Safety Assessment of *Citrus* Plant- and Seed-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, D.P.A. This report was prepared by Christina Burnett, Senior Scientific Analyst/Writer.

Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: September 2, 2016
Subject: Draft Final Safety Assessment on *Citrus* Plant- and Seed-Derived Ingredients

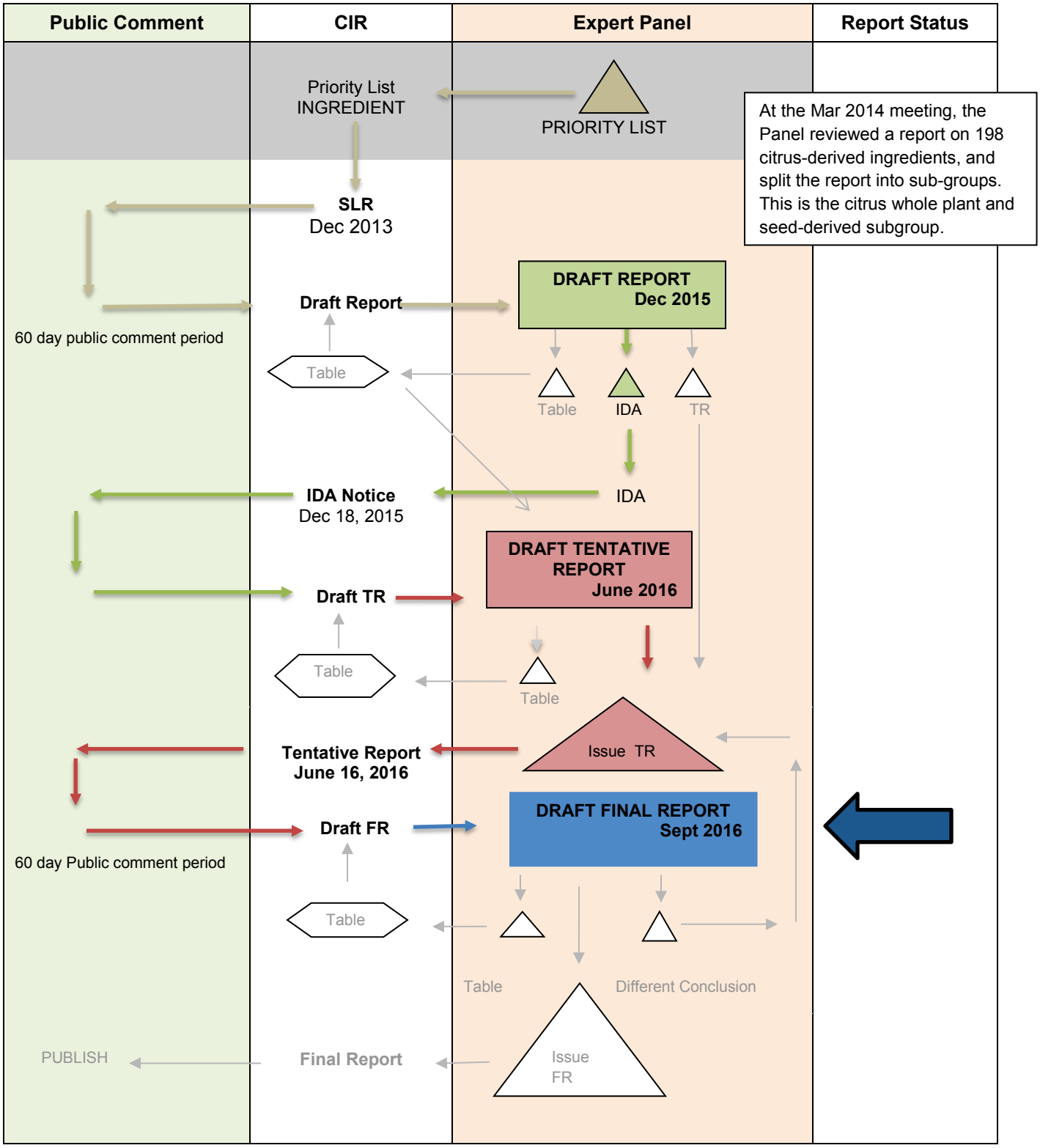
Enclosed is the Draft Final Report of the Safety Assessment of *Citrus* Plant- and Seed-Derived Ingredients as Used in Cosmetics. (It is identified as *cplant092016rep* in the pdf document).

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 32 Citrus plant- and seed-derived ingredients included in this report are safe under the intended conditions of use in cosmetic formulations. The data requested by the Panel included:

- Method of manufacturing for all these ingredients, except the seed extracts
- Chemical composition and impurities for all these ingredients, except the seed oils and seed extracts
- Irritation and sensitization, especially human repeated insult patch tests (HRIPT) on Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil and Citrus Grandis (Grapefruit) Seed Extract at maximum use concentrations or greater.
- If the composition for these *Citrus* plant- and seed-derived ingredients are significantly different from that of the *Citrus* peel-, flower-, and leaf-derived ingredients, then data on systemic endpoints such as a 28-day dermal toxicity, reproductive and developmental toxicity, and genotoxicity, as well as UV absorption spectra are needed.

Since June, CIR staff received an unpublished data submission on 0.15% Citrus Grandis (Grapefruit) Seed Extract that described a 48-h occlusive patch study in humans. No other data were received. Additional information on the GRAS status of Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil and IFRA standards for linalool and limonene has been added to the report. All new data have been incorporated into the report and highlighted with |brackets| in text or shaded in tables. At the June meeting, the Panel asked that the data on Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil be moved from the *Citrus* flower- and leaf-derived ingredients report to this report; this data has also been highlighted in this report for ease of review. Comments provided by Council on the draft tentative and tentative reports have been considered. The comments are included in this report package (*cplant092016pcpc1-2).*

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.


Public Comment
CIR
Expert Panel
Report Status
Priority List
INGREDIENT
PRIORITY LIST
At the Mar 2014 meeting, the Panel reviewed a report on 198 citrus-derived ingredients, and split the report into sub-groups. This is the citrus whole plant and seed-derived subgroup.
SLR
Dec 2013
Draft Report
DRAFT REPORT
Dec 2015
60 day public comment period
Table
Table
IDA
TR
IDA Notice
Dec 18, 2015
IDA
DRAFT TENTATIVE REPORT
June 2016
Draft TR
Table
Table
Issue TR
Tentative Report
June 16, 2016
DRAFT FINAL REPORT
Sept 2016
Draft FR
60 day Public comment period
Table
Table
Different Conclusion
Issue
FR
PUBLISH
Final Report

Citrus Plant- and Seed-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 Panel requested additional data to support the safety of the 33 *Citrus* plant- and seed-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) leaf/twig oil and citrus grandis (grapefruit) seed extract at maximum use concentrations or greater
- If the composition for these *Citrus* plant- and seed-derived ingredients are significantly different from that of the *Citrus* peel-, flower-, and leaf-derived ingredients, then data on systemic endpoints such as a 28-day dermal toxicity, reproductive and developmental toxicity, and genotoxicity, as well as UV absorption spectra are needed

June 2016 - The Panel issued a tentative report with the conclusion that the available data are insufficient to make a determination that the 32 *Citrus* plant- and seed-derived ingredients included in this report are safe under the intended conditions of use in cosmetic formulations. The data requested by the Panel included:

- Method of manufacturing for all these ingredients, except the seed extracts
- Chemical composition and impurities for all these ingredients, except the seed oils and seed extracts
- Irritation and sensitization, especially human repeated insult patch tests (HRIPT) on Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil and Citrus Grandis (Grapefruit) Seed Extract at maximum use concentrations or greater.
- If the composition for these *Citrus* plant- and seed-derived ingredients are significantly different from that of the *Citrus* peel-, flower-, and leaf-derived

ingredients, then data on systemic endpoints such as a 28-day dermal toxicity, reproductive and developmental toxicity, and genotoxicity, as well as UV absorption spectra are needed.

The Panel removed Citrus Tangerina (Tangerine) Extract from this report because it was identical to another ingredient in the *Citrus* fruit-derived ingredient report, bringing the total number of ingredients in this report to 32.

Citrus Plant- and Seed-Derived Ingredients Data Profile – September 2016 – Writer, Christina Burnett											
	In-Use	**Physical/Chemical Properties**	**Method of Manufacturing**	**Composition/Impurities**	**Acute Toxicity**	**Carcinogenicity**	**Irritation/Sensitization - Nonhuman**	**Irritation/Sensitization - Clinical**	**Ocular/Mucosal**	**Phototoxicity**	**Case Studies**
Citrus Aurantifolia (Lime) Oil	X										
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil	X		X	X	X		X	X		X	
Citrus Aurantium Dulcis (Orange) Oil	X										
Citrus Aurantium Dulcis (Orange) Seed Extract	X										
Citrus Aurantium Sinensis Powder	X										
Citrus Australasica Seed Oil		X		X							
Citrus Glauca Seed Oil		X		X							
Citrus Grandis (Grapefruit) Extract	X										
Citrus Grandis (Grapefruit) Seed Extract	X							X			
Citrus Junos Extract	X										
Citrus Junos Seed Extract	X		X	X							
Citrus Junos Seed Oil	X										
Citrus Limon (Lemon) Flower/Leaf/Stem Extract	X										
Citrus Nobilis (Mandarin Orange)	X										
Citrus Nobilis (Mandarin Orange) Oil	X										
Citrus Paradisi (Grapefruit) Seed Extract	X		X	X							
Citrus Reticulata (Tangerine) Extract	X										
Citrus Tangerine (Tangerine) Extract	X										
Citrus Aurantium (Bitter Orange) Oil (not INCI ingredient)	X										
Citrus sinensis leaves and branches				X							
Citrus sinensis seed flour				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 Plant- and Seed-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 toxicity" or "citrus AND irritation"– 0 new relevant references found.
Updated searches February –May 2016 with the term "citrus seed composition" (29 hits) and "citrus plant composition" (555 hits) and "citrus branch composition" (5 hits) and "citrus stem composition" (7 hits) – 4 relevant references found.
Updated search 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 Plant- and Seed-Derived Ingredients
June 6-7, 2016

Dr. Marks' Team

DR. MARKS: Okay. I think we will move on to the next ingredient, and that will be the citrus plant and seed.

MS. BURNETT: This one should be easy.

DR. MARKS: That's what Ron Hill said with the last two.

DR. HILL: No, I said the last two were going to be progressively easier.

DR. MARKS: We are now to the citrus plant, and see the derived ingredients memo from Christina dated May 13 of this year. At the December meeting last year, the Panel issued an insufficient data announcement for the 33 citrus plant and seed derived ingredients.

It looks pretty similar, method of manufacture, chemical composition and impurities, irritation and sensitization to several ingredients, and then the composition was significantly different from the citrus peel, and data on systemic endpoints like a 28 day dermal tox, reproductive, developmental, et cetera.

DR. SHANK: Data needs are the same as we had in December.

DR. SLAGA: We didn't get any irritation and sensitization.

DR. SHANK: Most of these are used in very low concentrations,.005 percent. Is that right?

DR. HELDRETH: Yes.

DR. SHANK: Concentration.

DR. HELDRETH: Skin -- miscellaneous.

DR. MARKS: The only one I have -- there were a couple at.36 and.15 with a lot of uses. The lime oil is.36, highest concentration, a leave on, and then grapefruit seed extract was.15, 144 uses total. We didn't have the concentration of bitter orange oil, which is not an INCI ingredient, but that has a lot of uses, 295.

MS. BURNETT: We think that is a misclassification, but I can maybe talk to the FDA people. We believe it is probably a peel oil but it was categorized -- it doesn't have a category, so it's falling under this, and we want to encompass it because it has so many uses.

DR. MARKS: So, where do we stand now? Ron and Tom?

DR. HILL: We didn't talk about moving the tangerine extract?

DR. MARKS: No.

MS. BURNETT: No.

DR. SLAGA: I know we discussed it before, we talked about the whole plant. Leaf and flower is part of that or not?

MS. BURNETT: No. We don't know.

DR. SLAGA: We should have a better definition of the plant.

MS. BURNETT: I don't write the definitions.

DR. HILL: They are sometimes informative, it says oil obtained from the whole plant, I'm assuming they mean the whole plant, but does that include the bark? It's a tree. Or these are small baby plants and they have baby bark. I don't mean to be facetious, I'm serious.

DR. SLAGA: It must be a small plant.

DR. HILL: I would think, if it is really is the whole plant, roots and all.

DR. SLAGA: I don't know.

DR. HILL: It seems to me for method of manufacture, there is a little more than the definition.

DR. MARKS: We have a little data, but the data needs is basically the same as what we had in December?

DR. SLAGA: I think so, yes.

DR. MARKS: Method of manufacture, chemical composition and impurities, HRIPT, orange oil, grapefruit seed, extract, and if not GRAS -- presumably, I will be seconding a motion that a tentative report will be issued with an insufficient conclusion. Ron Hill, I was saving that --

DR. HILL: Sorry.

DR. MARKS: No, we have to deal with it. In the memo from Christina, there is the last sentence in the bottom of the memo, and in the paragraph right before it, "This report includes citrus tangerina extract. On closer review of the definition, this ingredient should have been included in the citrus fruit derived ingredient report.

Would the Panel like to remove this ingredient from this report and administratively add it to the citrus fruit derived?"

DR. HILL: Yes.

MS. BURNETT: I know in comments that I received from the Council, they have also posed the same question for the seed oils, since they have already been reviewed, we could administratively add those possibly. I don't know if that report has been published yet. If it's not published, it might be okay, easy. I'm not sure. If it's been published --

DR. HELDRETH: We have talked about administrative additions, and the Panel has agreed. We need to come up with more of a process as to how that is going to be administered, whether we are going to change the document that is available in InfoBase or through the CIR Web site, with maybe an addendum page at the back of the report.

MS. BURNETT: Since the fruit was just finalized in December and it hadn't gone to publication yet, that one is easy. The seed oils, I think it might have been published.

DR. HILL: That report was all seed oils, right?

MS. BURNETT: Yes, it included some citrus seeds. We didn't capture these for whatever reason, at the time we didn't recognize them as --

DR. MARKS: I would be very interested in what Lillian's response to this was, Lillian Gill. To me, even though it is administrative, you are taking a conclusion you had before, which I think was 80 ingredients, and now you are making it 81.

Other than administratively, normally when we change a conclusion, we send it out for public review. I understand why we don't want to do that because it is just this one ingredient.

DR. HELDRETH: I talked to Lillian about it, and to your point, we typically only do an administrative add where it is a complete no brainer, where it just seems to be the same ingredient with a different name, that's an easy administrative act.

Here, where we are talking about something that is similar, and isn't actually the same ingredient, an administrative add probably isn't appropriate.

DR. MARKS: Okay. This is a significant change in the conclusion, if you are adding an ingredient.

DR. SHANK: With no data on it.

DR. MARKS: Yes.

DR. HELDRETH: For example, the Panel talked about where we had some apple ingredients, it is the same ingredient as far as we understand it, just a different name. The administrative add is appropriate.

DR. MARKS: Yes, but this isn't the same.

MS. BURNETT: For?

DR. HELDRETH: This was for apple.

MS. BURNETT: No, I meant in this report.

DR. MARKS: In this report, I get the sense we do not want to administratively add.

DR. HILL: The tangerine extract?

DR. MARKS: Yes. That is why I asked what was Lillian's recommendation. That was the sense I had, too. This is an important ingredient and if somebody wants it to be added to that report, it can be reopened in the future to add it.

DR. HELDRETH: Alternatively, if you want to take care of the safety assessment here and now, we could have a different conclusion for it, and later on do a re-review.

DR. HILL: Do we know what other tangerines are in that other report?

MS. BURNETT: So, I have the fruit report open, included in that was citrus reticulata tangerine fruit extract.

DR. HILL: Just reticulata?

MS. BURNETT: Right. Tangerine, that report included citrus tangerine and tangerine fruit, but not an extract, fruit water in the fruit but not the extract. Under the main reticulata, yes, under the main tangerine, no.

DR. HILL: In my humble opinion, we drop it from this report and when it shows up 15 years from now (Inaudible).

DR. MARKS: Ron Shank?

DR. HILL: I don't have any safety concerns that would cause me to think that would be a bad idea.

DR. SHANK: (Inaudible) For such a small thing.

MS. BURNETT: Prefer not to. I would prefer not to.

DR. MARKS: I think, if I get the sense of the team, remove it from this report, and that is it, just remove it, and then wait for it to be reopened in the future to add it.

DR. HELDRETH: Do you feel you have enough information in front of you to say it is safe or unsafe?

DR. SLAGA: No data.

DR. HELDRETH: And dissimilar.

DR. MARKS: Remove.

DR. HILL: If I understand correctly, we think it is probably a food extract, we don't know that it is not the whole plant extract, right?

MS. BURNETT: Based on the definition, it is the fruit.

DR. MARKS: I think what we should do, remove it from this report, don't add it to the fruit report, and wait until a re-review.

DR. SHANK: 15 years.

DR. SLAGA: 15 years?

DR. MARKS: No, it could be less than that if somebody feels it is important.

DR. SLAGA: You just want to delete it?

DR. MARKS: Yes, at this point.

DR. ANSELL: That it has been misclassified, as to whether there is sufficient data to support it, if we put it within all the other fruits is a separate question. We just think it doesn't belong in this report.

DR. MARKS: Right.

DR. HELDRETH: I concur.

DR. MARKS: I assume the Belsito team will bring that up, but if they don't, I will bring it up tomorrow, that we recommend removing it.

MS. BURNETT: Leave the seed oils as is?

DR. MARKS: Yes. Any other comments? So, just to review our discussion, I will be seconding a tentative report tomorrow with an insufficient conclusion. There are now 32 ingredients, since we removed one. We got a little data but not enough.

MS. BURNETT: Okay, that works for me.

DR. MARKS: If not, GRAS or food additive. Team, any other comments? (No response) Have we had enough citrus now?

DR. HILL: Never can get enough citrus.

Dr. Belsito's Team

DR. BELSITO: Okay, the last. Citrus plant and seed. So again, we had an insufficient in the December 2015 meeting. Since that time we've got method of manufacture, ingredient composition for some. And no other data including the requested data on irritation and sensitization were submitted. Nothing in Wave-2. We do have updated frequency of use concentration which again has changed. Some of these are lower use concentrations that we had assumed before. And the question is, where are we with this group?

DR. LIEBLER: Just about nowhere.

DR. BELSITO: Yeah.

DR. LIEBLER: I mean everything in this is insufficient for something.

DR. BELSITO: Yeah.

DR. EISENMANN: Well I thought maybe the seed oils. And if you bring over the information on the leaf and twig oil, bitter orange leaf and twig oil that's in the leaf report, the Food Chemical Codex has petitgrain oil, Paraguay- type which is described as a volatile oil obtained by steam distillation from the leaves and small twigs of the bitter orange tree and the material contains not less than 45 percent and not more than 60 percent of esters calculated as linalyl acetate. That's what Food Chemical Codex says about what I would consider the leaf, twig oil.

DR. LIEBLER: So when I looked at this I wasn't aware of the potential of bringing those data that you just pointed out in the last discussion over into this one.

DR. EISENMANN: Since I --

DR. LIEBLER: And the seed oils are the ones I flagged on my PDF page 18, the introduction. I flagged a few seed oils as at least meeting method of manufacture and impurities.

DR. EISENMANN: Because as we look at the composition of these seed oils compared to citrus seed oils that were included in the oils report, they're very similar.

DR. LIEBLER: Right, so I could probably go with that. The rest of this stuff we have just about nothing on.

DR. BELSITO: Okay, now Christina in her memo posed the question that the tangerine extract, in looking at the definition, it should've been included in the citrus fruit- derived report. And would we like to remove the ingredient from this report and administratively add it to the citrus fruit-derived ingredient reports?

And I thought we should, but it's a question that we need to answer.

DR. LIEBLER: I agree with that.

DR. SNYDER: I don't agree.

DR. BELSITO: But then we have to reopen that report. Is that correct? Then we would have to -- that report has already gone final.

MS. BURNETT: Correct.

DR. BERGFELD: Correct.

DR. BELSITO: So we would have to reopen the report.

DR. GILL: We don't have a written policy on administrative adds, so we'll have to develop that. We have added some as we've gone through the reports. Individually the panel has decided to add it, but we don't have an overall policy on adding. I think that was the question from counsel. Can you administratively add and we've said, yes, we could.

DR. EISENMANN: In this case I would think yes because this is another name. It's essentially, they put in a duplicate name because you already have a tangerina and reticulata, I think are the same. So you're -- you've sort of reviewed this already in that because it's another name. But if it was completely different, I don't know how the process would be. In other cases --

DR. GILL: Right, and we agree that I think in some other -- in discussing other ingredients if it's the same name then we add it because it's another name for it, it's another recognized name for it. But if you needed data to show equivalence of, that's a different issue.

DR. BELSITO: Okay, so where does that leave us?
(Laughs)

DR. GILL: If it's a -- and this appears to be one that's -- it's another name for the tangerine. So I think we can add this.

DR. BELSITO: So we take it out of this report and move it to the other.

DR. GILL: And we just move it into the other. It's an administrative --

DR. BELSITO: Right.

DR. GILL: -- because it is the same name.

DR. BELSITO: Okay, so this is another group down when -- where I remained uncomfortable with a grouping particularly because when you look on page 17 -- oh, no, not page 17. Where is this? I just put the comment on 17, but when you look at composition, we still need a lot more in terms of manufacturing. But composition of the seed, the water extraction versus the organic extraction, the composition was very different.

DR. LIEBLER: As it should be.

DR. BELSITO: As it should be.

DR. LIEBLER: Right.

DR. BELSITO: And what is being used? And are we -- you know, again, you may say we're -- you know, it's a -- I mean -- I don't know. You know, when I look at grouping, I think we should be looking at a group that has a similar chemical composition. And I'm not certain that's what we're looking at here, but that's your purview not mine.

DR. LIEBLER: Well, so I agree with that as a general rule and -- that we should have things that are -- have similar chemical, physical properties and composition. On the other hand, sometimes we're presented with these ingredients that their similarity is that they're from a similar precursor material or a set of precursor materials that may be extracted in different ways like aqueous versus organic. In that case, I think Liebler's law of parsimonium reporting suggests that you go ahead with the construct we have which is keep the origin materials as the thing that brings the report together. I think we've essentially made that decision already. And we inevitably are going to be faced with some dissimilarities in the range of properties of some of the component extracts of the components within this family. But I still think that the logic of grouping them, seeds and twigs, makes it the most sense.

DR. BELSITO: So we're moving the seed and twig over to this report.

DR. LEIBLER: This plant and seed oil. I'm sorry. No, (inaudible), I'm satisfied with it because you're here.

DR. BELSITO: Because Carol was pointing out that we had data on the seed twig in the other report.

DR. LEIBLER: But that was one ingredient that was - - didn't belong in the other report.

DR. BELSITO: Right, so we're moving --

DR. LIEBLER: Because she clarified the nature of the material and now that really belongs over here.

DR. BELSITO: So we are moving that over, okay.

MS. BURNETT: I believe she's already here. It's just the data on the ingredient is in the leaf.

SPEAKER: Turn (inaudible).

DR. BELSITO: Okay.

MS. BURNETT: It is the data that goes with the bitter orange leaf and twig.

DR. BELSITO: Okay.

MS. BURNETT: So it was generic data referring to petitgrain bigarade oil which has since been clarified what it is exactly. What part of the plants it's derived from? And based on that, it should belong in the plant report, not the leaf --

DR. BELSITO: Right.

MS. BURNETT: -- report.

DR. BELSITO: Okay, okie doke. And then another carryover with the RIFM on page 18, Christina. You say four of the citrus. It's three of the plant seed.

MS. BURNETT: Okay.

DR. BELSITO: And these, just to point out, that again, looking at Table 4 constituents, these are constituents of the -- of what?

MS. BURNETT: That's just the generic constituents that are considered to be contact allergens.

DR. BELSITO: Right, but --

MS. BURNETT: But --

DR. BELSITO: -- this -- these are -- but you have categorized according to the number of patients reacting positively against the number of patients. So when you -- so these numbers refer not to the range of parts per million, but patients that were tested that reacted to these specific -- I don't understand. It says -- see of the constituent in the first column and in the second column is categorized according to the number of patients reacting positively and the number of patients tested greater than a thousand patients tested unless indicated. So 11 to 100 reacted to non-oxidized dl- limonene and 101 to 1,000 reacted to the oxidized. But these aren't parts per million of what's in these components, is that correct?

MS. BURNETT: I believe -- I'm checking that, the source right now. It's slow.

DR. BELSITO: Yeah, I mean I -- because I find it hard to believe that the amount of oxidized dl-limonene is like a thousand parts per million in limonene, but you know, - - but that would be a constituent of great concern if --

MS. BURNETT: I believe it's number of patients.

DR. BELSITO: Right, okay.

MS. BURNETT: The website's really slowly opening, so.

DR. BELSITO: So that just should be --

MS. BURNETT: If it's -- is it not helpful it can --

DR. BELSITO: It's just confusing and I think you need to, you know, --

MS. BURNETT: Would it be better just to list the --

DR. BELSITO: To list --

MS. BURNETT: -- constituents?

DR. BELSITO: -- the ingredients and I'll put those numbers there. You know, these are constituents of concern as defined by --

SPEAKER: Known (inaudible)

DR. BELSITO: -- known sensitizers or --

SPEAKER: Yeah, yeah.

DR. BELSITO: -- something, yeah.

MS. BURNETT: Okay, so just delete the column that has all the --

DR. BELSITO: Yeah, --

MS. BURNETT: -- data.

DR. BELSITO: -- I mean because, you know, you're relying on Jim and myself to come and say okay, you know, carbone isn't really a strong sensitizer nor is limonene unless it's oxidized, linalool unless it's oxidized. But that table left me extremely confused and tried to figure out exactly -- you know, I assumed that it meant that a thousand - - you know, more than a thousand patients were tested and in some studies there were up to a thousand patients who reacted to the hydroperoxides of limonene. That's not surprising, you know, particularly if they were sensitized to limonene. But, you know, I would get rid of that column and just say constituents of concern.

MS. BURNETT: I believe this table is in the other queue, --

DR. BELSITO: Yes, the same thing, yeah.

MS. BURNETT: -- so I have to back and -- the other ones, yes.

DR. BELSITO: So getting back to the question. I thought it remained insufficient. We need more methods of manufacture, composition. Anything else? Sensitization, maximum concentration of use.

DR. EISENMANN: But I was hoping that maybe the seed oils could be moved to save them and focus on the other ingredients because of composition of the seed oils. I mean these aren't essential oils, these are fixed oils.

DR. BELSITO: Dan?

DR. LIEBLER: Yeah, I think I'm comfortable with that. But I'm not sure that -- the only extra data we have on safety are these data you're bringing in from the other report. I guess the question I would have is whether or not they represent enough coverage on the seed oils?

DR. EISENMANN: You see, the difficulty I have is their not used. These seed oils are not used. So I can't get data on products containing them because I have no companies reporting them to be used. So I -- if you leave them -- so in other words, the suppliers have provided composition -- some suppliers have provided composition information, but I don't --

DR. SNYDER: But they're not in use.

DR. EISENMANN: Right, but they're not in use, so I'm not going to get the other parts. If you still say, you know, you have composition information on the seed, some of the seed oils.

DR. LIEBLER: Yeah, then I think we're still going to have a problem.

DR. EISENMANN: Because -- then they're not insufficient for composition. They're insufficient for other reasons, so.

DR. LIEBLER: Correct.

DR. BELSITO: So then let's make sure that I have what we're insufficient then on. We need more method of manufacturing for what? The plant-derived ingredients, but we're okay with the seed? What are we asking for here? And we want more information on the composition of the seed oil we're okay with? And what about the leaf twig oil or is it just the seed oils? So we're -- the actual oils of the -- we're looking at plant and seed-derived ingredients. So when it says citrus aurantium lime oil, the first on Table 6, is that seed oil? Is that plant oil? Where's that oil coming from? When it just says oil, it's plant?

MS. BURNETT: I'm sorry, which page are you on?

DR. BELSITO: PDF 27. I'm just really confused about this group and what the heck we have in it. So, if you just look, the first --

MS. BURNETT: The lime oil?

DR. BELSITO: Yeah, lime oil, bitter orange oil, orange oil. When it just says oil, is that plant or is that seed?

MS. BURNETT: Per the definition for the lime oil it's the whole plant.

DR. BELSITO: Okay.

MS. BURNETT: Now we do have the outlier on the bitter orange oil where it was reported in the VCRP database, but it's not in the dictionary. We believe it's a misclassification by the VCRP, but we have no verification. Based on the name, we felt it fell into this category. It has 295 uses. But the other oils that are listed in here, according to the definition in the dictionary, they are whole plant-derived.

DR. BELSITO: Okay, so what are our method of manufacturing needs? Can you help me out with that?

DR. SNYDER: We only have it for the seed extract.

DR. BELSITO: Okay.

DR. SNYDER: So we need it for everything else, correct then? Constituents and composition, we have it for the seed oil, the seed extract. So we need it for everything else.

DR. BELSITO: So for method of manufacture we need it for everything except --

DR. LIEBLER: Except citrus junos seed extract and citrus paradisi seed extract.

DR. BELSITO: Well, are we assuming that all the other seed extracts are made the same?

DR. LIEBLER: I think that's reasonable.

DR. BELSITO: Okay, so we need method of manufacture for all the components except seed extract.

DR. LIEBLER: Yes, yes.

DR. BELSITO: Okay, and then composition?

DR. LIEBLER: Composition, we only have seed oils and seed extracts.

DR. SNYDER: Correct.

DR. LIEBLER: We do have this citrus sinensis, but I had a question of whether that is an analysis of a material that is representative of a cosmetic ingredient? And I don't know if you could tell.

MS. BURNETT: (inaudible) which ingredient again?

DR. SNYDER: The last one there, citrus sinensis.

DR. LIEBLER: Yeah, under constituents, composition. This is the bottom of PDF 19. The GCMS analysis of essential oils from the leaves and green branches of Egyptian navel oranges, trees.

MS. BURNETT: And that's a generic representation.

DR. LIEBLER: Yeah.

DR. BELSITO: Okay.

DR. LIEBLER: So I just asked --

DR. BELSITO: What?

DR. LIEBLER: -- whether or not that was a cosmetic ingredient. What was analyzed? Was it cosmetic ingredient or just trees?

MS. BURNETT: Just trees.

DR. LIEBLER: Yeah, so I'm not sure that that helps us. I mean it's useful. It's okay to leave it in.

DR. BELSITO: We simply said --

MS. BURNETT: Okay.

DR. BELSITO: -- we'd look for manufacturing ingredients.

DR. LIEBLER: But it (inaudible) It doesn't really deal with the fact that we don't have -- this is all we've got from the whole plant; leaves and green branches.

DR. BELSITO: Okay, so we're going insufficient. We need more in the method of manufacture for everything except the seed extract. We need composition for everything except the seed oil and the seed extract. We remain okay with the grouping. And then any other data needs from the tox endpoint?

DR. SNYDER: Well, there was only -- Dan did make a -- the comment that the composition of the water versus the solvent --

DR. BELSITO: Right.

DR. SNYDER: -- extracts would be different. So we need to clarify that we need both solvent and water extract composition.

DR. BELSITO: But that was for the seed and we're already saying we don't need it for the seed oil and seed extract. That was the seed extract that was different. So are we comfortable with that? Yeah?

DR. SNYDER: No, it -- I'm just -- it doesn't specify under the constituents and composition section whether it was solvents or water. So even when we get all that --

DR. EISENMANN: But it's the same reference that presumed, you know. That the method of manufacture and the composition is on the same material.

DR. LIEBLER: So even when we get all the composition and impurities that we can get, we still have no safety data.

DR. BELSITO: I mean we have nothing. We have --

DR. LIEBLER: Right.

DR. BELSITO: The only thing we would be able to do is take method of manufacture to exclude any materials of -- residual materials of concern. And then to look at composition and see whether that can be cleared based upon the composition of the other citrus reports. But I think what we need to say is, essentially, that we want composition for everything except seed oil and seed extract. And depending upon that -- other endpoints, for me, it's sensitization, irritation may be needed.

DR. EISENMANN: And like I said I think you should consider bringing over some sensitization data on the seed oils that are in the seed oil report. For example, --

DR. BELSITO: So I thought we already said that we're going safe as used for the seed oil. Was that not correct?

DR. EISENMANN: I didn't understand that
(inaudible).

DR. BELSITO: I thought that's what Dan said.

DR. EISENMANN: That you still wanted sensitization data.

DR. LIEBLER: Yep, the report doesn't list any safety data at all.

DR. BELSITO: So we need to bring in safety data --

DR. LIEBLER: We need to bring in the stuff from the seed oil (inaudible) --

DR. BELSITO: -- from the seed oil data and then look at it, okay.

DR. LIEBLER: Unless we get some truly new data.

DR. EISENMANN: Mm-hmm, and the leaf and twig of bitter orange might be okay also based on data on the other report. It -- was it -- it's older RIFM data.

DR. BELSITO: Okay, so let me clarify again. We're remaining insufficient, method of manufacture for everything except the seed extract. Composition for everything except the seed oil and seed extract. Bringing the data from the seed oil report to presumably clear the citrus seed oils as safe as used.

DR. LIEBLER: Correct.

DR. BELSITO: And then depending upon the method of manufacture and composition, other data may be needed. Do we want to specify that other data or --

DR. SNYDER: So we're going -- this is the second time we're going insufficient?

DR. BELSITO: Well, no. The first time we sort of split it up and said these were our needs. So yeah, I guess it is this. I don't know. Where are we technically with this? (Laughs)

DR. LIEBLER: We already went into this.

DR. EISENMANN: This is tentative.

MS. BURNETT: This is tentative. It was an insufficient data announcement in the summer.

DR. BELSITO: So this is tentative?

MS. BURNETT: We are tentative (inaudible).

DR. BELSITO: So we're -- this is going to come back to us as a final next time we see it. A final insufficient.

MS. BURNETT: A draft final.

DR. BELSITO: Right.

DR. SNYDER: But we're -- but we're of -- we have the caveat that if we find out there's a constituent that we may want additional (inaudible) or we may want repro or -- so --

DR. BELSITO: Right.

DR. SNYDER: Should we specify that now or how --

DR. BELSITO: I mean that's what I'm asking.

DR. SNYDER: Yeah.

DR. BELSITO: Do we just say other toxicity endpoints --

DR. SNYDER: We can't just keep going insufficient.

DR. BELSITO: -- may be needed or --

DR. SNYDER: Yeah, we just can't keep going insufficient.

DR. BELSITO: I mean that's what I'm asking. What other data do you need? Because I think we're going to -- you know, once we get the chemical composition for these, we probably can clear them all based upon sensitization and irritation data that we have in the other reports, right?

DR. LIEBLER: I agree, that's probably the only way we're going to make much progress with this report.

DR. BELSITO: So is there anything other than sensitization and irritation that you think you're going to want to see?

DR. SNYDER: Can we table it until we receive that because we can't --

DR. BELSITO: No.

DR. GILL: Let's ask for it and this is (inaudible).

DR. SNYDER: Okay, okay.

DR. BELSITO: So we're asking for method of manufacture for everything except seed extract, composition for everything except seed oil and seed extract. We're going to bring in data from the seed oil report that we assume will clear the citrus seed oils. Do we want to say, based upon manufacturing, composition, other data may be needed? And if we want to say that, do we want to specify other data? That's what I'm asking you. I have no other data needs from my areas. Do you from what you're -- sorry to interrupt.

DR. SNYDER: Not likely, but we don't (inaudible)

DR. BELSITO: Okay, so do you want to make it vague and say other data or do you want to specify?

DR. SNYDER: Well we can't specify.

MS. BURNETT: You had specified in December the irritation and sensitization based on the content. Whatever had that greatest concentration of use at the time. And then you had the caveat, if the composition of the ingredients are significantly different from those of the peel, flower, leaf ingredients systemic in plants.

DR. SNYDER: Okay.

MS. BURNETT: Such as 28 data -- dermal.

DR. SNYDER: That's stays then. That stays.

DR. BELSITO: Then --

MS. BURNETT: So you want that?

DR. SNYDER: Yes, that's still insufficient for that then.

DR. BELSITO: Yeah, so I mean --

DR. SNYDER: It's okay.

DR. BELSITO: -- we can keep the --

DR. SNYDER: Yeah.

DR. BELSITO: -- sensitization, irritation too.

MS. BURNETT: Okay.

DR. BELSITO: We can just -- the --

DR. SNYDER: Thank you. That's exactly what we need.

MS. BURNETT: Okay, so essentially repeat what the peel deletions.

DR. SNYDER: Still insufficient for those data needs.

MS. BURNETT: Right.

DR. BELSITO: The composition differs --

DR. SNYDER: Significantly (inaudible). She has the wording.

DR. BELSITO: And that's coming from which report there, Christine? It's the December 2015?

MS. BURNETT: That's from the announcement of the December 2015 meeting.

DR. BELSITO: Okay.

SPEAKER: I think we should do a whole meeting on the (inaudible).

MS. BURNETT: It's -- the data, if you want to look, you have it on PDF page 2 in the memo.

DR. BELSITO: So yes it says if it composition for the citrus plant seed derived yeah, that's perfect.

MS. BURNETT: Okay.

Full Panel Meeting

DR. BERGFELD: Going on to the plant -- citrus plant and seed. Dr. Belsito?

DR. BELSITO: Yeah, so this is the last of the splits that we made with the citrus-derived ingredients. I wasn't so comfortable with this grouping, but Dan felt it was okay. And we thought that this report, in particular, was insufficient. We needed more information about method of manufacturing for all of the components except the seed extract. The composition of the components except seed oil and seed extract. And we wanted to bring in data from the seed oil report, not the citrus seed oil, but we previously did a seed oil report, that may allow us to clear the citrus seed oils. There was some information on composition in that report that was not brought over to this one. But at this point, insufficient for method of manufacturer for everything except seed extract. Composition for everything except seed oil and extract and the data from the prior seed oil report.

DR. BERGFELD: And that's a motion?

DR. BELSITO: That's a motion.

DR. MARKS: Yeah, we also felt a tentative report with an insufficient conclusion on these 32 ingredients. We also wanted to see sensitization data on it as we requested before in the December meeting on lime orange/bitter orange oils, maybe that's what you're talking about -- bringing the oils in and grapefruit seed extract. And then if these ingredients are not GRAS or food additive, then the fourth bullet below, we wanted to have more tox information. And that's in the memo, the fourth bullet. And then we felt we could remove tangerine extract from this report.

DR. BELSITO: Remove it from --

DR. MARKS: Remove it from this report.

DR. BELSITO: And put it in the --

DR. MARKS: Well, we --

DR. BELSITO: -- report it should have belonged in to, because that would require reopening that report.

DR. MARKS: No, we felt don't add to the fruit report at this time, wait until there's a re-review. So 15 years down from now. But it didn't fit in to this report, so we just didn't want to put an ingredient that really didn't fit in to this group in this report. And we didn't want to reopen the fruit report.

DR. BERGFELD: Any other comments?

DR. BELSITO: We just felt we'd keep it here with some memo that when we reopen the report, we'd move it over. But, I mean, I don't feel strongly one way or the other. I just don't want to reopen the other report.

DR. MARKS: We certainly agree on that. And, again, I don't think our team felt that strongly. We just thought if industry wanted this ingredient review, they could before the 15-year re-review, could always be called, and then we would reopen the food report to review it if needed.

DR. BELSITO: I guess -- I mean I know if this is something that, you know, Lillian and others would have to answer, but if we remove it from this report does that mean we think it's insufficient and it goes on a notification list or it's simply that we've decided that it was incorrectly grouped and therefore decided not to review it at all. I mean how does that work?

DR. GILL: I wouldn't consider it insufficient, I would just say it didn't belong in the groups. But we heard from the Council, I believe, that it's just another name for an ingredient that we've already reviewed.

DR. LANGE: Right, the ingredient has two names. So the name in the other report actually encompasses it. So it's already been reviewed and included. So it's actually a dual name for the same ingredient.

DR. BELSITO: Okay.

DR. BERGFELD: That settles it. Now, there've been added insufficient declarations, I guess we would call them or responses. Are you agreeable with all these new ones that Jim has put forward?

DR. BELSITO: I don't have a problem with them except that you're including like grapefruit seed extract, that the last time you asked for sensitization, it was reported to be as a two percent. But a lot of these have decreased. And particularly, grapefruit seed extract is now at 0.15 percent. Do you still want sensitization at those levels? I mean because that was one of the issues for all of these was that the concentrations in this go around of several of the different components had decreased significantly from what was reported before.

DR. MARKS: I would leave it in. We know some antigens certainly sensitized and that, obviously, there's a mixture, it's not a pure chemical. But for now since it's insufficient, we're issuing a tentative report insufficient. Let's see what we find.

DR. BELSITO: Okay.

DR. BERGFELD: All right. Do we need to repeat the needs?

DR. MARKS: They're essentially the same as was in the December meeting.

DR. BERGFELD: Okay. So you're comfortable?

DR. MARKS: Christina has them listed in her May 13th memo.

DR. BERGFELD: Okay. I was checking with Lillian who's typing away here. Okay, so it's been -- motion has been presented and seconded to go insufficient and the needs have been recorded. So if there are no other comments, I'll call for the question. All those in favor? Unanimous.

Safety Assessment of *Citrus* Plant- and Seed-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, D.P.A. This report was prepared by Christina Burnett, Senior Scientific Analyst/Writer.

ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 32 *Citrus* plant- and seed-derived ingredients, which are most frequently reported to function in cosmetics as fragrances and/or skin conditioning agents. 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 reviewed the available data presented and concluded that the data are insufficient to make a determination that these 32 ingredients are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This report assesses the safety of the 33 *Citrus* plant- and seed-derived ingredients listed below, which are reported in the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*) to mainly function as skin conditioning agents-miscellaneous in cosmetic products (Table 1).[1] Citrus Aurantium (Bitter Orange) Oil is not currently listed in the *Dictionary*, but has been included in this report because of its high reported number of uses in the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database and presumed similarities to the other ingredients in this report. Two ingredients (Citrus Sunki Seed Extract and Citrus Sunki Seed Oil) are reported to function as skin bleaching agents; use as a skin bleaching agent is classified as a drug use and, as such, does not fall under the purview of CIR.

Citrus Aurantifolia (Lime) Oil
Citrus Aurantium (Bitter Orange) Oil
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder
Citrus Aurantium Dulcis (Orange) Oil
Citrus Aurantium Dulcis (Orange) Seed Extract
Citrus Aurantium Sinensis Powder
Citrus Australasica Seed Oil
Citrus Depressa Seed Oil
Citrus Glauca Seed Oil
Citrus Grandis (Grapefruit)
Citrus Grandis (Grapefruit) Extract
Citrus Grandis Peel/Seed Extract
Citrus Grandis (Grapefruit) Seed Extract
Citrus Iyo Oil
Citrus Jabara Pericarp Extract
Citrus Junos Extract
Citrus Junos Seed Extract
Citrus Junos Seed Oil
Citrus Limon (Lemon) Flower/Leaf/Stem Extract
Citrus Limon (Lemon) Flower/Leaf/Stem Oil
Citrus Limon (Lemon) Leaf/Peel/Stem Oil
Citrus Nobilis (Mandarin Orange)
Citrus Nobilis (Mandarin Orange) Oil
Citrus Nobilis (Mandarin Orange) Water
Citrus Paradisi (Grapefruit) Seed Extract
Citrus Sunki Seed Extract
Citrus Sunki Seed Oil
Citrus Reticulata (Tangerine) Extract
Citrus Unshiu Extract
Citrus Unshiu Pericarp Extract

The Panel 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] The Panel has also reviewed the safety of Citrus Aurantifolia (Lime) Seed Oil, Citrus Aurantifolia (Lime) Seed Oil Unsaponifiables, Citrus Aurantium Dulcis (Orange) Seed Oil, Citrus Aurantium Dulcis (Orange) Seed Oil Unsaponifiables, Citrus Grandis (Grapefruit) Seed Oil, Citrus Grandis (Grapefruit) Seed Oil Unsaponifiables, Citrus Limon (Lemon) Seed Oil, and Citrus Paradisi (Grapefruit) Seed Oil, and concluded that these ingredients are safe in the present practices of use and concentration as described in the safety assessment of plant-derived fatty acid oils.[4] *Citrus* flower- and leaf-derived ingredients and *Citrus* peel-derived ingredients are being reviewed in separate reports.

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*, three of the *Citrus* plant- and seed-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.

Botanical ingredients are comprised of numerous constituents, some of which have the potential to cause toxic effects. For example, bergapten (aka 5-methoxysporalen or 5-MOP) is a naturally-occurring phototoxic furanocoumarin

(psoralen) found in some *Citrus* ingredients. In this assessment, CIR is reviewing the potential toxicity of each *Citrus* plant- or seed-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* plants and seeds from which the ingredients in this report are derived.

Note: In many of the published studies included in this assessment, the information provided is not sufficient to determine how well the substance being tested represents the cosmetic ingredient. In this safety assessment, if a substance tested in a study is not clearly a cosmetic ingredient, because of lack of information on the genus and species from which the substance was derived and/or the method of extraction used, the test substance will be referred to by a common name (e.g. lemon extract). If the substance is clearly a cosmetic ingredient, the International Nomenclature of Cosmetic Ingredients (INCI) name will be used (e.g. "Citrus Limon (Lemon) Extract"). Additionally, some inconsistencies were noted in both taxonomic and INCI naming conventions. For example, this report includes the sweet orange ingredient described as Citrus Aurantium Dulcis (Orange) in the *Dictionary*.[1] In contrast, most of the published literature and the FDA 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 pomelo, which may also be referred to as *Citrus maxima*. *Citrus paradisi* appears to be the more widely accepted nomenclature for grapefruit. Finally, Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil is also known as petitgrain bigarade oil. The INCI Committee of the Personal Care Products Council (Council) is working to correct some of these inconsistencies. The genus and species names associated with the ingredient names designated by the INCI Committee are listed in Table 3.[5]

CHEMISTRY

Definition and General Characterization

The definitions and functions of the *Citrus* plant- and seed-derived ingredients included in this report are provided in Table 1. The definition indicates what part(s) of the plant from which an ingredient is obtained. In some cases, the definition provides insight on the method(s) of manufacture. Essential oils are the hydrophobic, liquid, volatile aromatic compounds in the insoluble condensate fraction, and typically are small molecules, but their chemical structures can vary rather widely. Fixed oils, on the other hand, are hydrophobic, nonvolatile, fatty compounds from plants (including *Citrus* seeds), 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 use as fragrances is not their only reported function.

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.

Physical and Chemical Properties

Citrus Australasica Seed Oil

Citrus Australasica Seed Oil is reported to be a straw/yellow colored liquid with a refractive index of 1.476 (specification range 1.450-1.490 at 20º C) and a specific gravity of 0.917 (specification range 0.900-0.940 at 20º C).[6]

Citrus Glauca Seed Oil

According to a supplier, Citrus Glauca Seed Oil is a light brown to dark brown liquid.[7] At 20º C, the refractive index is 1.472 (specification range 1.450-1.490) and the specific gravity is 0.921 (specification range 0.900-0.940).

Method of Manufacturing

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil

According to the *Food Chemicals Codex*, "petitgrain oil, Paraguay type" is a volatile oil obtained by steam distillation from the leaves and small twigs of the bitter orange tree, *Citrus aurantium* L. subspecies *amara*.[8]

Citrus Junos Seed Extract

A supplier has reported that Citrus Junos Seed Extract is produced by extracting dried seeds with 90% ethanolic solution, which is then filtered.[9] The material then undergoes sedimentation, filtration, and adjustment before packaging.

Citrus Paradisi (Grapefruit) Seed Extract

A supplier reported that Citrus Paradisi (Grapefruit) Seed Extract is manufactured by first grinding grapefruit seeds and then extracting in a mix of water and glycerin.[10] The mixture is then clarified and decontaminated by heat.

Constituents/Composition

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).[11] Table 5 lists the fatty acid profiles for Citrus seed-derived oils that were previously reviewed in the safety assessment of plant-derived fatty acid oils.[4]

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."[12,13]

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil

According to the Food Chemicals Codex, "petitgrain oil, Paraguay type" contains not less than 45.0% and not more than 60% esters calculated as linalyl acetate.[8] A fragrance raw materials monograph lists the components of petitgrain bigarade oil as α-pinene, β-pinene, sabinene, myrcene, limonene, cis-β-ocimene, trans-β-ocimene, linalool, linalyl acetate, terpineol-4, β-caryophyllene, α-terpineol, neryl acetate, geranyl acetate, nrol, geraniol, and nerolidol.[14] A breakdown of the key constituents of Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil is detailed in Table 6.

Citrus Australasica Seed Oil and Citrus Glauca Seed Oil

The fatty acid profiles for Citrus Australasica Seed Oil and Citrus Glauca Seed Oil are listed in Table 7.

Citrus Junos Seed Extract

A supplier reports that Citrus Junos Seed Extract is composed of saponin and sugar.[9] The concentrations of heavy metal impurities are not more than 20 ppm and the concentration of arsenic is not more than 2 ppm.

The fatty acid profile for *Citrus junos* Sieb. ex Tanaka is also listed in Table 7.

Citrus Paradisi (Grapefruit) Seed Extract

A supplier reported that a trade name material contains 67.0% to 73.0% glycerin, 26.0% to 32.8% water, and 0.2% to 1.0% Citrus Paradisi (Grapefruit) Seed Extract.[10]

Citrus Sinensis

In gas chromatography and gas chromatography-mass spectroscopy analysis of the essential oils from the leaves and green branches of Egyptian navel orange trees (*Citrus sinensis* (L.) Osbeck var. Malesy), 33 and 24 compounds were identified for the leaves and branches, respectively.[15] These compounds made up 96.0% and 97.9%, respectively, of the total detected constituents. The major constituents were sabinene (36.5% leaves, 33.0% branches), terpinen-4-ol (8.2% leaves, 6.2% branches), δ-3-carene (7.0% leaves, 9.4% branches), limonene (6.8% leaves, 18.7% branches), trans-ocimene (6.7% leaves, 6.1% branches), and β-myrcene (4.5% leaves, 9.4% branches).

The composition of samples of dehulled sweet orange (Citrus *sinensis*) seed flour (dry weight) was reported to be 54.2% fat, 28.5% carbohydrate, 5.5% crude fiber, 3.1% crude protein, and 2.5% ash.[16] Mineral analysis showed high levels of calcium and potassium.

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the 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 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 (Bitter Orange) Oil has the most reported uses of the cosmetic ingredients in this report, with a total of 295; more than half are in leave-on skin care preparations (Table 8).[17] This ingredient is not currently in the *Dictionary*, but has been included in this report because of the number of uses and presumed similarities to the other ingredients in this report. The ingredients with the next highest frequency of use are Citrus Aurantifolia (Lime) Oil (169 total uses) and Citrus Grandis (Grapefruit) Seed Extract (144 total uses); a majority of the uses for these ingredients are in leave-on skin care preparations. The results of the concentration of use survey indicate Citrus Aurantium Dulcis (Orange) Oil has the highest reported maximum concentration of use; it is used at up to 1% in a body and hand formulation.[18] Citrus Aurantifolia (Lime) Oil had the second highest reported maximum concentration of use; it is used at up to 0.36% in a lipstick.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided. For example, Citrus Limon (Lemon) Flower/Leaf/Stem Extract is reported to be used in 8 formulations, but no use concentration data were available. In other cases, no uses were reported to the VCRP, but a maximum use concentration was provided in the industry survey. For example, Citrus Junos Seed Oil was not reported in the VCRP database, but the industry survey indicated that it is used in face and neck and body and hand formulations at up to 0.1%. It is presumed that Citrus Junos Seed Oil is used in at least one cosmetic formulation.

Table 9 lists all *Citrus* plant- and seed-derived ingredients not currently 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 come into contact with the eye or mucous membranes. For example, Citrus Aurantifolia (Lime) Oil is used in a lipstick at up to 0.36%. Additionally, some of these ingredients were reported to be used in hair sprays, fragrance preparations, face powder and body powders, spray deodorants, and spray skin care preparations and could possibly be inhaled. For example, Citrus Aurantifolia (Lime) Oil was reported to be used in body and hand sprays at a maximum concentration of 0.12% and Citrus Junos Seed Oil was reported to be used in face powders at up to 0.1%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.[19-22] 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.[20,21] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[21] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. 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.[23-25]

The *Citrus* ingredients described in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU). However, furocoumarins are prohibited from use in cosmetics, except for normal content in natural essences and in sun protection and bronzing products where the content shall be below 1 mg/kg.[26]

Non-Cosmetic

Petitgrain bigarade oil (Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil) is generally recognized as safe (GRAS) for intended use in foods for human consumption (21CFR182.20) and in animal drugs, feeds, and related products (21CFR582.20).

TOXICOKINETICS

No relevant published toxicokinetics studies on *Citrus* plant- and seed-derived ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted; toxicokinetics data are not expected to be found because botanical ingredients are mixtures of hundreds of constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity

Dermal – Animal

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil

The dermal LD_{50} of Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil) was reported to be greater than 2 g/kg in rabbits; however, only 2 rabbits were used in the study.[14] An occlusive patch of undiluted test material was applied for 24 h.

Repeated Dose Toxicity

No relevant published repeated dose toxicity studies on *Citrus* plant- and seed-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* plant- and seed-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* plant- and seed-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* plant- and seed-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 10.[14,27,28] In rabbit studies, slight erythema was observed after exposure to 2g/kg Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil). In human subjects, no irritation was observed after topical exposure to petitgrain bigarade oil (up to 8% in petrolatum) or Citrus Grandis (Grapefruit) Seed Extract (0.15% in formulation).

Dermal Sensitization

Dermal sensitization studies are presented in Table 11.[14,29] Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil) at up to 8% in petrolatum was not sensitizing.

Photosensitization

Photosensitization studies are presented in Table 12.[30] Undiluted Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil) was not photosensitizing in tests with hairless mice or miniature swine.

CLINICAL STUDIES

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

SUMMARY

The 32 *Citrus* plant- and seed-derived ingredients described in this report function primarily as skin conditioning agents-miscellaneous. Botanical ingredients are composed of hundreds of constituents, some of which have the potential to cause toxic effects; for example, bergapten (aka 5-methoxypsoralen or 5-MOP) is a naturally-occurring, phototoxic furanocoumarin (psoralen) in *Citrus*. Presently, CIR reviewed the information available on the potential toxicity of each *Citrus* plant- and seed-derived ingredient as a whole, complex substance; CIR does not review the potential toxicity information on the individual constituents of which the *Citrus* plant- and seed-derived ingredients are comprised.

Citrus seed oils are fixed oils that are composed primarily of glycerides, and to some extent, free fatty acids while the other *Citrus* oils in this safety assessment are essential oils that primarily contain volatile compounds. No composition information was found for ingredients defined as being derived from the whole plant.

Citrus Aurantium (Bitter Orange) Oil has the most reported uses of the ingredients in this report in cosmetic products, with a total of 295; more than half of the uses are in leave-on skin care preparations. This ingredient is not currently in the *Dictionary* but has been included in this report because of its high reported number of uses and presumed similarities to the other ingredients in this report. The ingredients with the next highest frequency of use are Citrus Aurantifolia (Lime) Oil (169 total uses) and Citrus Grandis (Grapefruit) Seed Extract (144 total uses); a majority of the uses for these ingredients are in leave-on skin care preparations. The results of the concentration of use survey indicate Citrus Aurantium Dulcis (Orange) Oil has the highest reported maximum concentration of use; it is used at up to 1% in a body and hand formulation. Citrus Aurantifolia (Lime) Oil had the second highest reported maximum concentration of use; it is used at up to 0.36% in a lipstick.

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

Citrus Auranium Amara (Bitter Orange) Leaf/Twig Oil is considered GRAS in foods for human consumption and in animal drugs, feed, and related products.

The dermal LD_{50} of Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil) was reported as greater than 2 g/kg in rabbits.

In rabbit dermal irritation studies, slight erythema was observed after exposure to unreported concentrations of Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil). In human subjects, no irritation was observed after topical exposure to petitgrain bigarade oil (up to 8%).

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil) at up to 8% was not sensitizing and undiluted petitgrain bigarade oil was not photosensitizing in tests with hairless mice or miniature swine.

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

DISCUSSION

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients 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 are limonene, citral, and furocoumarins (such as 5- MOP).

The issue of incidental inhalation exposure from hair sprays, fragrance preparations, face powder and body powders, spray deodorants, and spray skin care preparations was discussed by the Panel. There were no inhalation toxicity data available. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols 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.

Pesticide residues and heavy metals may be present in botanical ingredients. The Panel 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 on the safety of the 32 *Citrus* plant- and seed-derived ingredients found in this safety assessment. The data that are needed to properly evaluate the safety of these ingredients are:

- Method of manufacturing for all these ingredients, except the seed extracts
- Chemical composition and impurities for all these ingredients, except the seed oils and seed extracts
- Irritation and sensitization, especially human repeated insult patch tests (HRIPT) on Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil and Citrus Grandis (Grapefruit) Seed Extract at maximum use concentrations or greater.
- If the composition for these *Citrus* plant- and seed-derived ingredients are significantly different from that of the *Citrus* peel-, flower-, and leaf-derived ingredients, then data on systemic endpoints such as a 28-day dermal toxicity, reproductive and developmental toxicity, and genotoxicity, as well as UV absorption spectra are needed.

CONCLUSION

The CIR Expert Panel concluded that the available data are insufficient to make a determination that the following 32 ingredients are safe under the intended conditions of use in cosmetic formulations.

Citrus Aurantifolia (Lime) Oil
Citrus Aurantium (Bitter Orange) Oil
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract*
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder*
Citrus Aurantium Dulcis (Orange) Oil
Citrus Aurantium Dulcis (Orange) Seed Extract
Citrus Aurantium Sinensis Powder
Citrus Australasica Seed Oil*
Citrus Depressa Seed Oil*
Citrus Glauca Seed Oil*
Citrus Grandis (Grapefruit)*
Citrus Grandis (Grapefruit) Extract
Citrus Grandis Peel/Seed Extract*
Citrus Grandis (Grapefruit) Seed Extract
Citrus Iyo Oil*
Citrus Jabara Pericarp Extract*
Citrus Junos Extract
Citrus Junos Seed Extract
Citrus Junos Seed Oil
Citrus Limon (Lemon) Flower/Leaf/Stem Extract
Citrus Limon (Lemon) Flower/Leaf/Stem Oil*
Citrus Limon (Lemon) Leaf/Peel/Stem Oil*
Citrus Nobilis (Mandarin Orange)
Citrus Nobilis (Mandarin Orange) Oil
Citrus Nobilis (Mandarin Orange) Water*
Citrus Paradisi (Grapefruit) Seed Extract
Citrus Sunki Seed Extract*
Citrus Sunki Seed Oil*
Citrus Reticulata (Tangerine) Extract
Citrus Unshiu Extract*
Citrus Unshiu Pericarp 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.

TABLES

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

Ingredient	Definition*	Function
Citrus Aurantifolia (Lime) Oil CAS No. 8008-26-2	Citrus Aurantifolia (Lime) Oil is the volatile oil obtained from the whole plant, *Citrus aurantifolia.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium (Bitter Orange) Oil	Not in *Dictionary.*	Not in *Dictionary.*
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract CAS No. 72968-50-4; 8016-38-4	Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract is the extract of the leaves and twigs of *Citrus aurantium amara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil	Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil is the volatile oil obtained from the leaves and twigs of *Citrus aurantium amara.*	Flavoring Agents; Fragrance Ingredients
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder	Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder is the powder obtained from the dried, ground flowers, leaves and stems of *Citrus aurantium dulcis.*	Exfoliants
Citrus Aurantium Dulcis (Orange) Oil	Citrus Aurantium Dulcis (Orange) Oil is the volatile oil obtained from the whole plant, *Citrus aurantium dulcis*.	Fragrance Ingredients
Citrus Aurantium Dulcis (Orange) Seed Extract	Citrus Aurantium Dulcis (Orange) Seed Extract is the extract of the seeds of *Citrus aurantium dulcis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Sinensis Powder	Citrus Aurantium Sinensis Powder is the powder obtained the dried ground plant, *Citrus aurantium sinensis.*	Exfoliants
Citrus Australasica Seed Oil CAS No. 1174331-57-7 (generic)	Citrus Australasica Seed Oil is the fixed oil expressed from the seeds of *Citrus australasica.*	Antioxidants; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents - Miscellaneous
Citrus Depressa Seed Oil	Citrus Depressa Seed Oil is the oil expressed from the seeds of *Citrus depressa.*	Skin-Conditioning Agents - Emollient
Citrus Glauca Seed Oil	Citrus Glauca Seed Oil is the oil expressed from the seeds of *Citrus glauca.*	Antioxidants; Humectants; Skin Protectants; Skin-Conditioning Agents - Emollient; Skin-Conditioning Agents - Humectant
Citrus Grandis (Grapefruit)	Citrus Grandis (Grapefruit) is a plant material derived from the whole plant, *Citrus grandis.*	Not reported
Citrus Grandis (Grapefruit) Extract	Citrus Grandis (Grapefruit) Extract is the extract of the whole plant, *Citrus grandis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Grandis Peel/Seed Extract	Citrus Grandis Peel/Seed Extract is the extract of the peel and seeds of *Citrus grandis.*	Antifungal Agents; Antimicrobial Agents; Preservatives
Citrus Grandis (Grapefruit) Seed Extract	Citrus Grandis (Grapefruit) Seed Extract is the extract of the seeds of Citrus grandis.	Preservatives; Skin-Conditioning Agents - Miscellaneous
Citrus Iyo Oil	Citrus Iyo Oil is the oil expressed from the whole plant, *Citrus iyo*.	Skin-Conditioning Agents - Emollient
Citrus Jabara Pericarp Extract	Citrus Jabara Pericarp Extract is the extract of the pericarp of *Citrus jabara.*	Humectants; Skin-Conditioning Agents - Miscellaneous
Citrus Junos Extract	Citrus Junos Extract is the extract of the whole plant, *Citrus junos.*	Antioxidants
Citrus Junos Seed Extract	Citrus Junos Seed Extract is the extract of the seeds of *Citrus junos.*	Antioxidants
Citrus Junos Seed Oil	Citrus Junos Seed Oil is the oil expressed from the seeds of *Citrus junos.*	Skin-Conditioning Agents - Emollient
Citrus Limon (Lemon) Flower/Leaf/Stem Extract CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Flower/Leaf/Stem Extract is the extract of the flowers, leaves and stems of *Citrus limon.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Flower/Leaf/Stem Oil CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Flower/Leaf/Stem Oil is the volatile oil obtained from the flowers, leaves and stems of *Citrus limon.*	Fragrance Ingredients
Citrus Limon (Lemon) Leaf/Peel/Stem Oil CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Leaf/Peel/Stem Oil is the volatile oil obtained from the leaves, peels, and stems of *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Nobilis (Mandarin Orange)	Citrus Nobilis (Mandarin Orange) is a plant material derived from the whole plant, *Citrus nobilis.*	Not reported
Citrus Nobilis (Mandarin Orange) Oil	Citrus Nobilis (Mandarin Orange) Oil is the volatile oil obtained from the whole plant, *Citrus nobilis.*	Fragrance Ingredients
Citrus Nobilis (Mandarin Orange) Water	Citrus Nobilis (Mandarin Orange) Water is an aqueous solution of the steam distillate obtained from *Citrus nobilis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Paradisi (Grapefruit) Seed Extract CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Seed Extract is the extract of the seeds of *Citrus paradisi.*	Skin-Conditioning Agents - Miscellaneous
Citrus Reticulata (Tangerine) Extract	Citrus Reticulata (Tangerine) Extract is the extract of the whole plant, *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Citrus Sunki Seed Extract	Citrus Sunki Seed Extract is the extract of the seeds of *Citrus sunki.*	Antioxidants; Skin Bleaching Agents; Skin-Conditioning Agents - Miscellaneous
Citrus Sunki Seed Oil	Citrus Sunki Seed Oil is the oil expressed from the seeds of *Citrus sunki.*	Antioxidants; Skin Bleaching Agents; Skin-Conditioning Agents - Miscellaneous

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

Ingredient	Definition*	Function
Citrus Unshiu Extract CAS No. 98106-71-9	Citrus Unshiu Extract is the extract of the whole plant, *Citrus unshiu.*	Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu Pericarp Extract	Citrus Unshiu Pericarp Extract is the extract of the pericarp of *Citrus unshiu.*	Skin-Conditioning Agents - Miscellaneous

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

Table 2. *Citrus* plant- and seed-derived ingredients that potentially function solely as fragrance ingredients.

Citrus Aurantium Dulcis (Orange) Oil
Citrus Limon (Lemon) Flower/Leaf/Stem Oil
Citrus Nobilis (Mandarin Orange) Oil

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Table 3.Review of *Citrus* species names[5]

Species Name Used in INCI Names (common name)	Accepted 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. Constituents that are established contact allergens in humans, according to the SCCS

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. Total fatty acid composition of Citrus seed oils, as previously reported (%).[4]

Fatty Acids	Citrus Aurantifolia (Lime) Seed Oil	Citrus Aurantium Dulcis (Orange) Seed Oil	Citrus Grandis (Grapefruit) Seed Oil	Citrus Limon (Lemon) Seed Oil	Citrus Paradisi (Seed) Oil
Lauric (C12)			1.5		2.95
Myristic (C14)	1		1		1.01
Palmitic (C16)	20-30	14-22	18-30	18.8	36.25
Heptadecanoic (C17:0)				0.08	
Stearic (C18)	3-8	2-6	2-8	3.5	5.95
Oleic (C18:1)	20-38	26-35	20-38	30.1	18.34
Linoleic (C18:2)	30-45	35-45	30-48	33.4	29.26
Linolenic (C18:3)	5-15	2-6	2-6	13.5	3.58
Arachidic (C20)	2	0.5		0.3	0.38
Eicosenoic (C20:1)				0.03	0.84
Behenic (C22)				0.08	
Lignoceric (C24)				0.2	
Others				C23:0 = <0.01; C26:0 = 0.01	C12:1=1.44

Table 6. Key constituents (%) of Citrus Aurantium Amara (Bitter) Leaf /Twig Oil*[31]

	Bigarade Type	Paraguayan Type
linalyl acetate	51.0-71.0	47.4-58.0
linalool	12.3-24.2	20.8-25.2
(+)-limonene	0.4-8.0	0.3-1.1
α-terpineol	2.1-5.2	4.4-6.8
geranyl acetate	1.9-3.4	2.9-4.5
β -pinene	0.3-2.7	0.3-1.2
neryl acetate	0-2.6	2.1-3.0
geraniol	1.4-2.3	2.1-3.0
(E)-β-ocimene	0.2-2.2	0-2.0
β-myrcene	0-2.0	0-2.0
nerol	0.4-1.1	NR

NR = Not reported

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

Table 7. Fatty acid profiles (area %) by gas chromatography.[6,7,32]

Fatty acid	Citrus Australasica Seed Oil	Citrus Glauca Seed Oil	*Citrus junos* Sieb. ex Takana seed oil*
undecanoic acid	NR	NR	3.27
myristic acid	0.07	NR	NR
palmitic acid	10.50	8.07	19.16
palmitoleic acid	0.24	0.17	0.62
margaric acid	0.08	0.05	NR
heptadecanconic acid	0.07	NR	NR
stearic acid	3.36	2.52	3.76
elaidic acid	0.11	NR	NR
oleic acid	36.55	47.39	32.01
cis-vaccenic acid	1.67	2.00	NR
linolelaidic acid	0.05	NR	NR
linoleic acid	41.01	36.28	33.99
α-linolenic acid	4.70	1.28	2.05
arachadic acid	0.40	0.31	0.26
11-eicosenoic acid	0.28	0.42	NR
behenic acid	0.42	0.61	NR
lignoceric acid	0.15	0.32	NR
unknown	NR	NR	4.48

*Reported as acid methyl esters.

Table 8. Frequency and concentration of use according to duration and type of exposure for *Citrus* plant- and seed-derived ingredients.[17,18]

	# 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) Oil		**Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil[d]**		**Citrus Aurantium (Bitter Orange) Oil[e]**		**Citrus Aurantium Dulcis (Orange) Oil[f]**	
Totals[†]	**169**	**0.00000051-0.36**	**43**	**0.0000000026-0.0032**	**295**	**NR**	**4**	**0.0000032-1**
Duration of Use								
Leave-On	90	0.00049-0.36	25	0.00000014-0.0032	178	NR	3	0.000094-1
Rinse Off	69	0.00015-0.17	14	0.00000015-0.000013	96	NR	NR	0.000026-0.81
Diluted for (Bath) Use	10	0.00000051	4	0.0000000026	21	NR	1	0.0000032-0.94
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	0.00078-0.034
Incidental Ingestion	NR	0.0015-0.36	NR	NR	2	NR	NR	0.034-0.95
Incidental Inhalation-Spray	9; 34[a]; 29[b]	0.00049-0.12; 0.0015-0.1[a]; 0.00067[b]	11[a]; 11[b]	0.00000014-0.00000043; 0.0000025[a]	31; 37[a]; 49[b]	NR	1; 2[a]	0.0022-0.12; 0.0053-0.26[a]; 0.000094[b]
Incidental Inhalation-Powder	1[c]; 29[b]	0.022; 0.0075-0.023[c];0.00067	11[b]	0.000011[c]	1; 3[c]; 49[b]	NR	NR	0.0012-0.0014; 0.14-1[c]; 0.000094[b]
Dermal Contact	147	0.00000051-0.17	40	0.0000000026-0.0032	250	NR	3	0.0000032-1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	0.039[a]; 0.038-0.06[g]
Hair - Non-Coloring	22	0.00049-0.02	3	0.00000014-0.0000025	32	NR	1	0.0022-0.81
Hair-Coloring	NR	0.00015	NR	NR	11	NR	NR	0.000026-0.042
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	35	0.00000051-0.36	11	0.0000000026-0.000013	53	NR	1	0.0000032-0.95
Baby Products	3	NR	NR	NR	9	NR	NR	NR

	Citrus Aurantium Dulcis (Orange) Seed Extract[h]		**Citrus Aurantium Sinensis Powder[i]**		**Citrus Grandis (Grapefruit) Extract**		**Citrus Grandis (Grapefruit) Seed Extract**	
Totals[†]	**2**	**NR**	**1**	**NR**	**NR**	**0.0017-0.0059**	**144**	**0.0004-0.15**
Duration of Use								
Leave-On	2	NR	1	NR	NR	0.0017-0.003	85	0.076-0.15
Rinse Off	NR	NR	NR	NR	NR	0.0022-0.0059	51	0.0004-0.12
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	8	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	5	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	12	0.076
Incidental Inhalation-Spray	2[b]	NR	1[b]	NR	NR	0.0017-0.003	2; 28[a]; 17[b]	NR
Incidental Inhalation-Powder	2[b]	**NR**	1[b]	NR	NR	NR	17[b]; 2[c]	0.1[c]
Dermal Contact	2	NR	1	NR	NR	0.0022-0.0059	106	0.02-0.15
Deodorant (underarm)	NR	NR	NR	NR	NR	0.0024[g]	14[a]	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	0.0017-0.005	23	0.0004
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	0.0022-0.0059	26	0.076
Baby Products	NR	NR	NR	NR	NR	NR	7	NR

Table 8. Frequency and concentration of use according to duration and type of exposure for *Citrus* plant- and seed-derived ingredients.[17,18]

	# 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 Junos Extract		**Citrus Junos Seed Extract[j]**		**Citrus Junos Seed Oil**		**Citrus Limon (Lemon) Flower/Leaf/Stem Extract**	
Totals[†]	**NR**	**0.0001**	**7**	**0.001-0.0045**	**NR**	**0.001-0.1**	**8**	**NR**
Duration of Use								
Leave-On	NR	NR	7	0.001-0.0045	NR	0.01-0.1	8	NR
Rinse Off	NR	0.0001	NR	0.001	NR	0.001	NR	NR
Diluted for (Bath) Use	NR	NR	NR	0.001	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	1	0.001	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	4[a]; 2[b]	NR	NR	NR	6[a]; 1[b]	NR
Incidental Inhalation-Powder	NR	NR	2[b]	0.0045[c]	NR	0.1; 0.1[c]	1[b]	NR
Dermal Contact	NR	NR	7	0.001-0.0045	NR	0.001-0.1	8	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	0.01	NR	NR
Hair-Coloring	NR	0.0001	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	0.001	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Nobilis (Mandarin Orange)		**Citrus Nobilis (Mandarin Orange) Oil**		**Citrus Paradisi (Grapefruit) Seed Extract**		**Citrus Reticulata (Tangerine) Extract**	
Totals[†]	**NR**	**0.0005**	**36**	**0.0009-0.035**	**52**	**NR**	**NR**	**0.0001-0.0051**
Duration of Use								
Leave-On	NR	NR	28	NR	39	NR	NR	0.0002-0.0051
Rinse Off	NR	NR	4	0.0009-0.035	13	NR	NR	0.0001-0.005
Diluted for (Bath) Use	NR	NR	4	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	1	0.035	1	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	8; 2[a]; 4[b]	NR	16[a]; 17[b]	NR	NR	0.0051[a]
Incidental Inhalation-Powder	NR	NR	4[b]; 1[c]	NR	17[b]; 1[c]	NR	NR	0.0002[c]
Dermal Contact	NR	0.0005	35	0.0009-0.0017	50	NR	NR	0.0002
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.0005	NR	NR	1	NR	NR	0.0001-0.0051
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.0005	7	0.0009-0.035	8	NR	NR	NR
Baby Products	NR	NR	2	NR	2	NR	NR	NR

NR = Not reported.

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

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

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

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

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

[e] Only listed in the VCRP database, not in the INCI dictionary. Included because of assumed similarity.

[f] Listed as Citrus Sinensis (Sweet Orange) Plant Oil in the VCRP database.

[g]Not a spray deodorant.

[h] Listed as Citrus Sinensis (Sweet Orange) Seed Extract in the VCRP database.

[i] Listed as Citrus Sinensis (Orange) Powder in the VCRP database.

[j] Listed as Citrus Junos (Xiang Cheng) Seed Extract in the VCRP database.

Table 9. Ingredients that are not reported to be in use

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder
Citrus Australasica Seed Oil
Citrus Depressa Seed Oil
Citrus Glauca Seed Oil
Citrus Grandis (Grapefruit)
Citrus Grandis Peel/Seed Extract
Citrus Iyo Oil
Citrus Jabara Pericarp Extract
Citrus Limon (Lemon) Flower/Leaf/Stem Oil
Citrus Limon (Lemon) Leaf/Peel/Stem Oil
Citrus Nobilis (Mandarin Orange) Water
Citrus Sunki Seed Extract
Citrus Sunki Seed Oil
Citrus Unshiu Extract
Citrus Unshiu Pericarp Extract

Table 10. Dermal irritation studies for *Citrus* plant- and seed-derived ingredients.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			ANIMAL		
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	2g/kg; undiluted	2 rabbits	24-h occlusive, single dose study	slight erythema	[14]
			HUMAN		
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	0.1%, 2% or 5%; multiple vehicles	48 subjects at 0.1%, 30 subjects at 2%, and 30 subjects at 5%	24-72 h occlusive patch tests	no irritation	[27]
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	8% in petrolatum	25 subjects	48 h occlusive patch applied to the forearm or back	no irritation	[14]
Citrus Grandis (Grapefruit) Seed Extract	0.15% in a foot gel	12 subjects with normal, lesion-free skin	48 h occlusive patch (Finn chambers) on external arm, single application of 0.02 ml	no irritation (mean irritation index = 0.13)	[28]

Table 11. Sensitization studies for *Citrus* plant- and seed-derived ingredients.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			HUMAN		
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	2% in paraffin	200 patients with dermatitis tested with 35 essential oils plus an additional 50 patients with balsam sensitivity	sensitization patch study, details not provided	3 positive reactions, details not provided	[29]
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	8% in petrolatum	25 subjects	maximization study, details not provided	not sensitizing	[14]

Table 12. Photosensitization studies.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	undiluted	hairless mice (#/group not stated)	test material was applied, and the test sites were irradiated with UVA irradiation by blacklight or xenon lamp	not photosensitizing	[30]
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	undiluted	miniature swine (#/group not stated)	test material was applied, and the test sites were irradiated with UVA irradiation by blacklight or xenon lamp	not photosensitizing	[30]

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2016 FDA VCRP RAW DATA – Citrus Plant and Seed

01A - Baby Shampoos	CITRUS AURANTIFOLIA (LIME) OIL	1
01B - Baby Lotions, Oils, Powders, and Creams	CITRUS AURANTIFOLIA (LIME) OIL	1
01C - Other Baby Products	CITRUS AURANTIFOLIA (LIME) OIL	1
02A - Bath Oils, Tablets, and Salts	CITRUS AURANTIFOLIA (LIME) OIL	6
02B - Bubble Baths	CITRUS AURANTIFOLIA (LIME) OIL	4
04B - Perfumes	CITRUS AURANTIFOLIA (LIME) OIL	1
04E - Other Fragrance Preparation	CITRUS AURANTIFOLIA (LIME) OIL	8
05A - Hair Conditioner	CITRUS AURANTIFOLIA (LIME) OIL	9
05F - Shampoos (non-coloring)	CITRUS AURANTIFOLIA (LIME) OIL	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS AURANTIFOLIA (LIME) OIL	5
05I - Other Hair Preparations	CITRUS AURANTIFOLIA (LIME) OIL	1
07F - Makeup Bases	CITRUS AURANTIFOLIA (LIME) OIL	1
07I - Other Makeup Preparations	CITRUS AURANTIFOLIA (LIME) OIL	3
10A - Bath Soaps and Detergents	CITRUS AURANTIFOLIA (LIME) OIL	17
10E - Other Personal Cleanliness Products	CITRUS AURANTIFOLIA (LIME) OIL	8
11B - Beard Softeners	CITRUS AURANTIFOLIA (LIME) OIL	6
11D - Preshave Lotions (all types)	CITRUS AURANTIFOLIA (LIME) OIL	1
11E - Shaving Cream	CITRUS AURANTIFOLIA (LIME) OIL	5
11F - Shaving Soap	CITRUS AURANTIFOLIA (LIME) OIL	1
11G - Other Shaving Preparation Products	CITRUS AURANTIFOLIA (LIME) OIL	2
12A - Cleansing	CITRUS AURANTIFOLIA (LIME) OIL	18
12C - Face and Neck (exc shave)	CITRUS AURANTIFOLIA (LIME) OIL	17
12D - Body and Hand (exc shave)	CITRUS AURANTIFOLIA (LIME) OIL	12
12F - Moisturizing	CITRUS AURANTIFOLIA (LIME) OIL	21
12G - Night	CITRUS AURANTIFOLIA (LIME) OIL	1
12H - Paste Masks (mud packs)	CITRUS AURANTIFOLIA (LIME) OIL	1
12I - Skin Fresheners	CITRUS AURANTIFOLIA (LIME) OIL	6
12J - Other Skin Care Preps	CITRUS AURANTIFOLIA (LIME) OIL	5
13A - Suntan Gels, Creams, and Liquids	CITRUS AURANTIFOLIA (LIME) OIL	1
02A - Bath Oils, Tablets, and Salts	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	3
02B - Bubble Baths	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	1
05A - Hair Conditioner	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	2
05F - Shampoos (non-coloring)	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	1

10A - Bath Soaps and Detergents	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	5
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	2
12A - Cleansing	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	4
12C - Face and Neck (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	6
12D - Body and Hand (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	5
12F - Moisturizing	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	7
12G - Night	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	4
12J - Other Skin Care Preps	CITRUS AURANTIUM (BITTER ORANGE) LEAF/TWIG OIL	3
01A - Baby Shampoos	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
01B - Baby Lotions, Oils, Powders, and Creams	CITRUS AURANTIUM (BITTER ORANGE) OIL	3
01C - Other Baby Products	CITRUS AURANTIUM (BITTER ORANGE) OIL	5
02A - Bath Oils, Tablets, and Salts	CITRUS AURANTIUM (BITTER ORANGE) OIL	16
02B - Bubble Baths	CITRUS AURANTIUM (BITTER ORANGE) OIL	3
02C - Bath Capsules	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
02D - Other Bath Preparations	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
04A - Cologne and Toilet waters	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
04B - Perfumes	CITRUS AURANTIUM (BITTER ORANGE) OIL	14
04E - Other Fragrance Preparation	CITRUS AURANTIUM (BITTER ORANGE) OIL	15
05A - Hair Conditioner	CITRUS AURANTIUM (BITTER ORANGE) OIL	10
05B - Hair Spray (aerosol fixatives)	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
05C - Hair Straighteners	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
05E - Rinses (non-coloring)	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
05F - Shampoos (non-coloring)	CITRUS AURANTIUM (BITTER ORANGE) OIL	13
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS AURANTIUM (BITTER ORANGE) OIL	4
05I - Other Hair Preparations	CITRUS AURANTIUM (BITTER ORANGE) OIL	2
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	CITRUS AURANTIUM (BITTER ORANGE) OIL	4
06D - Hair Shampoos (coloring)	CITRUS AURANTIUM (BITTER ORANGE) OIL	7
07E - Lipstick	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
07F - Makeup Bases	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
07G - Rouges	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
07I - Other Makeup Preparations	CITRUS AURANTIUM (BITTER ORANGE) OIL	3
09C - Other Oral Hygiene Products	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
10A - Bath Soaps and	CITRUS AURANTIUM (BITTER ORANGE) OIL	20

Detergents		
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM (BITTER ORANGE) OIL	10
11E - Shaving Cream	CITRUS AURANTIUM (BITTER ORANGE) OIL	2
12A - Cleansing	CITRUS AURANTIUM (BITTER ORANGE) OIL	23
12C - Face and Neck (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) OIL	14
12D - Body and Hand (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) OIL	35
12F - Moisturizing	CITRUS AURANTIUM (BITTER ORANGE) OIL	24
12G - Night	CITRUS AURANTIUM (BITTER ORANGE) OIL	2
12H - Paste Masks (mud packs)	CITRUS AURANTIUM (BITTER ORANGE) OIL	4
12I - Skin Fresheners	CITRUS AURANTIUM (BITTER ORANGE) OIL	6
12J - Other Skin Care Preps	CITRUS AURANTIUM (BITTER ORANGE) OIL	44
13B - Indoor Tanning Preparations	CITRUS AURANTIUM (BITTER ORANGE) OIL	1
01B - Baby Lotions, Oils, Powders, and Creams	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	2
01C - Other Baby Products	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	5
02A - Bath Oils, Tablets, and Salts	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	5
02B - Bubble Baths	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	3
03D - Eye Lotion	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	2
03F - Mascara	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	3
04E - Other Fragrance Preparation	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	1
05A - Hair Conditioner	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	8
05B - Hair Spray (aerosol fixatives)	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	1
05E - Rinses (non-coloring)	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	1
05F - Shampoos (non-coloring)	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	9
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	4
07C - Foundations	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	10
07F - Makeup Bases	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	1
09A - Dentifrices	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	9
09B - Mouthwashes and Breath Fresheners	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	2
09C - Other Oral Hygiene Products	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	6
10B - Deodorants (underarm)	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	14
12A - Cleansing	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	13
12C - Face and Neck (exc shave)	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	6
12D - Body and Hand (exc	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	11

shave)		
12F - Moisturizing	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	10
12H - Paste Masks (mud packs)	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	2
12I - Skin Fresheners	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	12
12J - Other Skin Care Preps	CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT	3
03G - Other Eye Makeup Preparations	CITRUS JUNOS (XIANG CHENG) SEED EXTRACT	1
12C - Face and Neck (exc shave)	CITRUS JUNOS (XIANG CHENG) SEED EXTRACT	1
12D - Body and Hand (exc shave)	CITRUS JUNOS (XIANG CHENG) SEED EXTRACT	1
12F - Moisturizing	CITRUS JUNOS (XIANG CHENG) SEED EXTRACT	4
12C - Face and Neck (exc shave)	CITRUS LIMON (LEMON) FLOWER/LEAF/STEM EXTRACT	1
12F - Moisturizing	CITRUS LIMON (LEMON) FLOWER/LEAF/STEM EXTRACT	6
12J - Other Skin Care Preps	CITRUS LIMON (LEMON) FLOWER/LEAF/STEM EXTRACT	1
01B - Baby Lotions, Oils, Powders, and Creams	CITRUS NOBILIS (MANDARIN ORANGE) OIL	1
01C - Other Baby Products	CITRUS NOBILIS (MANDARIN ORANGE) OIL	1
02A - Bath Oils, Tablets, and Salts	CITRUS NOBILIS (MANDARIN ORANGE) OIL	4
04B - Perfumes	CITRUS NOBILIS (MANDARIN ORANGE) OIL	4
04E - Other Fragrance Preparation	CITRUS NOBILIS (MANDARIN ORANGE) OIL	4
07I - Other Makeup Preparations	CITRUS NOBILIS (MANDARIN ORANGE) OIL	1
09A - Dentifrices	CITRUS NOBILIS (MANDARIN ORANGE) OIL	1
10A - Bath Soaps and Detergents	CITRUS NOBILIS (MANDARIN ORANGE) OIL	2
12A - Cleansing	CITRUS NOBILIS (MANDARIN ORANGE) OIL	1
12D - Body and Hand (exc shave)	CITRUS NOBILIS (MANDARIN ORANGE) OIL	4
12F - Moisturizing	CITRUS NOBILIS (MANDARIN ORANGE) OIL	2
12J - Other Skin Care Preps	CITRUS NOBILIS (MANDARIN ORANGE) OIL	11
01B - Baby Lotions, Oils, Powders, and Creams	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	1
01C - Other Baby Products	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	1
05A - Hair Conditioner	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	1
07I - Other Makeup Preparations	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	1
09A - Dentifrices	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	7
11B - Beard Softeners	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	1

12A - Cleansing	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	4
12C - Face and Neck (exc shave)	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	4
12D - Body and Hand (exc shave)	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	13
12F - Moisturizing	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	14
12G - Night	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	1
12J - Other Skin Care Preps	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	2
13A - Suntan Gels, Creams, and Liquids	CITRUS PARADISI (GRAPEFRUIT) SEED EXTRACT	1
02A - Bath Oils, Tablets, and Salts	CITRUS SINENSIS (SWEET ORANGE) PLANT OIL	1
04B - Perfumes	CITRUS SINENSIS (SWEET ORANGE) PLANT OIL	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS SINENSIS (SWEET ORANGE) PLANT OIL	1
12I - Skin Fresheners	CITRUS SINENSIS (SWEET ORANGE) PLANT OIL	1
12C - Face and Neck (exc shave)	CITRUS SINENSIS (SWEET ORANGE) POWDER	1
12D - Body and Hand (exc shave)	CITRUS SINENSIS (SWEET ORANGE) SEED EXTRACT	2
04E - Other Fragrance Preparation	CITRUS TANGERINA (TANGERINE) EXTRACT	1
05A - Hair Conditioner	CITRUS TANGERINA (TANGERINE) EXTRACT	4
05F - Shampoos (non-coloring)	CITRUS TANGERINA (TANGERINE) EXTRACT	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS TANGERINA (TANGERINE) EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS TANGERINA (TANGERINE) EXTRACT	2
12C - Face and Neck (exc shave)	CITRUS TANGERINA (TANGERINE) EXTRACT	1
12D - Body and Hand (exc shave)	CITRUS TANGERINA (TANGERINE) EXTRACT	1
12J - Other Skin Care Preps	CITRUS TANGERINA (TANGERINE) EXTRACT	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: July 6, 2016

SUBJECT: Citrus Grandis (Grapefruit) Seed Extract

Anonymous. 2016. Study of acute skin compatibility of a test item (foot gel containing 0.15% Citrus Grandis (Grapefruit) Seed Extract): 48-hours occlusive patch-test.

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Study title	**STUDY OF ACUTE SKIN COMPATIBILITY OF A TEST ITEM: 48-HOURS OCCLUSIVE PATCH-TEST**
Product	***FOOT GEL WITH 0.15% OF CITRUS GRANDIS (GRAPEFRUIT) SEED EXTRACT***
Study dates	From March 8 to 10, 2016
Objective of study	Assess the irritant potential of the studied test item after its unique application, maintained for 48 hours in contact with the skin, with the help of an occlusive patch.
Application conditions	Single application of 0.02 ml of the studied test item pure, on the external face of the arm, maintained for 48 hours in contact with the skin, with the help of an occlusive patch (Finn Chamber).
Assessment methods	The clinical quotation is made 30 minutes after the patch removal and takes in account the erythema, the papules, the vesicles and the blisters. According to their intensity, the quotation is spread out from 0 to 3. The total sum of the scores, divided by the number of volunteers, defines the mean irritation index (M.I.I.), which allows to classify arbitrarily the test item according the following scale: - M.I.I. ≤ 0,20 : Non irritant - 0,20 < M.I.I. ≤ 0,50 : Slightly irritant - 0,50 < M.I.I. ≤ 2 : Moderately irritant - 2 < M.I.I. ≤ 3 : Very irritant
Volunteers' characteristics	12 volunteers of the female or male sex from 18 to 65 years of age, with a normal skin, without any dermatological lesion on the experimental area, were analyzed.
Results	Mean irritation index (M.I.I.) of the test item : 0.13
Conclusion	The test item applied pure, can be considered as **non irritant** after an application with the help of an occlusive patch (Finn Chambers) for 48 consecutive hours on 12 volunteers. This result is conform to that obtained for the test item of same class.

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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* Plant- and Seed-Derived Ingredients as Used in Cosmetics (prepared for the June 6-7, 2016 meeting)

Key Issue

As noted for the flower, leaf report, petitgrain bigarade oil is a preparation from the leaves and small twigs of *Citrus aurantium amara*. Therefore, 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 or the information on petitgrain bigarade oil needs to be moved to this report. The *Food Chemical Codex* includes "Petitgrain Oil, Paraguay Type" which is 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.

What is the process for administratively adding an ingredient to a completed report? Citrus Tangerina (Tangerine) Extract (defined as an extract of the fruit) can be considered another name for Citrus Reticulata (Tangerine) Fruit Extract which is already included in the Citrus fruit report. Therefore, adding Citrus Tangerina (Tangerine) Extract to the Citrus fruit report is acceptable. Can the seed oil ingredients be administratively added to the seed oil report? The composition of the seed oils in this report is similar to the seed oils, e.g., lemon seed oil, in the seed oil report. Therefore, the information used to support the safety of the seed oil ingredients should be used to support the safety of the Citrus seed oils in this report.

Additional Considerations

Cosmetic Use - It is not clear why the IFRA limits for what appears to be peel-derived ingredients are included in this report.

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

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Table 3, it is not necessary to include that part of the definition in Table 1. A footnote should be added to Table 1 to indicate that accepted scientific names are shown in Table 3.

Table 5 - The spelling of "Australisca" in the column heading needs to be corrected to "Australasica"

Tables 6 and 7 - Citrus Limon (Lemon) Flower/Leaf/Stem Oil is not included in either Table 6 or Table 7.

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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* Plant- and Seed-Derived Ingredients as Used in Cosmetics (released June 17, 2016)

Key Issue

As the ingredients in this report are different from each other based on composition and source, it would be helpful to organize the report into at least three ingredient groups:

1. seed oils which are fixed oils similar in composition to citrus seed oils previously reviewed (all the citrus seed oils contain predominantly palmitic, oleic and linoleic acids) and found safe as used (seed oil report: maximum use concentration in leave-on products 20% Citrus Paradisi (Grapefruit) Seed Oil; maximum leave-on use concentration of a seed oil in current report 0.1% Citrus Junos Seed Oil);
2. ingredients derived from specific plant parts including the seed extracts and leaf and twig preparations (composition and some safety data available for Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (also called petitgrain bigarade oil)
3. ingredients derived from the "whole plant" for which no composition or safety data are available

The key constituent information for petitgrain bigarade oil found on p. 374 of Tissarand and Young Essential Oil Safety (2nd edition) should be added to this report. Among the main components, this reference indicates that this essential oil contains 51-71% linalyl acetate and 12.3-24.2% linalool, and the Paraguayan oil contains 47.2-58% linalyl acetate and 20.8-25.2% linalool[1]. It should be noted that Tissarand and Young provide composition information for components down to a concentration of 1%, or lower for known toxic constituents. In the profile for this essential oil, Tissarand and Young note that

[1]Cited to: Lawrence 1995g. Essential oils 1988-1991. Allured Publishing, Wheaton. p.107-110

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"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." Based on the composition, no other limits are recommended by Tissarand and Young for use of this essential oil. They also note that this essential oil has GRAS status.

The composition information for petitgrain bigarade oil from reference 24 (Ford et al. 1992) should also be added to this report as it was the material that was tested in the safety studies described in this reference.

Summary - The Summary should include some general information about the composition of these ingredients. For example, it should state that the seed oils are fixed oils, while the other "oil" ingredients are essential oils which primarily contain volatile components. It should also be stated that no composition information was found for ingredients defined as being derived from the whole plant.

Additional Considerations

Introduction - In the first paragraph "in cosmetic ingredients" needs to be corrected to "in cosmetic products"

Chemistry - The Chemistry section should also describe how a "water" is produced. This information can be found in the Introduction of the Dictionary.

Dermal Irritation, Dermal Sensitization - Please check reference 24. Rabbits were treated with 2 g/kg undiluted petitgrain bigarade oil (not unspecified concentrations as stated in the text). The vehicle used in the human maximization studies was petrolatum (Table 9 says "not specified").

Discussion - The Discussion should make it clear that it is the oxidation products of the monoterpenes that are potential sensitizers rather than the monoterpenes themselves.

Table 1 - Table 1 should make it clear that Citrus Aurantium (Bitter Orange) Oil is not in the Dictionary.

Table 9 - It should be noted that the petitgrain bigarade oil applied to rabbits was undiluted and the vehicle used in the human study was petrolatum (reference 24).