm)	1,00
UV-Vis Ave. Time (sec)	0,1000
Beam Mode	Dual Beam
Baseline Correction	On
Baseline Type	Baseline correction
Baseline File Name	D:\Résultats analyses\2015\Oranger fleur ext huileux BIO tournesol (510033)\150715 CIAT1407L1-HBIO 0.1% cyclohexane.BSW
Baseline Std Ref File Name	
Cycle Mode	Off
Comments	Oranger fleur ext huileux BIO (Tournesol) (510033) : CIAT1407L1-HBIO 0.1 % Baseline : cyclohexane

Sample Name: **CIAT1407L1-HBIO 0.1%**
Collection Time 15/07/2015 12:34:42

Peak Table	
Peak Style	Maximum Peak
Peak Threshold	0,0100
Range	800,0nm to 200,0nm
Wavelength (nm)	Abs
215,0	2,564

Peak Table	
Peak Style	Peaks
Peak Threshold	0,0100
Range	800,0nm to 200,0nm
Wavelength (nm)	Abs
235,0	1,689
230,0	1,684
217,0	2,558
215,0	2,564
208,0	1,977

Data Interval 10,00
X-Y Pairs Table

Wavelength (nm)	Abs	Wavelength (nm)	Abs	Wavelength (nm)	Abs
800,0	0,012	600,0	0,014	400,0	0,013
790,0	0,012	590,0	0,014	390,0	0,013
780,0	0,013	580,0	0,014	380,0	0,013
770,0	0,014	570,0	0,014	370,0	0,014
760,0	0,014	560,0	0,014	360,0	0,014
750,0	0,014	550,0	0,014	350,0	0,014
740,0	0,014	540,0	0,014	340,0	0,014
730,0	0,014	530,0	0,014	330,0	0,015
720,0	0,014	520,0	0,014	320,0	0,016
710,0	0,014	510,0	0,014	310,0	0,018
700,0	0,014	500,0	0,013	300,0	0,025
690,0	0,014	490,0	0,013	290,0	0,040
680,0	0,014	480,0	0,013	280,0	0,062
670,0	0,014	470,0	0,013	270,0	0,121
660,0	0,014	460,0	0,013	260,0	0,189
650,0	0,014	450,0	0,013	250,0	0,705
640,0	0,014	440,0	0,013	240,0	1,488
630,0	0,014	430,0	0,013	230,0	1,684
620,0	0,014	420,0	0,013	220,0	2,538
610,0	0,014	410,0	0,013	210,0	2,114

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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: August 2, 2016

SUBJECT: Updated 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 Aurantium Amara (Bitter Orange) Flower Extract
Citrus Aurantium Amara (Bitter Orange) Flower Oil
Citrus Aurantium Amara (Bitter Orange) Flower Water
Citrus Aurantium Amara (Bitter Orange) Flower Wax
Citrus Aurantium Dulcis (Orange) Flower
Citrus Aurantium Dulcis (Orange) Flower Extract
Citrus Aurantium Dulcis (Orange) Flower Oil
Citrus Aurantium Dulcis (Orange) Flower Wax
Citrus Depressa Flower Water
Citrus Junos Flower Oil
Citrus Limon (Lemon) Flower Water
Citrus Natsudaidai Flower Oil
Citrus Natsudaidai Flower Water
Citrus Sinensis (Orange) Flower Water
Citrus Tamurana Flower Extract
Citrus Unshiu Flower Extract
Citrus Unshiu Flower Powder
Citrus Unshiu Flower Water
Citrus Aurantifolia (Lime) Leaf Oil
Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract
Citrus Aurantium Bergamia (Bergamot) Leaf Extract
Citrus Aurantium Bergamia (Bergamot) Leaf Oil
Citrus Clementina Leaf Cell Extract
Citrus Aurantium Dulcis (Orange) Leaf Extract
Citrus Grandis (Grapefruit) Leaf Extract
Citrus Hystrix Leaf Extract
Citrus Limon (Lemon) Leaf Cell Extract
Citrus Limon (Lemon) Leaf Extract
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	Hair conditioners	0.001%
Citrus Aurantium Dulcis (Orange) Flower	Shampoos (noncoloring)	0.00008-0.005%
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	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	Bath soaps and detergents	0.01-0.04%
Citrus Aurantium Dulcis (Orange) Flower Extract	Other personal cleanliness products	0.01%
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%
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	Body and hand products	

Oil	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

Updated August 2, 2016: Citrus Aurantium Dulcis (Orange) Flower: deleted colognes and toilet waters, other personal cleanliness products, shaving cream, body and hand products; Citrus Aurantium Dulcis (Orange) Flower Extract: deleted eyeliners, eye shadows, lipstick; removed 0.75% concentration from body and hand products; added other personal cleanliness products 0.01%

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Memorandum

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

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

DATE: August 19, 2016

SUBJECT: Information on Citrus Aurantium Amara (Bitter Orange) Flower Extract

Turowski A. 2008. Safety assessment for Flowerpone® Orange Blossom (contains Citrus Aurantium Amara (Bitter Orange) Flower Extract).

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Safety Assessment

for

Flowerpone® Orange Blossom

Author: Dr. Angelika Turowski
Date: June 2008

Substance Identification

Botanical name:	Citrus aurantium L. ssp. amara
Botanical family:	Rutaceae
Synonym(s)	Citrus aurantium L. ssp. Amara (L) Engl; Citrus amara Link, Citrus bigaradia Risso & Poiteau
Common name(s):	Bitter Orange, Seville Orange, Sour Orange, Bigarade, Bouquetier, Citrus bergamia, zhi shi
INCI Name (EU):	Citrus Aurantium Amara Flower Extract
INCI name (USA):	Citrus Aurantium Amara (Bitter Orange) Flower Extract
CAS register number:	72968-50-4
EINECS / ELINCS number:	277-143-2
INCI name(s) formulation:	Water (Aqua), Pentylene Glycol, PEG-40 Hydrogenated Castor Oil, Trideceth-9, Bisabolol, Citrus Aurantium Amara (Bitter Orange) Flower Extract (Global) Aqua, Pentylene Glycol, PEG-40 Hydrogenated Castor Oil, Trideceth-9, Bisabolol, Citrus Aurantium Amara Flower Extract (EU)
Part(s) used:	Flowers
Geographic origin:	The plant is native to Northeastern India, and is cultivated in Southern China, Southern Europe and the United States.
Manufacturing process:	Bitter orange trees (Citrus aurantium L. subsp. Amara (L) Engler) used for Flowerpone® Orange Blossom are grown in Morocco. The components of fresh orange blossoms are hydrocarbon extracted, treated with ethanol and filtrated. The extract is then concentrated and purified by distillation to obtain an orange flower

absolue.

Standardization/Equivalence: 1 kg of Flowerpone® Orange Blossom corresponds to approx. 1 kg of fresh orange blossoms

Fresh Plant Material - Extract – Ratio: approx. 1 : 1

Recommended Use in Cosmetics

Leave-on product types: e.g. body lotions, hand creams and lotions, moisturizing preparations, day & night skin care preparations, skin-conditioning products

Concentration: 1-5%

Rinse-off product types: e.g. hair shampoos, hair conditioners, bath soaps, hand wash lotion, cleansing products, bubble baths, shower gels / preparations

Concentration: 1-5%

Oral hygiene products: Concentration: 1-5%

Spray products: Concentration: -

Chemical Composition of bitter orange flower extract

Constituents of C. aurantium include flavonone glycosides and flavone aglycones, coumarins, psoralens, polymethoxyflavones, waxes, aldehydes, amines, and monoterpenes (ARS USDA); the psoralens found in Citrus species include bergapten and epoxybergamottin (Dugo et al., 1996).

Neroli oil and orange flower extracts are obtained from the carefully harvested flowers of bitter orange. The essential oil (Neroli, CAS 8016-38-4) of bitter orange flowers are comprised of the following constituents as described by the committee of experts on cosmetic products (2001):

- monoterpenes: limonene 15%; dipentene; alpha- and beta-pinene 11%; camphene; linalool 30-60%; linalyl acetate 6-17%; nerol and neryl acetate; geraniol; nerolidol 6%; alpha-terpineol; citral
- sesquiterpenes: farnesol
- aldehydes: nonanal; decanal; dodecanal
- ketone: jasmone
- phenylethylalcohol; indole; methyl anthranilate 0.5-1.2%
- organic acids: acetic acid, phenyl acetic and benzoic acid in esterified form
- paraffins
- other compounds in traces: cis-8-heptadecene; 2,5-dimethyl-2-vinyl-4- hexenal; valeric acid

An analysis of Neroli oil identified more than 125 components. The principal ones are shown in the following table (Mookherjee and Wilson, 1996). Of the eleven constituents only linalool can be said to contribute directly to the characteristic aroma of orange flower oil.

Components of neroli oil (Mookherjee and Wilson, 1996)		
Component	***CAS***	***Concentration (%)***
linalool	78-70-6	36.0
β-pinene	127-91-3	16.0
limonene	138-86-3	11.6
linalyl acetate	115-95-7	5.8
trans-*β*-ocimene	3779-61-1	5.1
α-terpineol	98-55-5	4.0
trans-nerolidol	7212-44-4	3.9
geranyl acetate	16409-44-2	2.8

geraniol	106-24-1	2.4
myrcene	123-35-3	1.8
sabinene	3387-41-5	1.2
total		90.6

Three simple terpenic compounds, each present at less than 0.01%, also contribute directly to the characteristic aroma of orange flower oil: α-terpenyl methyl ether (CAS 1457-68-0), geranyl methyl ether (CAS 2565-82-4), and linalyl methyl ether (CAS 60763-44-2).

Huang et al. (2001) have also studied the chemical constituents of the flower of Citrus aurantium. Eleven compounds have been isolated and identified including neohesperidin, synephrin, 5,8-epidioxyergosta-6,22-dien-3 beta-ol, adenosine, asparagine, tyrosine, valine, isoleucine, alanine, beta-sitosterol and beta-daucosterol.

Carnat et al. (1999) standardized the flavonoid composition of sour orange flowers and leaves. Dried flowers (1 batch) and leaves (6 batches) of sour orange Citrus aurantium L. showed a similar flavonoid pattern, but the flavonoid levels of flowers were higher than those of leaves. The mean levels of the principal flavonoid compounds were respectively: total flavonoids 12.35% and 1.06%, neohesperidin 5.44% and 0.08%, naringin 1.93% and 0.06%, eriocitrin 0.38% and 0.25%. The level of neohesperidin in the flowers is always greater than those of naringin.

A hydrocarbon extract of bitter orange flowers comprises the volatile etherial fraction besides higher fatty acids as well as many of the non-volatile compounds. By treatment with ethanol waxes, hydrocarbons (including terpenoids) as well as most of the odourless material are removed from the extract.

Lawrence (1997) reviewed and compared the major components of orange flower absolue, orange flower water absolue and neroli oil: In 1981, Prager and Miskiewicz used GC and GC/MS to examine the composition of a number of samples of neroli oil, orange flower water absolue and orange flower absolue with the following result for the latter:

Chemical composition (%) of orange flower absolue (Prager and Miskiewicz, 1981)		
Compound	***% Range***	***Average***
Linalool	34.0 – 48.0	42.0

Linalyl acetate	14.0 – 21.0	18.0
Farnesol	3.6 – 15.4	8.7
Nerolidol	4.9 – 8.9	6.8
Indole	2.6 – 9.9	4.5
Methyl anthranilate	1.0 – 4.3	2.8
α-terpineol	1.5 – 3.7	2.1
Limonene	0 -3.6	2.0
Geraniol	0 - 2.0	1.1
Geranyl acetate	0 – 1.3	1.0
(E)-β-ocimene	0 – 2.2	1.0
2-phenethyl alcohol	0 – 2.1	0.9
β -pinene	0 – 2.7	0.9
Benzyl cyanide	0 – 1.1	0.7
Nerol	0 – 1.1	0.6
Neryl acetate	0 – 0.7	0.5
Terpinen-4-ol + β-caryophyllene	0 – 0.8	0.4
Myrcyne	0 – 0.5	0.2

By this analysis, five compounds (linalool, linalyl acetate, farnesol, nerolidol, indol) make up 80% of the orange flower absolute. Yang and Lee (1988) determined the bergapten content of Egyptian, French and Algerian orange flower absolue at 2650 ppm, 545 ppm and 680 ppm, respectively. The authors also identified bergamottin epoxide in orange

flower absolue.

The essential oils from bitter orange peel and orange juice have also been examined. Peel oil obtained by steam distillation is characterized to contain approx. 2.1% myrcene, 3.4% limonene, 7.2% p-cymene, 0.1% linalool (Veriotti et al. 2002), whereas by cold-pressing from the cortex the oil contains mainly monoterpenes (chiefly limonene 77.9%, alcohols, and one ketone, nootkatone) (Quintero et al., 2003). Oil from fresh bitter orange juice consists mainly of limonene, 90.3%, α-pinen 1.5%, linalool 1.5%, α-terpineol 1.1%, 3-heptanone1.3%, and other constituents <1% (Moufida et al. 2003).

Toxicological data from oils of bitter orange juice or cold pressed cortex oil are considered relevant for the evaluation of limonene contained in orange flower absolue.

Composition of Flowerpone® Orange Blossom

Flowerpone® Orange Blossom contains a preservative free, concentrated extract of bitter orange blossoms, prepared in water. To simplify analytical determination in a cosmetic product, a defined amount of 0.5% alpha-bisabolol has been added. PEG-40 hydrogenated castor oil is used in Flowerpone® Orange Blossom as solubilizer and pentylene glycol to protect the preparation.

The quantification of furanocoumarins in the orange blossom absolue extract resulted in 9082 ppm epoxybergamottin, 633 ppm psoralen, 583 ppm oxypeudecanin, 200 ppm bergapten, 117 ppm isoimperatorin, and 52 ppm imperatorin. Beta-pinene has been determined at 0.378%, ocimene at 0.143% and linalyl acetate at 12.346%.

Based on its content of 0.15% orange blossom absolue, Flowerpone® Orange Blossom contains furanocoumarin substances at a concentration of 0.0016% (ca.16 ppm) at the most (calculated): 0.95 ppm psoralen, 0.3 ppm bergapten, 0.88 ppm oxypeudecanin, 0.08 ppm imperatorin, 0.18 ppm isoimperatorin, and 13.62 ppm epoxybergamottin.

The contents of linalool, linalyl acetate, beta-pinene, and ocimene are 630 ppm, 185 ppm, 6 ppm, and 2 ppm respectively. The quantified content of total polyphenolic substances in Flowerpone® is 29 ppm (according to literature neohesperidin, naringin and eriocitrin).

The presence of bitter orange biogenic amines, such as synephrine, octopamine, and tyramine, can be excluded from analytical measurements (<0.008 ppm by HPLC-DAD).

Extract:	Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.15%
Additives:	Pentylene Glycol	5%

	PEG-40 Hydrogenated Castor Oil	3.25
	Trideceth-9	2.9%
	Bisabolol	0.5%
	Disodium EDTA	0.15%
	Sodium citrate	0.3%
Solvents:	Water	Add 100%
Impurities:	-	-
Special constituents:	26 Substances considered as allergens according to the 7th amendment to the EU Cosmetics Directive:	22 not detected (limit of detection 10 ppm) Farnesol: 0.010%; Geraniol: 0.001%; Limonene: 0.002%; Linalool: 0.063%

Physical/chemical Properties and Microbiology

Physical form:	Clear liquid, pH 5.5-7.5	
Color:	Colorless to pale yellow	
Flash point:	>100 °C	
Microbiological properties:	Total aerobic count	<100 cfu/ g
	Mould	<10 cfu/ g

Yeast	<10 cfu/ g
Escherichia coli	not detectable (0.1g)
Pseudomonas aeruginosa	not detectable (0.1g)
Candida albicans	not detectable (0.1g)
Coag. pos. staphylococci	not detectable (0.1g)

Toxicological Properties

Background

Citrus aurantium and extracts of its dried fruit and peel have been used for years in traditional Western medicines, Chinese and Japanese herbal medicines, and as flavorings in foods and beverages. Oil of bitter orange is used as a remedy for treatment-resistant fungal skin diseases.

Bitter orange is regulated by the U.S. FDA; the peel, oil, extracts, and oleoresins are generally recognized as safe (GRAS) as a direct additive to food. The peel is used in many pharmacopoeial preparations for flavoring and treatment of digestive problems. Additionally, bitter orange is reported to be an expectorant, laxative, hypertensive, nervine, tonic, and diuretic. Oils from the fruit, peel, and other plant parts are also used for flavoring and fragrance and do not contain alkaloids.

For linalyl acetate contained in Flowerpone® Orange Blossom, only scarce toxicological data are available. However, since linalyl acetate is very likely quickly hydrolysed by unspecific esterases in the skin, it is considered not to become systemically available.

The ingredients PEG-40 hydrogenated castor oil, citric acid, disodium EDTA and bisabolol in Flowerpone® Orange Blossom are considered safe on the basis of existing SCCP opinions or CTFA Cosmetic Ingredient Review (CIR) Panel publications, which are cited in the Margin-of-safety section. No CIR or SCCP safety assessment for pentylene glycol is available. Therefore, the safety assessment from the CIR report on butylene glycol and hexylene glycol (CIR, 1985) will be used and is cited in the Margin-of-safety section, too.

As no similar safety assessment is available for trideceth-9, a polyethylene glycol ether of tridecyl alcohol (average number of ethoxy units n=9), data from CIR reports on corresponding polyethylene glycol ethers of stearyl alcohol (steareth-n), oleyl alcohol (oleth-n) and cetearyl alcohol (ceteareth-n) will be used for safety assessment.

The total furanocoumarin content in Flowerpone® Orange Blossom amounts to 16 ppm. According to SCCNFP (2000) and SCCP (2003), the SCCP concluded for furanocoumarins that due to the phototoxic, photomutagenic and photocarcinogenic properties reported for certain furanocoumarins, they are not permitted for use in cosmetic products as such, except for the normal content in natural essences if the total concentration of furanocoumarin-like substances in the finished cosmetic product does not exceed 1 ppm (see Margin-of-safety section).

Acute oral toxicity

No acute oral toxicity study in animals is available for Flowerpone® Orange Blossom.

However, a conclusion on the acute oral toxicity hazard can be based on the following facts:

- according to the U.S. Food and Drug Administration (FDA), bitter orange, its peel, oil, extracts, and oleoresins are generally recognized as safe (GRAS) as a direct additive to food,
- in male mice treated by gavage with essential oil from C. aurantium peel (CAS 68916-04-1) (0.5 or 1.0 g/kg), the latency period of tonic seizures was increased. In addition, treatment with the higher dose significantly increased hypnotic activity and anxiolytic activity. No deaths were reported. Sprague-Dawley rats orally administered a single dose of a herbal drug mixture (up to 10 g/kg) containing about 10% of C. aurantium peel, showed no toxic signs or lethal effects (NTP, 2004).
- the acute toxicity of pure limonene (about 95% purity, d and d/l forms) after oral or dermal administration to rats and mice is fairly low. The LD_{50} values have been estimated at >5000 mg/kg (Josefsson, 1993). An oral lethal dose for humans has been estimated at 28-550 g, whereas an oral intake of 285 mg/kg d-limonene in man did not result in any toxicological signs. Limonene has been administered therapeutically to humans at doses of 20 g to dissolve gallstones (EPA, 1994),
- acute toxicity data for linalool indicate oral (gavage) LD_{50} values of 2.8 g/kg in rats, 2.2-3.5 g/kg in mice and a dermal LD_{50} of 2.2-3.5 g/kg in rabbits (Jenner et al. 1964, FEMA, 1997),
- the acute oral LD_{50} of disodium EDTA was about 3.7 mg/kg in male and female rats (CIR, 2002), corresponding to a calculated value of about 2000 mg/kg for Flowerpone® Orange Blossom, which contains 0.15% disodium EDTA,
- oleth-10 had an acute oral LD_{50} of >5000 mg/kg bw in rats (CIR, 1999c). For steareth-2, -10 and -20 oral LD_{50} values >2000 mg/kg bw in rats have been reported (CIR, 1988).

From this information, it can reasonably be assumed that Flowerpone® Orange Blossom,

containing 0.063% linalool, and 0.002% limonene, is unlikely to have any relevant acute toxicity after ingestion.

Irritation

Skin irritation

No skin irritation study is available for Flowerpone® Orange Blossom. However, a conclusion on the skin irritation hazard can be based on the following facts:

- the acute dermal LD_{50} value of bitter orange oil in rabbits exceeded 5g/kg (Opdyke, 1979),
- orange oil applied undiluted to backs of hairless mice was not irritating. It was moderately irritating when applied intact or abraded rabbit skin for 24 hours under occlusion (Opdyke, 1979),
- undiluted butylene glycol produced no more than minimal skin irritation when tested under occlusion on the skin of rabbits for 24 hours or daily for 4 consecutive days (CTFA, 1976; 1979). Undiluted hexylene glycol produced moderate irritation when 465 or 500 mg were applied to the skin of rabbits for 24 hours. A 24-hour application of 1.84 g/kg undiluted hexylene glycol to the skin of rabbits caused mild edema and erythema (NLM, 1982; Rowe, 1963). Several product formulations containing 5.0-21.4% butylene glycol and 1.0-1.6% hexylene glycol were tested for 24 hours under occlusion on rabbit skin. The products produced no or only moderate irritation depending upon the particular formulation tested. However, the degree of irritation did not correlate with the concentration of glycol (CTFA 1975, 1978, 1979, 1980),
- steareth-2 and -10 caused only minimal skin irritation when applied onto rabbit skin at 60% aqueous solution (CIR, 1988). Oleth-20 tested at 50% in an open patch test in rabbits caused minimal skin irritation (CIR, 1999c),
- undiluted PEG-40 hydrogenated castor oil reportedly caused reddening and scaling of the skin when applied to the backs of albino rabbits for 20 hours. Only slight transient reddening was reported when applications were made to the external ears of rabbits for 20 hours. The primary skin irritation potential of a formulation containing 0.25% PEG-40 hydrogenated castor oil was minimal (CIR, 1997).

From this information, it can reasonably be assumed that Flowerpone® Orange Blossom containing 0.15% blossom oil, 5% pentylene glycol, 3.25% PEG-40 hydrogenated castor oil and 2.9% trideceth-9, shows – if at all – only mild skin irritating properties.

Eye irritation

No eye irritation study is available for Flowerpone® Orange Blossom. However, a conclusion on the eye irritation hazard can be based on the following facts:

- steareth-2, -10 and -20 caused no eye irritation when instilled as 60% solution into the eyes of rabbits (CIR, 1988). Oleth-20, when instilled pure into the eyes of rabbits, caused moderate eye irritation (CIR, 1999c)
- 0.05 ml undiluted and 50% aqueous PEG-40 hydrogenated castor oil were instilled into the conjunctival sacs of rabbits and observations were made at 24 and 48 hours. Slight transient reddening of the conjunctiva was observed with both concentrations (CIR, 1997),
- the contents of bitter orange flower extract of 0.15%, pentylene glycol of 5% and PEG-40 hydrogenate castor oil of 3.25% in Flowerpone® Orange Blossom are so small that even if the pure constituents would have to be classified as 'eye irritating' (R 36) or as 'serious damage to the eyes' (R 41), Flowerpone® Orange Blossom as a preparation would not have to be classified and labelled as eye irritant according to the Dangerous Preparations Directive (1999/45/EG).

From this information, it can reasonably be assumed that Flowerpone® Orange Blossom is unlikely to have any relevant eye irritating properties.

Sensitization

Dermal sensitization studies

No skin sensitization study is available for Flowerpone® Orange Blossom. However, fragrance allergy is a well known phenomenon, mostly afflicted with are users of perfumes and antiperspirants. Occupational contact dermatitis can be found with hairdressers, beauticians, physiotherapists and many other jobs, too.

Some constituents of the orange blossom extract may cause sensitization (e.g. geraniol, farnesol) and phototoxic reactions (e.g. furanocoumarins) by skin contact. For those ingredients, which have been quantitatively identified in Flowerpone® Orange Blossom a risk assessment has been done (see section Margin-of Safety consideration).

A single case report described a bartender with hand dermatitis who developed allergic contact sensitivity to the skin (peel) of oranges, lemons, and limes. Although most reported cases of citrus peel allergy are due to d-limonene, in this instance geraniol and citral, two minor components of citrus peel oil, caused positive patch test reactions, whereas d-limonene was negative (Cardullo et al. 1989).

In another case report, Schubert (2006) investigated the occurrence of skin diseases in one-third of the staff of a perfume factory, in which 10 different perfume sprays were being manufactured. Site inspection, dermatological examination and patch testing of all 26 persons at risk with 4 perfume oils and 30 ingredients of them, showed that 6 bottlers were suffering from allergic contact dermatitis, 2 from irritant contact dermatitis, 12 workers showed different strong reactions to various fragrances. The main causes of allergic contact dermatitis were 2 perfume oils (12 cases) and their ingredients geraniol (12 cases), benzaldehyde (9), cinnamic aldehyde (6), linalool, neroli oil, terpenes of lemon oil and orange oil (4 each).

Roesyanto-Mahadi (1990) investigated sensitization to fragrance materials in Indonesian cosmetics. Two different groups of patients were patch tested with two test series A (diluted extracts of commercially available Indonesian fragrances) and B (extracts prepared from corresponding indigenous flowers and fruits). Group I consisted of 32 patients positive to fragrance-mix, of whom 25% had positive tests to one or more of the different extracts of fragrance raw materials. Reactions were observed to different extracts of Citrus species. Six of the patients had reactions to one or more of the components of fragrance-mix: oakmoss (3); cinnamic alcohol (2). isoeugenol (1); cinnamic aldehyde (1) and geraniol (1). Group 2 consisted of 159 patients patch tested on suspicion of contact dermatitis, but who were fragrance-mix negative. Only 2 (1.2%) had a positive patch test to the extracts of fragrance raw materials.

A formulation containing 1.35% ceteareth-15 did not cause skin sensitization in a human repeat insult patch test (CIR, 1999b). In human repeat insult patch tests, steareth-20 at 1.5%, 4% or 60% did not cause skin sensitization (CIR, 1999c).

Conclusion

While essential oil or absolue from bitter orange blossoms contain relevant amounts of skin allergens, such as linalool, farnesol, d-limonene, and geraniol, the concentration of these contact allergens in Flowerpone® Orange Blossom has been quantified at approx. 760 ppm (see section Margin-of Safety consideration).

Phototoxicity

The family Rutaceae is known to be a source of some phototoxic chemical compounds that cause photodermatitis (phytophotodermatitis).

Several case reports of non-allergic phytophotodermatitis have been reported by e.g. Weber et al. (1999), Egan and Sterling (1993) and Wagner et al. (2002).

Gross et al. (1987) described phototoxic dermatitis in 97 (16%) of 622 children and 7 (7%) of 104 counsellors. The eruptions were confined to the hands, wrists and forearms, and appeared as discrete and confluent polymorphous patches and linear streaks. The cause was attributed to the making of pomander balls (sachets). The makers punctured the skin

of limes (the principal component) with scissors, releasing oils known to contain photoreactive furanocoumarin (psoralen) compounds.

Conclusion

Due to the phototoxic, photomutagenic and photocarcinogenic properties reported for certain furanocoumarins, furanocoumarins are not permitted for use in cosmetic products as such, except for the normal content in natural essences if the total concentration of furanocoumarin-like substances in the finished cosmetic product does not exceed 1 ppm (SCCP, 2003; 2005).

Based on its content of 0.15% orange blossoms absolue, Flowerpone® Orange Blossom contains furanocoumarin substances at a concentration of 0.0016% (ca.16 ppm) at the most.Therefore the use of Flowerpone® Orange Blossom at concentration up to 5% in cosmetics is in agreement with the SCCP opinion (also see section Margin-of safety consideration).

Absorption, Distribution, Metabolism and Excretion

No data on the skin absorption of Flowerpone® Orange Blossom are available.

In general, the main constituents of essential oils, when taken orally, are secreted via the lungs, kidneys and skin. They are mildly irritant to the mucous membrane of the mouth and digestive tract; in the lungs they are slightly antiseptic and act to stimulate respiration and cardiac activity (Roe et al. 1965).

Linalool is generally found as a racemic mixture. The presence of the hydroxy group on linalool appears important since it enhances the excretion of linalool. When 500 mg/kg of radiolabeled linalool was given intragastrically to Wistar rats, there was no significant delay between dosing and appearance of radioactivity in the urine (Parke et al., 1974a). After several hours, substantial amounts of radiolabeled carbon dioxide appeared in the respired air, suggesting that linalool was entering catabolic pathways. Fecal excretion was occurring mainly between 36 and 48 hours after dosing, partly because of extensive biliary excretion and reabsorption of partially hydrolyzed glucuronic and sulfate conjugates. After 72 hours, 3% of the radioactivity remained in the tissues, mainly in the liver, gut, skin, and skeletal muscle.

The major metabolites detected in the urine of male rats administered 600 mg/kg of linalool orally each day for six days were 8-hydroxylinalool and 8-carboxylinalool, products of C-8 methyl oxidation. Dihydrolinalool and tetrahydrolinalool were not found (Chada and Madyastha, 1984).

Over much longer periods, cytochrome P450 levels showed a complex response to the administration of linalool. When 500 mg/kg of linalool was administered by gastric intubation to Wistar rats, an initial increase in P450 occurred. P450 levels became depressed by day seven. By day 30, however, P450 levels were elevated 50% and

remained that way throughout the 64-day study (Parke et al., 1974b).

The promoting effect of cyclic monoterpenes on the percutaneous absorption of different drugs have been investigated in different animal models. Drug absorption is markedly enhanced by the addition of d-limonene, whereas no effect was observed when the additives had hydroxyl or carbonyl groups (e.g. linalool).

d-Limonene was rapidly absorbed (43 min) through the intact, shaved abdominal skin of mice (Meyer and Meyer, 1959). Twelve Long-Evans male rats were administered single topical doses of 5 mg/kg bw ^{14}C-limonene; the treated area was then occluded for 3 hours (2 males) or 6 hours (10 males). Following occlusion, the residual dose was removed and the treated area was re-occluded. Pairs of treated rats were killed at 3, 6, 24, 48, and 72 hours, urine and faeces were collected from rats killed at 24, 48, and 72 hours, and plasma and tissue samples were taken at all time points. Peak concentrations of radioactivity in tissue samples were measured 3-6 hours after dosing in the gastrointestinal tract (0.1-0.4% dose/g), livers and kidneys (0.08-0.2% dose/g), and thyroid and fat (0.02-0.06% dose/g); except for the gastrointestinal tract, concentrations of radioactivity in all tissues were appreciably lower at 24 hours. After 6 hours of exposure, 48% of the radioactivity was recovered in the skin; at the 24-72 hours sampling times, 8-12% was excreted in urine, 1-3% was excreted in faeces, and 14-18% was expired in air. Total mean recovery of radioactivity was reported to be approximately 76% (FAO/WHO, 1993).

For safety assessment skin penetration rates of 52% for limonene and 5% for linalool will be assumed as a conservative approach.

Repeated dose toxicity

No repeated dose oral toxicity study in animals is available for Flowerpone® Orange Blossom. However the constituents linalool (and its esters) and limonene have been intensively investigated. Therefore, a conclusion on the repeated dose oral toxicity hazard can be based on the facts presented in the following.

Bitter orange peel, oil, oleoresins, and extracts are generally recognized as safe (GRAS) as a direct additive to food by the U.S. FDA.

In a repeated dose toxicity study, Wistar rats received 160, 400 or 1000 mg/kg bw/day linalool (72.9% linalool in essential oil) for 28 days. One male and one female of the high-dose group were found dead. Total protein/albumin was increased in males at 400 mg/kg/day and in both sexes at 1000 mg/kg/day. Calcium was increased in serum at the high dose in males only. Serum glucose levels were decreased in males of the mid and high dose. Liver weight was increased dose related and significantly at 400 and 1000 mg/kg/day. Kidney weight was increased in males of the mid dose group (relative kidney weight) and in all animals at the high dose (absolute kidney weight). Macroscopically this was accompanied by thickened liver lobes and pale areas on the kidneys. All treated

female groups showed hepatocellular cytoplasmic vacuolisation while the high-dose males had an increase in degenerative lesions in the renal cortex. Thickening of the stomach mucosa with concomitant lesions in the nonglandular part of the stomach, with some erosion, subacute inflammation and acanthosis were reported in mid and high dose animals. The NOAEL was derived at 160 mg/kg bw/day (equivalent to 117 mg/kg bw/day linalool) based on effects in liver and kidney (OECD, 2004).

Over a 16 day period groups of five mice of each sex received 0, 413, 825, 1650, 3300, or 6600 mg/kg d-limonene (CAS 5989-27-5) in corn oil by gavage once per day. Animals were housed five per cage and fed ad libitum. The animals were observed twice per day and weighed once per week. Necropsies were performed on all animals. All but one animal receiving 3300 or 6600 mg/kg bw/day limonene died within three days of study initiation. No treatment-related clinical signs were observed in mice receiving doses of 1650 mg/kg bw/day or lower(NOAEL1650 mg/kg bw/day) (NTP, 1990).

Groups of ten rats of each sex were administered 0, 150, 300, 600, 1200 or 2400 mg/kg bw/day d-limonene in corn oil by gavage once per day, five days a week for 13 weeks. Animals were housed five per cage and fed ad libitum. The animals were observed twice per day and weighed once per week. Necropsies were performed on all animals. Histological examinations were performed on all vehicle control and high dose animals and all female rats in the 1200 mg/kg group. Tissues examined included adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), femur, sternebrae or vertebrae including marrow, gross lesions and tissue masses with regional lymph nodes, heart kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroids, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, small intestine, spinal cord (if neurologic signs present), spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Kidneys were examined in all male rats. Ninety percent of female rats (9/10) and fifty percent of male rats (5/10) receiving 2400 mg/kg bw/day limonene died within the first week of the study. The final mean body weights of male rats receiving the three highest doses (600, 1200 or 2400 mg/kg bw/day) were reported to be 6%, 12%, or 23% lower than that of the controls, respectively. Rough hair coats, lethargy, and excessive lacrimation were observed for all animals at the two highest dose levels. Nephropathy was reported for all groups of male rats but a dose related increase in severity of the lesion was reported for the dosed groups. The nephropathy was characterized by degeneration of epithelium in the convoluted tubules, granular casts with tubular lumens, primarily in the outer stripe of the outer medulla, and regeneration of the tubular epithelium. Hyaline droplets were observed in the epithelium of the proximal convoluted tubules in all groups of male rats including vehicle controls. Upon further review to determine if there were differences in these findings between control and treated animals, the blinded slides revealed no definite differences in the accumulation of hyaline droplets. The NOAEL was 300 mg/kg bw/day (NTP, 1990).

A 90-day feeding study of oleth-20 was conducted in Wistar rats. Groups of 15 rats were fed diets containing 0.01, 0.04, 0.16, 0.64, 2.5 or 5.0% oleth-20. Body weight gain was

significantly reduced in the male rats fed 2.5 and 5% and in female rats fed 5%; corresponding decreases in feed intake were observed in these groups. No changes in haematological parameters were observed. No macroscopic or microscopic abnormalities were observed. In another study, beagle dogs were fed diets containing 0.04, 0.64 or 5.0% oleth-20 for 90 days. Dogs in the high dose group gained significantly less body weight than controls; feed intake paralleled these observations. No haematological, macroscopic or microscopic abnormalities were found (CIR, 1999c).

In a rat dermal subchronic study with a C9-11 linear primary alcohol 6-mole ethoxylate, there were no treatment-related effects at 1% and 10% aqueous concentrations, but at 25%, there was flaking of the skin and microscopic evidence of hyperkeratosis at the treatment site as the only compound-related effect (Gingell and Lu, 1991).

Conclusion

Form the use of linalool and limonene as food additives, it can reasonable be assumed that the very small exposure to these constituents from Flowerrpone® Orange Blossom at 5% in cosmetics is unlikely to result in any relevant systemic effects.

Assuming a skin penetration rate of 52% of limonene, this would result in a systemic exposure of 0.000208 mg/kg/day; and an assumed skin penetration rate of 5% for linalool will result in a systemic exposure of 0.002201 mg/kg/day.

The lowest reliable NOAEL of 160 mg/kg/day essential oil (equivalent to 117 mg/kg/day linalool) could be derived from the 28-day study in rats. This value is based on effects in liver and kidney (weight and macroscopic effects).

In a recent review of human exposure through food, the NOEL for linalool was set at 500 mg/kg bw/day based on data for linalyl cinnamate, because certain findings for linalool arguing for a limit of 50 mg/kg bw/d were discounted. This NOEL of 500 mg/kg bw/day is also supported by the upper limit of the UN Joint FAO/WHO Expert Committee on Food Additives ADI for total terpenoid alcohols in food products of 0–0.5 mg/kg bw (OECD, 2004).

In conclusion the use of citrus oils / extracts of bitter orange blossoms containing in Flowerpone® Orange Blossom, is unlikely to result in any relevant systemic effects as long as the SCCP recommended limit for furanocoumarins is not exceeded.

The NOEL of 0.64% oleth-20 in the diet corresponds to 256 mg/kg/day, assuming a feed consumption of 20 g/day and a body weight of 0.5 kg for rats. The NOEL of 0.64% in dogs corresponds to 480 mg/kg/day, assuming a body weight of 10 kg and a feed consumption of 750 g/day (OECD, 2002).

Mutagenicity / genotoxicity

Bacterial Mutagenicity Test in Vitro

No mutagenicity tests with Flowerpone® Orange Blossom are available.

Bala et al. (1989) investigated the antimutagenicity of several citrus fruits in a short-term bioassay in Salmonella typhimurium (Ames test). The antimutagenic effect was tested against the mutagenicity of N-nitro-o-phenylenediamine (NPD) in TA97a and sodium azide in TA100 tester strains. The protocol used for determining the antimutagenic potential was the same as used for determining the mutagenic potential. Each experiment was run in triplicate. A positive control (with mutagen but no juice sample) and a negative control (with juice sample but no mutagen) were also set. The dependence on pH, juice concentrations, and ranges of ascorbic and citric acids were also tested. The results showed that all citrus fruits significantly reduced the NPD- and sodium azide-induced increases in revertant colonies. There were no mutagenic effects of the juices tested without mutagens. The inhibitory activity was enhanced if the mutagen and juice were co-incubated; dilution with distilled water led to the reduction in the inhibitory activity. With pre-incubation, lime juice reduced the mutagenicity of NPD in Salmonella typhimurium strain TA97a by 73%, and the mutagenicity of sodium azide in TA100 by 76%.

Hosseinimehr et al. (2005) investigated the anticlastogenic activity of citrus extract using the micronucleus assay in mouse bone marrow cells. Mice were orally (gavage) pretreated with solutions of citrus peel extract (Citrus aurantium var. amara) prepared at three different doses (100, 200 and 400 mg/kg bw) for 7 consecutive days. Then mice were injected intraperitoneally with cyclophosphamide (50 mg/kg) and after 24 hours killed for the evaluation of micronucleated polychromatic erythrocytes (MnPCEs) in bone marrow cells. Non-protein thiol levels (glutathione, GSH) in liver were estimated in mice injected with citrus extract with or without cyclophosphamide treatment. Administration of citrus extract before cyclophosphamide treatment significantly reduced the frequency of MnPCEs in mice bone marrow compared with the group treated with cyclophosphamide alone ($p<0.05$). Citrus extract at a dose of 400 mg/kg/day reduced MnPCEs 2.8 fold. Administration of cyclophosphamide depleted the GSH level in liver. Citrus extract showed excellent scavenging effects on 1,1-diphenyl-2-picryl hydrazyl radical (DPPH) at a concentration of 1.6 mg/ml. Application of citrus extract 1 hour before cyclophosphamide treatment allowed GSH content to reach the normal level. It appeared that citrus extract, particularly flavonoids constituents with antioxidative activity, may return the GSH level to normal in stress conditions and reduces genotoxicity induced by cyclophosphamide in bone marrow cells.

Linalool has been tested in several in vitro studies. Apart from a single Bacillus subtilis recombination assay all other nine bacterial and non-bacterial tests located are negative. Specifically, a second B. subtilis assay, with the same strain characterisation as in the first positive test, also proved negative at even higher doses. Considering the overwhelming

negative evidence from bacterial and a non-bacterial test systems (chromosomal aberration test), it is assumed that the positive result in the first recombination assay was a chance event. In a mouse micronucleus assay, Swiss CD-1 mice received a single dose of 500, 1000 or 1500 mg/kg bw linalool. Mice were sacrificed and bone marrows were taken at 24 hours and for the highest dose in addition at 48 hours. As positive control 50 mg/kg bw cyclophosphamide was used. There was no significant difference between any of the vehicle control and linalool dosages groups. In summary, linalool was considered to have no mutagenic activity (OECD, 2004).

On the basis of available data, there is no evidence that d-limonene or its metabolites are genotoxic or mutagenic. Limonene and its epoxides were not mutagenic when tested at concentrations of 0.3–3333 µg/plate in in-vitro assays using different strains of Salmonella typhimurium, in the presence or absence of metabolic activation (NTP, 1990). *d*-limonene did not increase the frequency of forward mutation at the TK+/- locus in mouse L5178Y cells, did not induce cytogenetic damage in Chinese hamster ovary (CHO) cells and did not malignantly transform Syrian hamster embryo (SHE) cells. *d*-Limonene has been studied in a battery of short-term *in vitro* tests and found to be nongenotoxic (NTP, 1990).

No mutagenicity studies with steareth, oleth or ceteareth are available. However, various mutagenicity assays of polyethylene glycols (PEGs) and the corresponding stearyl, oleyl and cetearyl alcohols were negative and did not indicate any mutagenic properties of alcohol ethoxylates (CIR 1988; 1999b; 1999c). In addition, a bacterial mutagenicity (Ames) test with C9-11 linear primary alcohol 6-mole ethoxylate did not show any mutagenic activity (Gingell and Lu, 1991).

Conclusion

From the available mutagenicity studies on citrus fruits and extracts and taking into account the information about the constituents of the orange blossom extract, and given the widespread consumption of citrus oils, it can reasonably be assumed that orange blossom extract, and thus Flowerpone® Orange Blossom, is unlikely to have any relevant genotoxic properties as long as the SCCP recommended limit for furanocoumarins is not exceeded.

Carcinogenicity Studies

No carcinogenicity studies with Flowerpone® Orange Blossom are available.

In a 2-year study, d-limonene was administered (per os) 5 days/week to groups of 50 Fischer F344 rats (0, 75, or 150 mg/kg bw/day to males, and 0, 300, or 600 mg/kg bw/day

to females) for 103 weeks. The animals were observed twice per day and weighed once per week for 12 weeks and once per month thereafter. Necropsies were performed on all animals. Histological examinations were performed on all animals dying during the study; all vehicle control; all low dose female rats and all high dose animals. Tissues examined included adrenal glands, brain, cecum, colon, costochondral junction, duodenum, epididymus/seminal vesicles/tunica vaginalis/scrotal sac/prostrate/testes or ovaries/uterus, esophagus, eyes, femur or sternebrae or vertebrae including marrow, gross lesions and tissue masses with regional lymph nodes, heart, ileum, jejunum, kidneys, larynx and pharynx, liver, lungs and bronchi, mammary gland, mandibular or mesenteric lymph nodes, nasal cavity and turbinates, oral cavity, pancreas, parathyroids, pituitary gland, preputial or clitoral gland, rectum, salivary glands, sciatic nerve, skin, spinal cord, spleen, stomach, thigh muscle, thymus, thyroid gland, trachea, urinary bladder and Zymbal gland. Tissues examined in low dose male rat groups included adrenal glands, kidney, liver, spleen, and testis. Mean body weights for male rats administered 150 mg/kg bw/d *d*-limonene were generally 4-7% lower than vehicle controls from week 2 to study termination. Mean body weights of high dose females were generally 4-7% lower than vehicle controls from week 28 to study termination. No treatment related clinical signs were reported for the duration of the study. Survival of the high dose male group was significantly greater than that of the vehicle alone after week 81. Survival of the high dose female group was significantly lower than that of the vehicle controls after week 39. In the kidneys of male rats, dose-related increases in the incidences of mineralization and epithelial hyperplasia was observed. A dose-related increase in the severity of spontaneous nephropathy was reported in male rats administered limonene. Increased incidence of tubular cell hyperplasia and neoplasia was also reported in dosed male rats. Tubular cell adenoma incidence in high dose male rats and tubular cell adenoma or tubular cell carcinomas (combined) in dosed male rats were significantly greater than vehicle controls. The study authors determined that under the conditions of these 2-year gavage studies there was clear evidence of carcinogenic activity of *d*-limonene for male F344 rats as shown by increased incidences in tubular cell hyperplasia, adenomas, and adenocarcinomas of the kidney. There was no evidence of carcinogenic activity of *d*-limonene for female rats receiving 300 or 600 mg/kg/day. It has been demonstrated that renal lesions, which were observed in the NTP study, resulted from the accumulation of aggregates of α2μ-globulin (a low molecular-weight protein synthesized in the liver of male rats only) with limonene or its metabolites in the P2 segment of the renal proximal tubule. This phenomenon has only been observed in the male F344 rat. While humans produce low molecular weight serum proteins, which are reabsorbed by the kidney, there is no evidence that α2μ-globulin is produced. After careful review, it has been concluded that the mechanisms leading to the renal carcinogenic findings in the F344 male rat are largely known and strongly indicate that the nephropathy associated with *d*-limonene has no significance for human risk assessment (NTP, 1990).

For linalool, no increased incidence of pulmonary tumors was observed at any linalool dose up to a maximum total of 3 g/kg in a 1973 carcinogenicity test in mice. The protocol comprised thrice-weekly intraperitoneal administration and four different negative and positive controls groups, with 8 weeks exposure and 16 weeks post-exposure periods. In a

more recent (1989) co-carcinogenicity test using female rats, with a detailed protocol and statistics, mammary tumours were induced with a single dose of the tumor-promoting agent DMBA and linalool was administered orally by feed (1%) over a total of 20 weeks. The linalool experimental group had both a lower incidence of mammary tumors and a longer median latency until tumor occurrence, but both effects were not statistically significant (OECD, 2004). Based on the far better documented 1973 intraperitoneal carcinogenicity and the 1989 oral feed co-carcinogenicity tests, both with ample details, comprehensive control groups and statistical data, there is no reason to suspect linalool of carcinogenic activity (OECD, 2004).

Conclusion

Flowerpone® Orange Blossom is unlikely to have any relevant carcinogenic or photocarcinogenic properties as long as the SCCP recommended limit for furanocoumarins is not exceeded.

Reproductive toxicity

No reproductive toxicity studies with Flowerpone® Orange Blossom are available.

In a 1989 reproductive and developmental screening test according to old (1966) FDA guidelines under GLP, using essential oil of coriander with 72.9% linalool and 22.3% other identified terpenoids diluted with maize (corn) oil, female rats were treated once daily by gavage from 7 days premating for a maximum of 40 days (all animals killed at 4-5 days postpartum) while the males were not treated. In the dams, all dosages caused excess salivation, which was significant in the middle (500 mg/kg bw/day) and high dose (1000 mg/kg bw/day) groups. A significant number of high-dose dams had urine-stained fur. One or two of the high-dose group showed ataxia or decreased motor activity during treatment, which are considered toxic (pharmacological) effects of linalool. During the premating period, body weight gain and feed consumption were decreased in the high-dose group, but during gestation significant increases in absolute and relative body weight gain were seen in all three treatment groups including the low dose group (250 mg/kg bw/day). Based on these results, 500 mg/kg bw/day was proposed as the maternal NOAEL while the NOEL was below 250 mg/kg bw/day. On the offspring side, adverse effects were only noted in the maternal high-dose group, with foetal deaths *in utero,* a concomitant decrease in live litter size and a significant increase in pup morbidity and mortality during the first four or five days postpartum. However, even at the highest dose administered to dams, there were no effects on length of gestation, pup sex ratio, pup body weight or gross morphology. Based on this evidence, 500 mg/kg bw/day was the NOEL for the offspring. While at 1000 mg/kg bw/day there was significant foetal and pup mortality, there were no gross signs of teratogenicity in the pups (OECD, 2004).

Tsuji et al. (1975) reported a teratogenicity study with d-limonene. Four groups of 20 Wistar female rats each were administered 0, 591 or 2869 mg/kg bw/day *d*-limonene on days 9 -15 of gestation. At the highest dose level, increases in maternal mortality and decreases in maternal and fetal body weights were reported. Additionally, at the highest dose level, delayed ossification of fetal metacarpal bones and proximal phalanxes and decreased weights of the thymus, spleen, and ovaries were observed. The NOAEL for both maternal and offspring toxicity was reported to be 591 mg/kg bw/day.

Potential reproductive toxicity of a C9-11 linear primary alcohol 6-mole ethoxylate was tested in a two-generation study in Fischer rats. Rats were treated by dermal application of 1, 10 and 25% aqueous solution. No compound-related effects on the reproductive performance or on the growth and development of the offspring were detected (Gingell and Lu, 1991).

It is generally recognized that mono- and dialkyl esters of ethylene glycol with methanol and ethanol are reproductive and developmental toxins. However, this toxic effect decreases quickly with the length of the alkyl chain as well as with the number of monomer units in the polyethoxy chain. Generally, polyethylene glycol ethers of fatty alcohols are considered not to pose any developmental toxic hazard (CIR, 1996), which is also supported by the negative findings in the study of Gingell and Lu (1991).

Conclusion

Given the available data on its ingredients and the low use concentration in cosmetic products, it can reasonably be concluded that Flowerpone® Orange Blossom is unlikely to result in any developmental toxic effects.

Exposure information

Dietary exposure to bitter orange extracts and constituents

Bitter oranges are grown mainly for processing as preserves (especially marmalade) and syrup due to their tart flavour. The essential oil is used to add fragrance to beverages and liqueurs (e.g., Curacao and Grand Marnier), sweet foods like candies and cakes, soaps, detergents, cosmetics, perfumes, and in sauces for meats and poultry. The extract has been added to many dietary supplements and herbal weight loss formulas.

Human exposure to bitter orange peel and its constituents occurs primarily via ingestion of the fruit itself or its products (e.g., orange juice, marmalade, flavourings and fragrances, and dietary supplements). Weight loss formulas usually contain 100-200 mg bitter orange extract.

Exposure to linalool

Approximately 12,000 tons linalool are estimated by industry to be produced per annum, while natural biosynthesis through plants, mostly herbs, spices, trees and citrus fruits, is higher by dimensions. More than 95% of synthetic linalool is used for its fragrance and odorant qualities in cosmetics, soaps, perfumes, household cleaners, waxes and care products, while only approximately 1% is added to food and beverages for aroma and flavouring. Chemical production workers are rarely exposed to linalool, due to quasi-closed synthesis. The public, in contrast, is widely exposed to linalool, both from natural and synthetic sources, as an ingredient of formulated food and beverages, cosmetics and household products, but also as a natural constituent of fruits and spices.

Oral exposure to linalool, based on production and use volumes of linalool and eight of its common esters, from formulated food products was estimated at up to 72 µg/kg/day for Europe and the USA. Adding linalool from natural sources may possibly double this, resulting in an estimated maximal daily intake of 140 µg/kg/d. In 1999, JECFA (FAO/WHO Joint Expert Committee on Food Additives) revised its Acceptable Daily Intake (ADI) for the sum of alicyclic and acyclic terpenoid alcohols in food and beverages, with the new value of 0-0.5 mg/kg/day (OECD, 2004, UNEP publications).

Exposure to limonene

Limonene occurs naturally in certain trees and bushes, in fruits especially citrus fruits, vegetables, meats, and spices and is used in many food products. Limonene and other monoterpenes are released in large amounts mainly to the atmosphere. The Food and Drug Administration lists limonene as a generally recognized as safe (GRAS) food additive/flavoring and fragrance additive. Extracted *d*-limonene is used primarily as a lemon fragrance in soaps, detergents, creams, lotions and perfumes, and as a flavouring agent in foods, beverages and chewing gum. It is found in non-alcoholic beverages (31 ppm), ice cream and ices (68 ppm), candy (49 ppm), baked goods (120 ppm), gelatins and puddings (48-400 ppm), and chewing gum (2300 ppm) (NTP, 1990). A guidance value for the ingestion of limonene was calculated to be 0.1 mg/kg bw/day. At current estimated levels of exposure, limonene in foodstuffs does not appear to represent a significant risk to human health (WHO, 1998).

Flowerpone® Orange Blossom

Product No. 101401

Estimated topical exposure to linalool from Flowerpone® Orange Blossom								
Product category	Type of cosmetic product	Quantity per application (g)	Frequency of applications (no. per day)	Retention/ partition factor	Daily exposure to product (g/day)	Max. use conc. of Flowerpone® Orange Blossom (%)	Max. conc. of linalool in Flowerpone ® Orange Blossom (%)	Topical exposure to linalool constituent (mg/day)
Leave-on	Facial cream	0.8	2	1	1.6	5	0.063	0.05
	General purpose cream	1.2	2	1	2.4	5	0.063	0.0756
	Body lotion	8.0	1	1	8.0	5	0.063	0.252
	Antiperspirants	0.5	1	1	0.5	5	0.063	0.01575
	Hair styling	5.0	2	0.1	1.0	5	0.063	0.0315
	Eye make-up	0.01	2	1	0.02	5	0.063	0.00063
	Mascara	0.025	1	1	0.025	5	0.063	0.000788
	Lipstick	0.01	4	1	0.04	5	0.063	0.00126
	Eyeliner	0.005	1	1	0.005	5	0.063	0.000158
Rinse-off	Make-up remover	2.5	2	0.1	0.5	5	0.063	0.01575
	Hair conditioner	14.0	0.28	0.01	0.04	5	0.063	0.001235
	Shampoo	8.0	1	0.01	0.08	5	0.063	0.00252
	Shower gel	5.0	2	0.01	0.1	5	0.063	0.00315
	Mouthwash	10.00	3.00	0.10	3.00	5	0.063	0.0945
	toothpaste	1.40	2.00	0.17	0.476	5	0.063	0.01499
Sum								0.560

Margin-of Safety consideration

Bitter orange is regulated by the Food and Drug Administration (FDA), bitter orange peel, oil, oleoresins, and extracts are generally recognized as safe (GRAS) as a direct additive to food. In frozen concentrated orange juice, the volume of bitter orange that may be added cannot exceed 5%.

The International Fragrance Association (IFRA) standard for bitter orange peel oil is 1.25% in products applied to areas of the skin that are exposed to the sun.

The use of Flowerpone® Orange Blossom in cosmetic products at concentration up to 5% incorporates bitter orange blossom oil in concentrations of 0.0075% at the most.

MOS for linalool

For calculation of a MOS for linalool, the NOAEL of 117mg/kg bw/day from a 28-day repeated dose toxicity study will be used. As no information is available on the skin penetration rate, an estimated skin absorption rate of 5% will be assumed. For linalool constituting about 0.063% in Flowerpone® Orange Blossom, a systemic external exposure of 0.56 mg/person/day can be estimated, which is equivalent to an absorbed dose of about 0.56 mg/day x 5% 60 kg = 0.0022 mg/kg/day. The following margin of safety (MOS) for linalool in Flowerpone® Orange Blossom in cosmetics can be calculated:

MOS = 117 mg/kg/day / 0.0022 mg/kg/day = 53 182

For the exposure calculation the measured concentration of linalool was used. In addition, orange flower oil contains smaller amounts of linalyl esters, such as linalyl acetate, which will quickly be hydrolyzed in the skin and then may contribute to the systemic linalool dose. However, the MOS is sufficiently large to include the additional exposure from linalyl esters.

MOS for limonene

For calculation of a MOS for limonene, the NOAEL of 300 mg/kg/day from a 13 weeks repeated dose toxicity study will be used. A skin absorption rate of 52% will be assumed. For limonene constituting about 0.002% in Flowerpone® Orange Blossom, a systemic exposure of about 0.0002 mg/kg/day can be estimated. The following margin of safety (MOS) for limonene in Flowerpone® Orange Blossom in cosmetics can be calculated:

MOS = 300 mg/kg/day / 0.0002 mg/kg/day = 1,500,000

MOS for trideceth-9

For calculation of a MOS for trideceth-9, the NOAEL of 480 mg/kg/day from a 90-day study of oleth-20 in dogs will be used. As no information is available on the skin penetration rate, an estimated skin absorption rate of 10% will be assumed. For trideceth-9 constituting

about 2.9% in Flowerpone® Orange Blossom, a systemic exposure of about 0.12 mg/kg/day can be estimated. The following margin of safety (MOS) for trideceth-9 in Flowerpone® Orange Blossom in cosmetics can be calculated:

MOS = 480 mg/kg/day / 0.12 mg/kg/day = 4000

Evaluation of ingredients considered as allergens

Exposure

For skin sensitization, cosmetic products applied in the highest skin area dose (mg/cm²/day) are the most relevant product types. Taking into consideration in which product types plant extracts are usually used as ingredients, solid deodorants and facial cream are considered most relevant.

Exposure to solid deodorants and facial cream was estimated at 7.5 and 2.5 mg/cm²/day, respectively (Api et al., 2006). Assuming a use concentration of 5% for the botanical ingredient in the formulation this would result in skin exposure at 0.375 and 0.125 mg/cm²/day.

For the measured concentrations of sensitizing botanical components the following exposure would result:

	Deodorant	Facial cream	
Farnesol (0.01%):	0.038	0.013	µg/cm²/day
Geraniol (0.001%):	0.0038	0.0013	µg/cm²/day
Limonene (0.002%):	0.0075	0.0025	µg/cm²/day
Linalool (0.063%:	0.24	0.079	µg/cm²/day
Epoxybergamottin (0.00136%):	0.0051	0.0017	µg/cm²/day

This exposure has to be compared to an experimental no-expected-sensitization-induction-level after application of a sensitization assessment factor. These NESILs were taken from Api et al. (2006). Assessment factors of 300 have been proposed for deodorants and men's facial cream (Api et al., 2006). Application of the assessment factor leads to the following acceptable exposure levels in deodorants and facial cream:

	NESIL	Deodorant	Facial cream	
Farnesol:	2700 µg/cm²/day	9.0	9.0	µg/cm²/day
Geraniol:	12000 µg/cm²/day	40	40	µg/cm²/day
Limonene:	10000 µg/cm²/day	33	33	µg/cm²/day
Linalool:	15000 µg/cm²/day	50	50	µg/cm²/day

Epoxybergamottin: no data

The estimated consumer exposure levels are well below the derived acceptable exposure levels and therefore, their presence in a botanical at the concentrations given above is considered not to pose a relevant skin sensitization hazard.

No LLNA or HRIPT was found for epoxybergamottin; however, comparing dermal exposure to that of other botanical components or with the skin sensitization TTC derived below, it can be considered not to pose a relevant skin sensitization risk; but it should be noted that epoxybergamottin belongs to the furanocoumarins that due to the phototoxic, photomutagenic and photocarcinogenic properties reported for certain furanocoumarins, are not permitted for use in cosmetic products as such, except for the normal content in natural essences if the total concentration of furanocoumarin-like substances in the finished cosmetic product does not exceed 1 ppm SCCP (2003; 2005).

Skin sensitization TTC

A provisional skin sensitization threshold of concern is based on the most potent of the 26 fragrance ingredients that have to be labeled on cosmetic products in the EU: from experimental data it was concluded that 120 µg/cm²/day methyl 2-octy-noate (methyl heptine carbonate) would not induce sensitization (Api et al., 2006). Applying a skin sensitization assessment factor of 300 (Api et al., 2006) and an additional modifying factor of 10 to account for the limited selection on skin sensitizers and a possible higher sensitization potency of an uncharacterized sensitizers, giving a total factor of 3000, a provisional skin sensitization TTC of 0.04 µg/cm²/day can be derived. Components with likely skin sensitization potential but unknown potency for which the skin area exposure is below this value can be considered not to pose any risk of inducing skin sensitization.

Furanocoumarins

According to earlier SCCNFP Opinions (SCCNFP/0392/00, SCCNFP/0765/03), the SCCP concluded for furanocoumarins, including 5- (bergapten) and 8-methoxypsoralen (xanthotoxin) that due to the phototoxic, photomutagenic and photocarcinogenic properties reported for certain furanocoumarins, they are not permitted for use in cosmetic products as such, except for the normal content in natural essences if the total concentration of furanocoumarin-like substances in the finished cosmetic product does not exceed 1 ppm.

Analytical quantification of 16 furanocoumarins including 15 components mentioned by the SCCP (2005) revealed in a total concentration of approx. 10667 ppm in the orange blossom concentrate. Flowerpone® Orange Blossom contains in total 16 ppm (calculated) furanocoumarins. Therefore, the use of Flowerpone® Orange Blossom at the maximum recommended use concentration in all cosmetic products, except sprays, will meet the requirement of the SCCP in that the total concentration of furanocoumarin-like substances should not exceed 1 ppm in the finished cosmetic product.

EDTA

Human exposure to EDTA and its salts arises directly from the use in food additives, medicines, hygiene products and personal care. Typical use of disodium EDTA in cosmetic formulations ranges at 0.001-0.8%. Exposure to EDTA from drinking-water is probably very small in comparison with that from other sources. The ADI for EDTA as the free acid is 0.6 mg/litre (WHO, 2003). Calcium disodium EDTA is poorly absorbed from the gut. The long-term toxicity of EDTA is complicated by its ability to chelate essential and toxic metals. Those toxicological studies that are available indicate that the apparent toxicological effects of EDTA have in fact been due to zinc deficiency as a consequence of complexation. EDTA does not appear to be teratogenic or carcinogenic in animals. The lowest dose reported to cause a toxic effect in animals was 750 mg/kg/day. A clinical study using male subjects reported almost no absorption of calcium disodium EDTA following dermal exposure, penetrating the skin resulting in systemic levels well below those shown to produce adverse effects in the oral dosing studies. The CIR Expert Panel concluded that disodium EDTA is safe as used in cosmetic formulations (CIR, 2002).

Citric acid

Citric acid is used as an additive in Flowerpone® Orange Blossom, resulting in a final maximum concentration of 0.01% in the cosmetic product. Citric acid is generally recognized as safe for use in cosmetics, medicines and food (US law 21 CFR 184.1033). Also the level is well below the use concentrations of α-hydroxy acids that have been considered safe by the SCCNFP (2004).

(-)-α-Bisabolol

(-)-α-Bisabolol is an unsaturated monocyclic terpene alcolhol used in cosmetic formulations as a skin conditioning agent. The use as a tracer additive in Flowerpone® Orange Blossom results in a final maximum concentration of 0.025% in the cosmetic product. This level is well below the level of 1% which was considered as safe by the Cosmetic Ingredient Review Panel (CIR, 1999).

PEG-40 hydrogenated castor oil

PEG-40 hydrogenated castor oil is regarded as safe for the use in cosmetic formulations as solubilizer based on published reports of the Cosmetic Ingredient Review Panel (CIR, 1997).

Pentylene glycol

Butylene glycol and hexylene glycol are regarded as safe for the use in cosmetic products based on the published report by the Cosmetic Ingredient Review Panel (CIR, 1985), and it is considered acceptable to extrapolate the results to pentylene glycol.

Taken together Flowerpone® Orange Blossom is considered not to pose any undue risk to consumers with regard to systemic effects.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: August 19, 2016

SUBJECT: Citrus Aurantium Amara (Bitter Orange) Flower Extract

Anonymous. 2016. Citrus Aurantium Amara (Bitter Orange) Flower Extract: Clinical safety testing summary.

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CIR

Citrus Aurantium Amara (Bitter Orange) Flower Extract

Clinical Safety Testing Summary

Human Repeated Insult Patch Test-1

% Citrus Aurantium Amara (Bitter Orange) Flower Extract	Product Type	Completed Subjects	Occlusivity	Did formula Induce an Allergic Response	Number of Subject showed Allergic Response
0.000100	Leave-on	207	Occlusive	No	0
0.000010	Rinse-off	207	Occlusive	No	0

HRIPT Protocol Testing Summary	
Test material applied to patch	50µl
Panelist discontinued due to reactions	0
Patch duration	48 hours
Induction patches	9
Weeks Induction	3 weeks
Week Rest Period	12 days
Challenge	original & alternative (naïve sites)
Challenge readings	48 & 96 hours post application

Human Repeated Insult Patch Test-2

% Citrus Aurantium Amara (Bitter Orange) Flower Extract	Product Type	Completed Subjects	Occlusivity	Did formula Induce an Allergic Response	Number of subject showed Allergic Response
0.000500	Wipe-off	212	Occlusive	No	0
0.000600 – 0.00080	Leave-on	212	Occlusive	No	0

HRIPT Protocol Testing Summary	
Test material applied to patch	0.1 ml
panelist discontinued due to reactions	0
patch duration	48 Hours
induction patches	9
weeks induction	3 weeks
week rest period	2 weeks
challenge	Original Site & naïve site on the opposite side of back
challenge readings	after 48 hours & 96 Hours

Human Repeated Insult Patch Test Scales - 1

Induction Grading Scale

Erythema and Elevated Responses

0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; or minimal edema; or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Effects on Superficial Layers of the Skin

A	0	Slight glazed appearance
B	1	Marked glazing
C	2	Glazing with peeling and cracking
D	3	Glazing with fissures
E	3	Film of dried serous exudate covering all or portion of the patch site
F	3	Small petechial erosions and/or scabs

Other Responses/Recording Designations

W	Weeping - evidence of release of fluid from a vesicular or bullous reaction
T	Marked reaction to adhesive (patch relocated)
X	Succeeding patch not applied and succeeding grade is for residual reaction
R	Subject did not remove the patch at the assigned time
L-1	Subject report of lost patch (came off) during first 12 hours of exposure
L-2	Subject report of lost patch (came off) between 12 and 48 hours of exposure
(-)	Subject absent

Human Repeated Insult Patch Test Scales -2

2.3.4 Scoring of Test Sites

Skin reactions at the patch sites were assigned using the following scale:

2.3.4.1 Induction Grading Scale

Erythema and Elevated responses:

0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; or minimal edema; or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Effects on superficial layers of the skin:

A	0	Slight glazed appearance
B	1	Marked glazing
C	2	Glazing with peeling and cracking
D	3	Glazing with fissures
E	3	Film of dried serous exudate covering all or portion of the patch site
F	3	Small petechial erosions and/or scabs

Other Responses/Recording Designations:

W	Weeping - evidence of release of fluid from a vesicular or bullous reaction.
T	Marked reaction to adhesive (patch relocated)
X	Succeeding patch not applied and succeeding grade is for residual reaction
R	Subject did not remove the patch at the assigned time
L-1	Subject report of lost patch (came off) during first twelve hours of exposure
L-2	Subject report of lost patch (came off) between 12 and 48 hours
(-)	Subject Absent

Cumulative Irritation Test - 1

% Citrus Aurantium Amara (Bitter Orange) Flower Extract	Product Type	Completed Subjects	Occlusivity	Irritation Classification*
0.0001000	Leave-on	26	Occlusive	Mild material no experimental irritation

Cumulative Irritation Test Protocol Summary	
Test material applied to patch	100µl
panelist discontinued due to reactions	0
patch duration	24 Hours
Total Number of patches	12
Irritation Readings frequency	24 Hours

Reference- Berger RS, Bowman JP. A reappraisal of the 21-day cumulative irritation test in man. J. Toxicol Cutaneous Ocul Toxicol. 1982:1(2):109-15.

Cumulative Irritation Test - 2

% Citrus Aurantium Amara (Bitter Orange) Flower Extract	Product Type	Completed Subjects	Occlusivity	Irritations classification*
0.0005 - 0.001	Leave-on	140	Occlusive	Mild material no experimental irritation

Cumulative Irritation Test Protocol Summary	
Test material applied to patch	20µl
panelist discontinued due to reactions	0
patch duration	22 ± 1 hour
Total Number of patches	12
Irritation Readings frequency	24 Hours

Reference- Berger RS, Bowman JP. A reappraisal of the 21-day cumulative irritation test in man. J. Toxicol Cutaneous Ocul Toxicol. 1982;1(2):109-15.

Photo Toxicity Testing

% Citrus Aurantium Amara (Bitter Orange) Flower Extract	Product Type	Completed Subjects	Occlusivity	No of Subjects exhibiting phototoxic response
0.0001 - 0.002	Leave-on	92	Occlusive	0

Phototoxicity Protocol Summary	
Test material applied to patch	20µl
Panelist discontinued due to reactions	0
Patch duration	24 Hours
Total Number of patches	1 Patch
Irritation Readings frequency	24, 48 & 72 hours
Duration of UVA radiation	17 mins

PhotoToxicity Scales

SCORING SYSTEM:*

0	=	No visible reaction	E	=	Edema	HR	=	Hours after patch application
±	=	Faint, minimal erythema	DR	=	Dryness	BI	=	Before Irradiation
1	=	Erythema	^	=	Hyperpigmentation	AI	=	After Irradiation
2	=	Intense erythema	S	=	Staining			
3	=	Erythema with induration	P	=	Peeling			
4	=	Wheal-flare blister (vesicles)	-	=	No irradiation and/or reading			

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

Photoallergy Testing

% Citrus Aurantium Amara (Bitter Orange) Flower Extract	Product Type	Completed Subjects	Occlusivity	No of Subjects Exhibiting Photoallergic Response
0.0001 - 0.002	Leave-on	247	Occlusive	0

Photoallergy Testing Protocol Summary	
Test material applied to patch	0.2gm
Panelist discontinued due to reactions	0
Patch duration	24 Hours
Total Number of patches	6 Patches
Irritation Readings frequency	48 & 72 & 96 hours
Duration of UVA radiation	17 mins

Photoallergy Scales

SCORING SYSTEM*

0	=	No visible reaction
±	=	Faint, minimal erythema
1	=	Erythema
2	=	Intense erythema
3	=	Intense erythema, induration, vesicles
4	=	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	=	Edema
DR	=	Dryness
P	=	Peeling
S	=	Staining
T	=	Tan
^	=	Hyperpigmentation
C	=	Change in test site
(-)	=	No patch application and/or reading
X	=	Discontinued
B	=	Before irradiation
A	=	After irradiation
ST	=	Skin Type

*International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27

Thank you

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Memorandum

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

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

DATE: June 1, 2016

SUBJECT: Comments on the Draft Safety Assessment of *Citrus* Flower- and Leaf-Derived Ingredients as Used in Cosmetics (prepared for the June 6-7, 2016 meeting)

Key Issues

Although some composition information has been added to this report, the published literature has much more additional information such as:

Dugo G and Mondell L. 2010. Citrus Oils: Composition, advanced analytical techniques, contaminants and biological activity. CRC Press, Taylor & Francis Group (includes a chapter on petitgrain oils and a chapter on bitter orange flower extracts)

Tisserand R and Young R. 2014. Essential Oil Safety: A guide for health care professionals, 2nd ed. Elsevier.

Although not yet noted in the CIR report, Tisserand and Young indicate that mandarin leaf oil (*Citrus reticulata*; syn *Citrus nobilis* may contain a significant amount of dimethyl anthranilate (up to 51.9%) (also called methyl N-methylanthranilate) for which IFRA has developed a limit of 0.1% for leave-on products based on phototoxicity and potential for nitrosamine formation.

Concerning petitgrain bigarade oil, reference 20 (from RIFM) states: "By steam distillation of the leaves and twigs of the bitter orange tree *Citrus aurantium* L. subsp. *amara*...". Therefore, either the information on petitgrain bigarade oil needs to be moved to the Citrus plant and seed report, or Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (as well as Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract) needs to be moved to the flower and leaf report. The *Food Chemical Codex* includes "Petitgrain Oil, Paraguay Type" which is also described as "the volatile oil obtained by steam distillation from the leaves and small twigs of the bitter orange tree, *Citrus aurantium* L. subspecies *amara*". This material contains not less than 45.0% and not more than 60% of esters calculated as linalyl acetate. [Note: Petitgrain Paraguay Essential Oil is a trade name listed under the INCI name Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil.]

Additional Considerations

Introduction - Only 14 of the 32 ingredients in this report have any reported uses, and the greatest use frequency is only 99. Therefore, it is not appropriate to state that these ingredients are "widely" use in cosmetics.

Cosmetic Use, Tables 9 and 10 - There are 32 ingredients included in this report; 14 ingredients plus *Citrus hystrix* leaf oil are included in the use table (Table 9), and 9 ingredients are in the no uses table (Table 10). The ingredients in Table 9 and 10 account for 23 of the ingredients. What about the other 9 ingredients?

Summary - If furanocoumarins are not found in the Citrus leaves or flowers, why is bergapten being used as an example of a constituent of concern in the Summary?

Table 1, Table 3 - It is misleading to include accepted scientific names with some of the ingredient definitions but not others. As the "accepted" scientific names are stated in Table 3, it is not necessary to include that part of each definition in Table 1. A footnote should be added to Table 1 to indicate that accepted scientific names (as stated in INCI definitions) are shown in Table 3.

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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: July 11, 2016

SUBJECT: Comments on the Tentative Report: Safety Assessment of *Citrus* Flower- and Leaf-Derived Ingredients as Used in Cosmetics (released June 16, 2016)

Key Issues

The addition of composition information from reference 32 (Tisserand and Young) in Table 7 is helpful, but additional information from this book should be added to this report. For example, a footnote should be added to Table 7 to indicate that Tissarand and Young provide composition information for components down to a concentration of 1%, or lower for known toxic constituents. Additional information about how some of these ingredients are made should also be stated. For example, the material called Citrus Aurantium Amara (Bitter Orange) Flower Water in Table 7 is described as an absolute (ethanol extract) made from the distillation water of bitter orange flowers. Based on composition, Tisserand and Young also provided safety recommendations. No limits are recommended for *Citrus hystrix* leaf oil, Citrus Aurantium Amara (Bitter Orange) Flower Oil (neroli), bitter orange flower extract, or bitter orange leaf extract (described as an absolute). Based on the dimethylanthranilate content, a dermal use limit of 0.17% is recommended for Citrus Reticulata (Mandarin) Leaf Oil (maximum use concentration reported 0.1%). Based on benzyl cyanide content, a maximum dermal use limit of 1% is recommended for bitter orange flower extract (maximum use concentration reported 0.032%). To avoid skin sensitization, Tissarand and Young recommend a maximum dermal use concentration of 1.2% for *Citrus limon* (lemon) leaf oil (not INCI; not in the report). For ingredients containing linalool it should be noted that Tissarand and Young state: "According to IFRA, essential oils rich in linalool should only be used when the level of peroxides is kept to the lowest practical value. The addition of antioxidants such as 0.1% BHT or α-tocopherol at the time of production is recommended."

The information in Table 7 on Citrus Aurantium Amara (Bitter Orange) Leaf Oil needs to be moved to the plant, seed report as this is actually petitgrain bigarade oil (leaf twig).

Please check Forbes et al. (1977) (reference 27 of the plant, seed report) as it appears they also

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tested two types of neroli oil (Citrus Aurantium Amara (Bitter Orange) Flower Oil) for photosensitzation. Both were negative.

Constituents/Composition/Impurities, Summary - Please add more text to this section describing differences in composition among the ingredients included in this report. For example, Table 7 indicates that Citrus Aurantium Amara (Bitter Orange) Flower Oil is 31.4-54.3% linalool, the absolute of bitter orange flower water is 67.5% linalool plus 2-phenylethanol, Citrus Reticulata (Mandarin) Leaf Oil is 43.2-51.9% dimethyl anthranilate and *Citrus hystrix* leaf oil is 58.9-81.5% citronellal.

Additional Considerations

Introduction - The information about the previously reviewed *Citrus* seed oil ingredients is not relevant to this report on *Citrus* flower- and leaf-derived ingredients.

Chemistry - General information about how waters are made as provided in the Dictionary should be added to the Chemistry section.

Non-Cosmetic Use - Please add that *Citrus hystrix* (kaffir lime) leaves are a common ingredient used in Southeast Asian cuisine.

Acute Toxicity - It should also state that sweet orange flowers are considered GRAS (correctly stated in the Non-Cosmetic Use section).

Summary - Please restate which ingredients are considered GRAS in the Summary.

Discussion - In the paragraph before the list of data needs, "seed-derived" needs to be corrected to "leaf-derived".

As Citrus Aurantium Amara (Bitter Orange) Flower Wax was included in concentration of use surveys completed in 2013 and in 2016 it was not included in a new survey. Because it has not yet been surveyed, a concentration of use survey for *Citrus hystrix* leaf oil is under way.

Table 1 - Please make it clear that *Citrus hystrix* leaf oil is not in the Dictionary.