Safety Assessment of Citrus Fruit-Derived Ingredients as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
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The 2015 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Christina Burnett, Senior Scientific Analyst/Writer.

Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina Burnett, Senior Scientific Writer/Analyst
Date: May 22, 2015
Subject: Draft Tentative Safety Assessment on Citrus Fruit-Derived Ingredients

Enclosed is the draft Tentative Report of the Safety Assessment of Citrus Fruit-Derived Ingredients as Used in Cosmetics. (It is identified as *cfruit062015rep* in the pdf document.)

At the March 2015 CIR Panel Meeting, the Expert Panel requested additional data to support the safety of citrus fruit-derived ingredients. The additional data needs were: (1) methods of manufacture; (2) chemical composition and impurities data; (3) irritation and sensitization data, specifically HRIPT on citrus aurantium dulcis (orange) fruit water, citrus limon (lemon) fruit extract, and citrus grandis (grapefruit) fruit extract at maximum use concentrations; (4) confirmation from RIFM that citrus aurantium bergamia (bergamot) fruit oil, citrus junos fruit oil, citrus junos fruit water, citrus natsudaidai flower water, citrus reticulata (tangerine) fruit water, and citrus unshiu/citrus reticulata/citrus iyo fruit water has, or will be, assessed by RIFM; and (5) confirmation on which species of citrus fruit are not GRAS food ingredients from the FDA.

Since the March meeting, the Council has provided unpublished data on product specifications and safety test data for several citrus fruit extracts and waters. These data have been incorporated into the report and are provided in this report package for your review (*cfruit062015data1* to *cfruit062015data8*). The new data have been highlighted by |margin brackets| in text and by pink shading in tables. The Council also provided comments prior to the March meeting, which have since been addressed (*cfruit062015pcpc*).

General composition data for some citrus fruit species have been identified in the published literature and have been briefly summarized in this report. This data is not specifically on the cosmetic-grade ingredients. If the Panel would like to further review this literature prior to the Panel meeting, please contact me.

We have received information from RIFM on which citrus fruit-derived ingredients are in the RIFM database and they have confirmed that citrus aurantium bergamia (bergamot) fruit oil falls under their purview. Since CIR does not review fragrance ingredients and this ingredient functions only as a fragrance in cosmetic products, citrus aurantium bergamia has been removed from this report. Citrus natsudaidai flower water was inadvertently listed as a citrus fruit-derived ingredient and has also been removed from this report. The remaining 4 ingredients that were identified as functioning only as fragrances by the International Cosmetic Dictionary and Handbook will be reviewed by the CIR Expert Panel.

Finally, further research was performed on the issue of what citrus fruits have GRAS status as foods according to the FDA. According to the Code of Federal regulations (21CFR§170.30), natural food ingredients that were consumed in the United States and substances commonly used in or as food outside of the United States with documented uses prior to 1958 have been determined as GRAS but will not be specifically listed in the regulations as they are too numerous. The regulation further states that persons claiming GRAS status for a substance based on its common use in food outside of the United

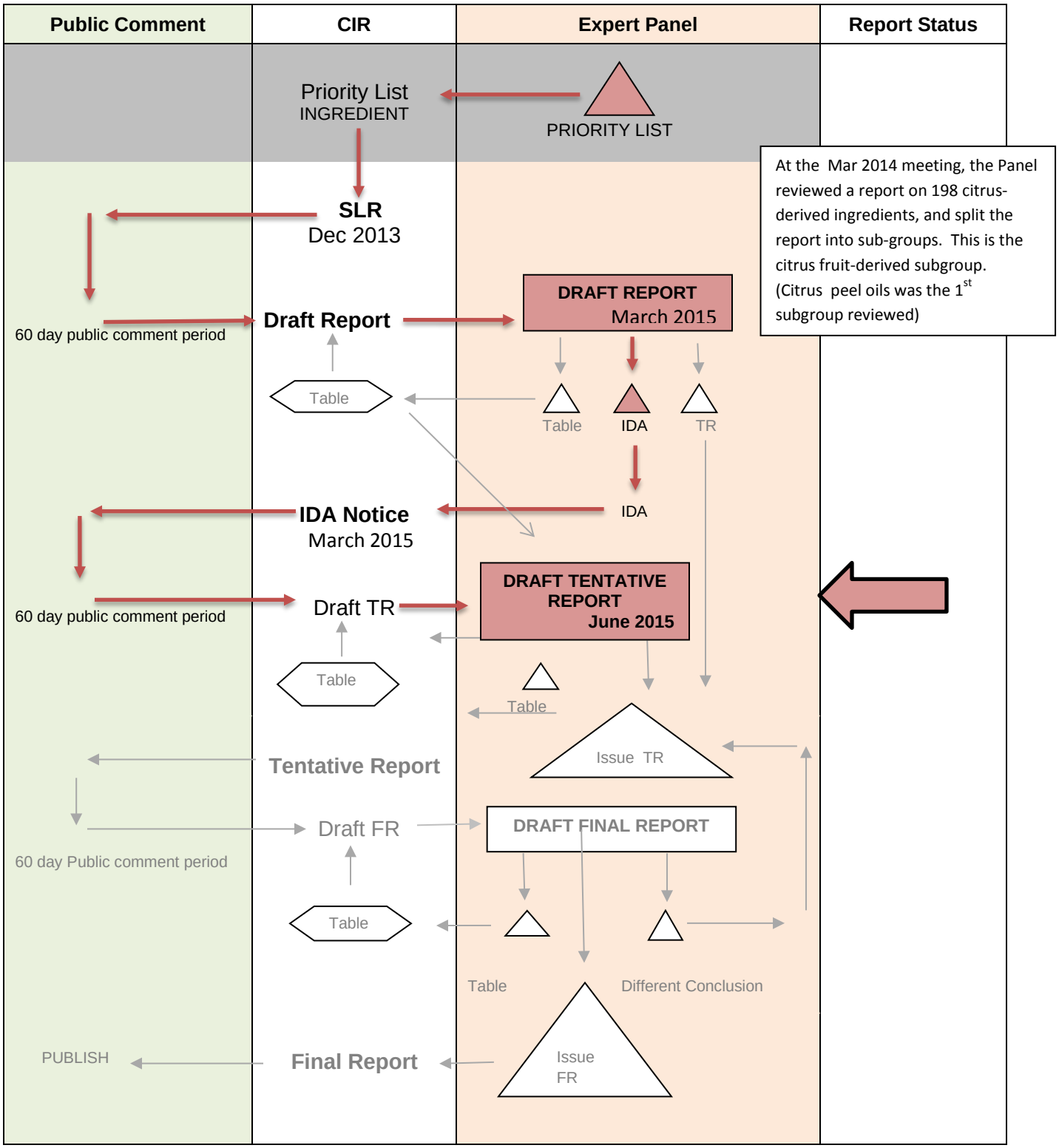
States should obtain FDA concurrence that the use of the substance is GRAS. From the initial research performed on this report, it appears that almost all of the citrus fruit species detailed in this report that are used in the preparation of cosmetic ingredients in some form or fashion either here in the United States or internationally.

The Panel should review all the available data, determine if the data needs have been met, and provide a robust discussion and a conclusion on the safety of these ingredients.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Citrus Fruit-Derived Ingredients

MEETING June 2015



Citrus Fruit 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.

September 2014 - The Panel issued a final report on citrus-derived peel oils in with the conclusion that the 14 citrus-derived peel oil 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). This report reflects the next group of citrus-derived ingredients with the greatest number of uses: citrus fruit-derived ingredients.

December 2014 – The Panel reviewed the report strategy for citrus fruit-derived ingredients and approved the inclusion of 80 ingredients in the safety assessment.

March 2015 – The Panel requested additional data to support the safety of 80 citrus fruit-derived ingredients. The additional data needs were: (1) methods of manufacture; (2) chemical composition and impurities data; (3) irritation and sensitization data, specifically HRIPT on citrus aurantium dulcis (orange) fruit water, citrus limon (lemon) fruit extract, and citrus grandis (grapefruit) fruit extract at maximum use concentrations; (4) confirmation from RIFM that citrus aurantium bergamia (bergamot) fruit oil, citrus junos fruit oil, citrus junos fruit water, citrus natsudaidai flower water, citrus reticulata (tangerine) fruit water, and citrus unshiu/citrus reticulata/citrus iyo fruit water has, or will be, assessed by RIFM; and (5) confirmation on which species of citrus fruit are not GRAS by the FDA.

Post-March 2015 – CIR received information from RIFM that citrus aurantium bergamia (bergamot) fruit oil falls under their purview.

Citrus Fruit-Derived Ingredients Data Profile – June 2015 – Writer, Christina Burnett										
	In-Use	**Physical/Chemical Properties**	**Method of Manufacturing**	**Composition**	**Carcinogenicity**	**Irritation/Sensitization - Nonhuman**	**Irritation/Sensitization - Clinical**	**Ocular/Mucosal**	**Phototoxicity**	**Case Studies**
Citrus aurantifolia (lime) fruit extract	X	X		X						
Citrus aurantifolia (lime) juice	X									X
Citrus aurantium amara (bitter orange) fruit extract	X									
Citrus aurantium (bitter orange) fruit water	X		X							
Citrus aurantium dulcis (orange) fruit extract	X	X		X			X		X	
Citrus aurantium dulcis (orange) fruit water	X		X				X			
Citrus bergamia (bergamot orange) fruit extract	X						X		X	
Citrus glauca fruit extract	X									
Citrus grandis (grapefruit) fruit extract	X	X	X	X		X	X	X		
Citrus grandis (grapefruit) juice	X									
Citrus grandis (grapefruit) fruit water	X		X							
Citrus japonica fruit extract	X									
Citrus junos fruit extract	X									
Citrus limon (lemon) fruit extract	X	X		X			X			
Citrus limon (lemon) fruit water			X	X			X			
Citrus limon (lemon) juice	X								X	X
Citrus madurensis fruit extract	X									
Citrus medica limonum (lemon) fruit water	X									
Citrus medica limonum (lemon) juice extract	X									
Citrus medica vulgaris fruit extract	X									
Citrus nobilis (mandarin orange) fruit extract	X		X	X			X	X		
Citrus paradisi (grapefruit) fruit extract	X	X		X						
Citrus paradisi (grapefruit) fruit juice	X									
Citrus paradisi (grapefruit) fruit water				X						
Citrus reticulata (tangerine) fruit extract	X									
Citrus reticulate (tangerine) fruit water				X						
Citrus sinensis (orange) fiber	X									
Citrus sinensis (orange) juice	X								X	
Citrus sinensis (orange) powder	X									
Citrus sinensis (orange) fruit extract	X								X	
Citrus sinensis (orange) fruit water	X		X	X						
Citrus tangerine (tangerine) extract	X									
Hydrolyzed citrus aurantium ducis fruit extract	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 Fruit-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 January 2015 using the terms "citrus fruit" – 13 new relevant references found.
Updated searches April 2015 with the terms "citrus fruit dermal" & "citrus fruit skin" – 0 new relevant references found.
Searched for "citrus fruit composition" March-April 2015 -4 relevant references identified and obtained.

Online Info

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

Citrus Fruit Ingredients
March 16-17, 2015

Dr. Belsito's Team

DR. BELSITO: Citrus. Well, I was surprised we didn't see a Wave 3 on citrus, and nothing in Wave 2. I was expecting to be bombarded with juice.

MS. BURNETT: I held off on the use table just so that we didn't -- the updated use table just so that we didn't give you stuff that wasn't super important right away.

DR. BELSITO: Okay. So I said -- I'm still not sure we should be lumping the rest together.

MS. BURNETT: Although this isn't quite the rest, there are still leaves and trees, and all that have to -- addressed.

DR. BELSITO: I know. I know. I'm okay with lumping the fruit water with limits on 5-MOP and the boilerplates for botanicals and inhalation, although not the peel oils, and I'm wondering if we shouldn't have added the peel oils with the oils. Or not the oils, but we should have added the oils with the peel oils.

MS. BURNETT: There's only like one or two --

DR. BELSITO: I know. There are a couple oils, but I'm still wondering if those shouldn't have been added with peel oils rather than here.

DR. LIEBLER: I think these maybe okay, but I would like to see method of manufacture information on -- well, actually most of it.

DR. BELSITO: That's what I have.

DR. LIEBLER: I mean, there's no method of manufacture except for the fruit waters, and the so the food extracts, and the food oils, I think we should get those. I think we should get some method on them, on the fermented ingredient.

DR. BELSITO: Right. So I said the others are insufficient, the method of manufacture, chemical composition, and then finally, do we expect clarification from RIFRAM regarding the fragrance-only material, or are we just adding them in at this point?

MS. BURNETT: We are awaiting -- we are waiting for confirmation. Until we get that, we'll just leave them in and -- like just with lemon peel oil, we didn't get that till later in the process so it might be, hopefully, Dr. Api heard our request earlier today at the other reading, and the other team, so maybe we should have made a note, and we'll come back with our data. We haven't requested it before, so.

DR. BELSITO: Right. Okay. So, Dan, I'm saying that the fruit water is okay with limitation of the 5-MOP and the boilerplates for botanicals in inhalation. I was also feeling that the oils were okay, but you are wanting method of manufacture for those?

DR. LIEBLER: Well, there's just information.

DR. BELSITO: Okay.

DR. LIEBLER: I mean, we should have that and we don't even have it for the food extracts for that matter.

DR. BELSITO: Right. So I said, fruit water is okay with limits on 5-MOP and boilerplate, while the others, method of manufacture, chemical composition and impurities.

DR. LIEBLER: Yeah.

DR. SNYDER: Why is the orange -- Do we know why orange bitter is on the NTP list?

MS. BURNETT: On the NTP list?

DR. SNYDER: The list for current study.

MS. BURNETT: I can't remember.

DR. SNYDER: If we could find that out, right, for the next time.

MS. BURNETT: Okay. That's bitter orange?

DR. SNYDER: Yeah.

DR. LIEBLER: So there will be representative examples for the food extracts, the fruit oils and this fermented ingredient? Is that right? Now I couldn't tell you what the difference is between a fruit water and a food extract.

DR. BELSITO: Mm-hmm. But the fruit waters are okay, we have enough information on them.

DR. LIEBLER: Oh. I think they are okay, yeah. And there is actually -- I mean, I see what the fruit water -- there is a schematic, actually, on the fruit waters, that pretty interesting. But I don't know how --

SPEAKER: I don't think you could see that.

DR. LIEBLER: -- how different that is from a fruit extract. The extract is such a generic term.

DR. BELSITO: Right.

DR. LIEBLER: So if we had two or three examples, of food extracts, I think it would be -- it's more of due diligence thing, that a real doubt I have, but I think we should cover it.

DR. BELSITO: Okay.

MS. BURNETT: And do you need any irritation or sensitization data?

DR. BELSITO: On the food -- on the fruit water?

MS. BURNETT: On any of it. We do not have anything.

DR. BELSITO: For some reason, I didn't ask for it, I said the fruit waters were okay as long as long as we limited 5-MOP in the boilerplate for botanicals. So then the -- I think we have -- we must have composition for the fruit water. I mean, this one I reviewed so long ago, I have to look.

MS. BURNETT: Right.

DR. BELSITO: So what do we have for composition on fruit water?

MS. BURNETT: That's in Table 4.

DR. BELSITO: Because the way we dealt with the botanicals for sensitization is that -- or other toxicity endpoints, is that the combination totality with other botanical ingredients, right?

MS. BURNETT: Right. I just want to verify, because it's -- that data point is completely empty, and since we save that for systemic, because you know, we eat it. We don't have any data points for it, but we don't --

DR. BELSITO: Yeah but -- Okay. But you have Table 4 which is cosmetic allergens, certificate from a manufacturer of orange, lemon, tangerine and grapefruit, fruit waters, and you look at the labeled ingredients which are the 26 most allergenic. Now for those of you who weren't aware, Europe is looking to push this to 100-plus fragrances that need to be labeled.

But when you look at the allergenicity, even of this 26 that need to be labeled, quite frankly, after you get past the first 10, they are all pretty weak sensitizers. And some of them have almost no case report. So, what are we concerned about in a fruit water that, in terms of sensitization and irritation, it really is a fragrance material?

MS. BURNETT: Yeah. I was just checking because out of the case studies its lime juice, it's more -- it's like, sort of, (inaudible) of juice.

DR. BELSITO: Yeah. But those are -- Yeah.

MS. BURNETT: And I know it's the 5-MOP.

DR. BELSITO: Right. So I think that -- what I'm saying is that the water is okay with the limit on 5-MOP, and a boilerplate for botanicals in inhalations, because really, with the -- what we are concerned about, is really out of the peel, and really was more the peel oils, because that's where the 5-MOP is in line. And it's not even all citrus, it's only a certain number of citruses, and even among lime, it turns out it's

like, Mexican lime had very high levels of 5-MOP, and what comes out of Florida has very low levels. So it's really where the lime is grown. So I thought if we just put the limits on 5-MOP we were fine.

MS. BURNETT: Okay.

DR. BELSITO: And the argument would be looking at Table 4, sensitizers would likely be fragrance ingredients, I mean the geraniol, the maximum content, 100 parts per million. Citral, which is a weak sensitizer, as you heard this morning from Dr. Api, 100 parts per million, and this is in the water. And then the water is not used at a 100 percent and then you have linalool which is really – Linalool isn't the issue, it's the hydro peroxides that are the issue, and even there you have it at a hundred parts per million in lemon fruit water. I don't think there are issues.

DR. SNYDER: So we are going to leave this Table 4 with really it is only is three lines -- well, it only needs to be three lines, right? Or, do we have it -- why are we listing all those things which are not present? I mean, this only for the fruit waters.

DR. BELSITO: Well, you could -- Well, I guess the advantage of listing everything there is so that people who aren't familiar with the 26 fragrance ingredients, that need to be labeled in Europe, and are considered the prime fragrance sensitizers by the Europeans, know what was being looked at.

DR. SNYDER: But does it beg the question then, this is only for the fruit waters, but what about all the other --

DR. BELSITO: We are going insufficient, for method of manufacture for chemical composition.

DR. SNYDER: Oh. Okay.

DR. LIEBLER: Yeah. I agree with you about that -- I agree with you about that, Paul.

DR. SNYDER: Yeah.

DR. LIEBLER: I think this stable is useful in as much as that it shows you that this list of organics that come from the fruits are present -- are all present in less than 2 PDM, except where noted, which is consistent with this being sort of -- kind of like a modified steam distillate or extract of these fruits, and most of these constituents, simply get left behind.

DR. SNYDER: But if you tested the extract instead of the fruit water, is the dilution factor so that the --

DR. BELSITO: We don't know what the extract is, that's the problem.

DR. SNYDER: That's a good point, a very good point. Okay.

DR. LIEBLER: That's the missing piece, yeah. That's what we are asking for.

DR. BELSITO: That's why we are asking.

DR. SNYDER: Okay. I understand.

DR. LIEBLER: But at least this fruit water process looks like it -- I'm not sure what it does give you, water?

DR. BELSITO: Lemonade.

MS. BURNETT: So, Dr. Snyder, a little -- just like the NTP study for bitter orange extract in that, it was researched because of dietary supplements, the federal-free dietary supplements, and they wanted to see the safety of use in that.

DR. SNYDER: Okay.

MS. BURNETT: So essentially an oral concentrate.

DR. SNYDER: Oral dietary. Okay. Thank you.

MS. BURNETT: You're welcome.

DR. BELSITO: Anything else on citrus?

DR. LIEBLER: That's basically it I think.

Dr. Marks' Team

DR. MARKS: Okay, let's now move on to the next ingredient, citrus.

SPEAKER: Citrus fruits.

MS. BURNETT: Last March, it was all citrus. Now it's just fruits.

DR. MARKS: Let me make sure I say this.

(Discussion off the record)

DR. MARKS: So, Christina correctly clarified that we're talking about the citrus fruit derived ingredients. This is the first time seeing these 80 citrus fruit ingredients. The GRAS -- we previously reviewed the peel oils and came to the conclusion -- an interesting conclusion, in my mind, because I think it's the first time that I recall we put not only non-irritating, but non- sensitizing, and had a limit of eight methoxypsoralen of less than 15 parts per million.

So with these 80 citrus fruit ingredients, Tom and Ron, were the ingredients okay? That's always our first step. Is there anything we need to delete from this long list? And then obviously, the next thing is what do we need to arrive at a safe conclusion?

DR. SLAGA: I have no trouble about having all of them (Inaudible).

DR. MARKS: So, all of them are okay from your point of -- Tom. Ron and Ron, all of the -- you like all of these fruits (Laughter)?

DR. SHANK: Some of these fruits and extracts are GRAS, and I think those can be handled very straightforward manner. The rest, I think we need irritation and sensitization data. If you see -- if formulated be non- irritating and non-sensitizing, then I guess you don't need that data. Bitter orange is not a common food, as far as I know. Neither is (Inaudible).

MS. BURNETT: I was told it is Earl Grey tea.

(Laughter)

SPEAKER: Yes.

DR. SHANK: It is.

MS. BURNETT: So it is considered --

DR. SHANK: So that's a water extract.

MS. BURNETT: -- edible (Laughter).

DR. SADRIEH: Can I just -- just because it's GRAS, this GRAS is for oral -- for food. So just because something is GRAS doesn't mean that it's okay to put it in a cosmetic and put it on your skin. We had a presentation this morning that olive oil, when you put in your skin is not as good as this, because you eat it and it's good for you.

I just wanted to say that because something is GRAS does not give it a green light for being safe to be formulated in a cosmetic product. And then, out of the 80 ingredients here, I just want to say that only about seven of them have a frequency of use VCRP. The rest of them do not have any frequency of use. So, I just wanted that indicated, that you know, if we're going to be doing eight ingredients at a time, less than 10 percent of them are actually in a few products, not even that many.

DR. SHANK: If FDA lists a chemical or a product as GRAS, we don't feel we need systemic toxicology. Reproductive, developmental, genotoxocity would not be required, even though it's applied to the skin. What we would need is skin effects -- irritation and dermatitis. But if it's a GRAS agent, we feel we don't need systemic toxicity data.

DR. MARKS: So Ron Hill, do you want to comment? And then I'll comment about the skin effects, because I agree with Ron Shank there. There's no (Laughter) irritation or sensitization. And even though we may end up with that conclusion, I hate to see a section that says irritation and sensitization, no data, and then come to a conclusion at the end. There's got to be some data.

So for me, I'll jump. I think there should be an insufficient data notice, and that we have HRIPT on lemon fruit extract at 1.2 percent, bitter orange at 19 percent, and grapefruit at 15 percent. And if we

get those, then I would feel comfortable moving forward, unless we have that conclusion. I'm trying to remember how we arrived at the non-sensitization. I didn't go back. You know, that was --

DR. SLAGA: We argued a lot.

SPEAKER: Four years ago, I think.

DR. MARKS: No. So, that's where I would. And then, we also need to clarify which are fragrances. There's six that there's a question mark. So again, with an insufficient data notice, we can get that clarified, hopefully, from RIFM, too. But Ron Hill, what comments do you have? So to me, that's where I would land. Insufficient data notice. And get sensitization data, preferably HRIPT on those three fruit ingredients.

DR. HILL: I just -- to respond to Dr. Sadrieh briefly, I do take into consideration really, always, that something that is eaten, where we haven't done toxicology studies at a thousand milligrams per kilogram orally, so that we're saturating everything, I always at least raise the question in my mind, something that was in a cosmetic product that might be applied to broad regions of the skin that might be able to enter the system dermally that would not get in orally, because our liver is very efficient, I do raise that question. And I think others in this panel, also, raise.

So, just because it's G-R-A-S, GRAS, we don't necessarily automatically a hundred percent of the time write it off if there's some substance of interest that we can see is likely to penetrate into the bloodstream. But usually. You know, you would think if somebody is eating -- and it's widespread dietary consumption, we are making the assumption that if there was going to be, for example, sensitization, that we would have seen it somewhere.

Yeah, in terms of the specifics of this ingredient category, the only one that intrigued me on this, because I had no idea what it is, and we don't have yet method of manufacture is defatted citrus unshiu fruit. And so what I wondered, because of that, there's no extract and no oil. Are they actually defatting the fruit in some way and then actually grinding it up and using it as is, or what's the story with that particular ingredient?

So, that one -- which of these things is not at all like the other, that one jumped out at me a little bit. I'm not suggesting we take it out. I think we should leave it in, but solicit information as to what exactly that stuff is. Because I really like, for example, that we had details of what do we mean when we have fruit water. How do they make that? I was really happy to see that kind of information.

DR. MARKS: Any other comments? Then tomorrow I presumably am going to seconding --

DR. SHANK: I have one.

DR. MARKS: Yeah, good.

DR. SHANK: For the non-GRAS fruit products, I would either remove them from the report or separate them out because those would need some systemic toxicology data.

DR. MARKS: Okay. I guess, again, going forward, just which are fragrances, which are non-GRAS, since we had the discussion about bergamot being in tea. Which are GRAS and which non-GRAS, and then if it's non-GRAS then we get into its use. As you've recommended, Ron, what's the systemic toxicity; it goes back to your question.

MS. BURNETT: If you are asking for data, I would like to ask do you feel that you have enough phototox data since we know what lime peel oil and lime juice, that it can be phototoxic, but if you have a caveat about the 5-psoralen or --

DR. MARKS: Yeah.

MS. BURNETT: -- the 5-MOPs, is that enough or would you like to see --

DR. MARKS: Yes.

MS. BURNETT: -- phototox data?

DR. MARKS: I think as long as we limit it to 15 parts per million of --

MS. BURNETT: Okay. The same --

DR. MARKS: -- 8-MOP --

MS. BURNETT: The same --

DR. MARKS: -- I think we'll have -- I think the conclusion, interestingly, may be the same as the peel oils. I just --

MS. BURNETT: Okay.

DR. MARKS: -- you know, I hate to put in a conclusion with formulate to be nonsensitizing when we don't even have any data on irritation or sensitization.

MS. BURNETT: Thank you. You would've had a very grumpy writer if you would've taken that report apart and then said okay. (Laughter)

DR. MARKS: Yeah.

MS. BURNETT: Thank you.

DR. MARKS: Yeah, you're welcome. Which are non- GRAS, I think, is important in here. I guess the other, Ron Shank, when we read across, since these are all fruit ingredients derived from citrus fruit, could you read across with some of these such as if the fruit extract is GRAS then would the juice, the water, etc., oil, all be okay if the extract is okay. I think that's another. But we certainly can find out which are non-GRAS ingredients.

MS. BURNETT: In the non-cosmetic section I have what the species of GRAS are. Just reviewing it quickly, it seems to me the only one listed, the only ingredient -- I'm going off the top of my head -- that might not be listed here is the Asian variety, the, I don't know how to say it, unshiu citrus.

SPEAKER: I'm sure I slaughtered it, so --

MS. BURNETT: Yeah.

DR. MARKS: Where is that on the list?

MS. BURNETT: It's on PDF page 27. If I go by the common name: Lime, bergamot, bitter orange, lemon, grapefruit, tangerine, mandarin, sweet orange -- they're all GRAS. The Asian varieties aren't listed.

DR. MARKS: Okay. Ron Shank, I might ask you to comment on that tomorrow. When we have the discussion with the Belsito team, I'll say, which are non-GRAS. We need systemic tox on those, and then Ron, I'll let you comment if you want to, if that would be good.

Again, I think since we're doing a lot of things with Read Across, could we do that? It certainly makes it simpler if it was all GRAS.

Any other comments? Just what I said, I hopefully will be moving a motion. I'll be seconding a motion to have an insufficient data notice, get the HR -- get the sensitization data for lemon fruit, bitter orange, and grapefruit, and then which are fragrances, clarify that, and which are non-GRAS, and do we need the systemic tox on those. Any other comments?

DR. HILL: I have a question.

DR. MARKS: Sure.

DR. HILL: On the GRAS, the GRAS items, how global in scope is that list? In other words, if we have a citrus fruit that's very commonly consumed in the Philippines, for example, is that likely to be on that list? Would it be -- I mean, I'm wondering. Some of these fruits I'm still not sure I know what they are.

DR. MARKS: The GRAS is a U.S. determination; is that correct? Even if it were consumed elsewhere, I wouldn't be totally reassured by that because in, remember, the ingredient we reviewed, which was consumed in the Pacific Islands as I remember, had neurologic effects. Now that wasn't GRAS, but again we don't consume here. I think go by GRAS and then, unless there's good evidence elsewhere, I wouldn't consider what's being done elsewhere.

DR. HILL: I guess what I was asking is Japan, for example, has the analogy to the FDA, it's Koro Sho I think. If they recognize something as the equivalent of the GRAS, could we consider adding it to the list based on whatever they have on it? I don't know. I'm asking for consideration of some of these.

MS. BURNETT: I will note that with the exception of possibly three ingredients, it appears that most of the non-typical species are not in use. I don't know if that has any bearing on anything, but in terms of receiving or finding out data it might be difficult.

DR. MARKS: Right.

DR. HILL: I guess what I'm asking is in that case would leaving them in the report but putting them insufficient, that would be an option here, right?

DR. SLAGA: One other thing. In Read Across, if one doesn't go by -- this goes by fruit extract or juice or fruit water, fruit oil, you would have a greater chance of Read Across by sticking to each category and comparing the fruit water, etc., etc., from the various forms gives one confidence that they're probably similar ingredients in all the fruit water ones or the juices would be similar.

DR. HILL: Me, I think the gray area is the extract because wasn't it this one where we saw one of the extracts as being made by supercritical fluid or is it one of the other reports? I think when it says extract we have no idea. That could be anywhere from steam distillation to grinding it and having it sit for days in ethanol to, who knows, hexane extraction.

I think one of the reasons why we started with the oil because we have a baseline and we have ingredients of concern that are likely to show up in any other oily ingredients that we see in these extracts.

I actually entertained that notion too when I looked at the table and I went in and highlighted all the fruit oils because they say fruit oils, but yet I ultimately concluded we'd be better off keeping them together. That was just the way I looked at it.

MS. FIUME: Is method of manufacture, since you're (inaudible) something you would want to add to the list of needs?

MS. BURNETT: What we've found with botanicals is the composition all depends on how they've extracted and what solvents they've used.

DR. HILL: Then there's what cultivar and what season does it grow in. That's always the case with natural things like this, but --

DR. MARKS: I didn't need anything more on method of manufacture. Did you need more?

DR. HILL: I think that comes back to the GRAS, yeah. It comes back to the GRAS maybe versus non-GRAS.

DR. MARKS: Okay. Shall we move on then? Insufficient data notice, HRIPTs, which are fragrance, which are non-GRAS.

Full Panel Meeting

DR. BERGFELD: The next ingredient reports advancing as citrus, Dr. Belsito.

DR. BELSITO: Okay, so this is the first time we're looking at this report on 80 ingredients after we decided to split the citrus group up. And the first ones we did were the peel oils. I'm still not sure that we can lump all of these together. But my team felt that the fruit water was okay with limits on 5- MOP and the boilerplate for botanicals and inhalation. And that the others were insufficient for method of manufacture and chemical composition. And we're also hoping that RIFM would finally let us know whether some of these were fragrance only materials.

DR. BERGFELD: Thank you. Dr. Marks?

DR. MARKS: So we thought there could be an insufficient data notice. Are you making a motion?

DR. BELSITO: We're saying the fruit waters are okay with limits on 5-MOP and the boilerplate for botanicals and irritations, and all the others are insufficient for method of manufacture or chemical composition.

DR. BERGFELD: Comment?

DR. BELSITO: And the question is, do we want to split the report into fruit waters and leave the other dangling? Or do we want to go with a mixed conclusion?

DR. BERGFELD: Comment from Dr. Marks.

DR. MARKS: So the fruit waters, they're okay even though you have no irritation or sensitization data? Is that because the conclusion says formulated to be non- irritating and non-sensitizing?

DR. BELSITO: No, it's because we do have data in table five, this the one? Okay, so table four, so basically what they've done is they've -- I mean, what you would be concerned about in botanicals basically are fragrance ingredients that are contained -- or ingredients that are used as fragrances that are contained in the botanicals in terms of sensitization. And they have there the 26 fragrances that are required by the EU to be labelled. Many of which are weak at best. And it should be pointed out the EU now wants over 100 fragrances labelled, many of which are hardly sensitizers at all in my opinion.

But anyway, of the 26 that are the most fragrance sensitizers, you see that at most, for instance, citral maximum concentration and citrus lemon fruit water is 100 part -- less than 100 parts per million. And that would be the highest for any of these. So we felt that they really did not contain things like linalool or citral or geraniol or any of the other sensitizers in any significant amount.

If we wanted to be consistent with botanicals, we could say, when formulated to be non-sensitizing, since they do contain some levels of citral that could be stacked onto others. But we felt that certainly based upon the limited composition information, but it was very good showing the content of the 26.

DR. SLAGA: Since this was the first time, shouldn't we wait -- the possibility we get something on the water for irritation or something else? I mean, it's -- with very little data in here, to me it's hard to make that conclusion.

MS. BURNETT: If you still want -- need data on the remaining ingredients, it's going to go as an insufficient data announcement.

DR. SLAGA: Yes.

DR. BELSITO: We can ask for sensitization, irritation where the fruit waters had concentration of use, if you want.

DR. MARKS: So what our team felt that -- what we would need in the insufficient data notice actually overlaps to a certain extent what you said on HRIPT for the lemon fruit extract at 1.2 percent. The bitter orange at 19 percent. So it's a high usage with bitter orange, and then grapefruit at 15 percent. So we could say the use concentrations are safe from an irritation, sensitization.

We also wanted to clarify, as you do, which one of these ingredients are actual fragrances. There were six that potentially are and RIFM is going to clarify that. And then the other comment was, which are non-GRAS, because if they're -- the GRAS ingredients, we don't need the systemic toxicity portion. Whereas if we identify which are non- GRAS, then we would need systemic toxicity for them. So that's how we arrived at the insufficient data notice. It gives time to react.

I think I like your reasoning for the water, and if we would go forward with that being safe, I think it's very important in the discussion to indicate why you came to the conclusions it's safe without any sensitization data.

DR. BERGFELD: Other comments from the various teams?

DR. SNYDER: I mean, just as a point of agreement, I think that this table actually gives us a lot of confidence, because it's looking at four different fruit waters, and it gives us the full spectrum of known allergens. And they just aren't there in significant levels. As opposed to if we got -- so my question is, if we ask for an HRIPT, are we going to ask on each of the individual fruit waters, the tangerine, the orange, the lemon? And so this actually is better data I think.

DR. MARKS: Yeah, I think the insufficient data notice will see what comes, and we can move forward the water based on what we know. We can't move forward, as you've already said, because insufficient we say the lemon fruit extract, the bitter orange and the grapefruit, they were the ones with high concentrations. And if we got the data on that, then we could move forward with those.

DR. BERGFELD: So for clarification, you're either agreeing with the proposal of the motion or -- what are you doing with this? Are you modifying it?

DR. MARKS: Our team would prefer to see an insufficient data notice rather than move forward with safe and in an insufficient. But that's --

DR. BELSITO: Trying to look at -- define what you mean by high concentrations.

DR. MARKS: Bitter orange, wasn't that used at 19 percent? And (inaudible) have to go to the table, but that's what I have in my notes. And grapefruit, the highest use was 15 percent. But am I wrong? Did I read that table incorrectly?

MS. BURNETT: Nineteen percent was in the rinse off fruit water, orange fruit water. There's a 15 percent leave on for grapefruit extract.

DR. MARKS: Okay, and lemon fruit extract was 1.2 percent. So what was the highest leave on for bitter orange? I just picked those I think also because they probably had high uses. Do they Christina?

MS. BURNETT: The lemon had the high use, extract has the high use. Bitter orange fruit extract has high use. Concentration is 0.002 percent.

DR. MARKS: In a leave on.

MS. BURNETT: Yes, but it's 292 uses.

DR. MARKS: So I'd probably just pick the highest use, the 19 percent and said what do we have there, even though it's a rinse off. Obviously that gives it a margin of safety there that --

DR. BELSITO: So you're going to ask for 19 percent?

DR. MARKS: No, I'm just going to ask for HRIPT on those three and whatever else we got, since that high usage, the lemon fruit extract, the bitter orange and then the grapefruit.

DR. BELSITO: Leave on was, what, 10 percent for the orange fruit water, no?

MS. BURNETT: Fifteen percent for grapefruit.

DR. BELSITO: Fifteen percent for grapefruit, okay.

DR. MARKS: I mean, we're in the stage now, we're obviously early on. We ask for this and we see what we get.

DR. BELSITO: Okay, but I think clearly we need manufacturing chemical composition for the others to decide whether this grouping is even reasonable, if we can get it. I think there seems to be -- and maybe you learn from your lesson, but there seems to be an issue necessarily, or that has been an issue where there was a mixed conclusion, and the insufficient part of that conclusion was not picked up to put it on a two year cycle. And that has been corrected at this meeting. Monice, refresh my memory.

MS. FIUME: (inaudible) propyl morpholine lattate.

DR. BELSITO: Right, where it was safe in leave on and insufficient in -- or safe in rinse off, insufficient in leave ons and that was not picked up.

DR. BERGFELD: So Don, you made the motion. Are you restating your motion at this time? Or are you going with the motion that you originally started?

DR. BELSITO: You know, we're partly insufficient. So I'm fine with saying that the fruit waters are -- we would like to see sensitization and irritation data on those of the higher use, which was the tangerine?

MS. BURNETT: Orange had the highest. Orange fruit water has highest concentration, but it's a rinse off.

DR. BELSITO: Right, leave ons --

MS. BURNETT: It's used in leave ons at 10 percent.

DR. BELSITO: Right, so one of the ones with the highest concentration of use, you said 15 percent for tangerine? For grapefruit.

MS. BURNETT: Keep the numbers straight. [laughs]

DR. BELSITO: Right.

DR. MARKS: And I'd put lemon fruit extract, since that has the highest use, even at just 1.2 percent.

DR. BELSITO: Okay, and then the others are insufficient for method of manufacture chemical composition.

DR. MARKS: And then clarify --

DR. BELSITO: Clarification from RIFM as to whether any of these are fragrance only ingredients.

DR. MARKS: And clarify which are non GRAS.

DR. BERGFELD: That is your motion Don? Are you seconding that Dr. Marks.

DR. MARKS: Yeah, I second the insufficient data notice.

DR. BERGFELD: So we are going to be voting on then the insufficient data notice as everyone understands what it will be? All those in favor please indicate by raising your hand. Thank you, unanimous.

Safety Assessment of Citrus Fruit-Derived Ingredients as Used in Cosmetics

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DRAFT ABSTRACT

The CIR Expert Panel assessed the safety of 79 citrus fruit-derived ingredients and concluded that these ingredients are (to be determined). The citrus fruit-derived ingredients are most frequently reported to function in cosmetics as fragrances and/or skin conditioning agents. The Panel reviewed the available animal and clinical data to determine the safety of these ingredients. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Industry should use good manufacturing practices to limit impurities that could be present in botanical ingredients.

INTRODUCTION

Citrus fruit-derived ingredients are widely used in cosmetics, and are most frequently reported to function in cosmetics as fragrances and/or skin conditioning agents (Table 1). This report assesses the safety of the following 79 citrus fruit-derived ingredients:

Citrus Aurantifolia (Lime)/Citrus Limon (Lemon) Fruit Water
Citrus Aurantifolia (Lime) Fruit
Citrus Aurantifolia (Lime) Fruit Extract
Citrus Aurantifolia (Lime) Fruit Water
Citrus Aurantifolia (Lime) Juice
Citrus Aurantium Amara (Bitter Orange) Fruit Extract
Citrus Aurantium Amara (Bitter Orange) Fruit Juice Extract
Citrus Aurantium Bergamia (Bergamot) Fruit Extract
Citrus Aurantium Bergamia (Bergamot) Fruit Water
Citrus Aurantium Dulcis (Orange) Fruit Extract
Citrus Aurantium Dulcis (Orange) Fruit Powder
Citrus Aurantium Dulcis (Orange) Fruit Water
Citrus Aurantium Dulcis (Orange) Juice
Citrus Clementina Fruit Extract
Citrus Clementina Juice
Citrus Depressa Fruit Extract
Citrus Depressa Fruit Water
Citrus Glauca Fruit Extract
Citrus Grandis (Grapefruit) Fruit Extract
Citrus Grandis (Grapefruit) Fruit/Peel Water
Citrus Grandis (Grapefruit) Fruit Water
Citrus Grandis (Grapefruit) Juice
Citrus Grandis/Paradisi Fruit Water
Citrus Hassaku Fruit Extract
Citrus Hassaku/Natsudaidai Fruit Juice
Citrus Hassaku/Natsudaidai Fruit Powder
Citrus Iyo Fruit Extract
Citrus Iyo Fruit Water
Citrus Jabara Juice
Citrus Japonica Fruit Extract
Citrus Junos Fruit Extract
Citrus Junos Fruit Juice
Citrus Junos Fruit Oil
Citrus Junos Fruit Powder
Citrus Junos Fruit Water
Citrus Limon (Lemon) Fruit Extract
Citrus Limon (Lemon) Fruit Oil
Citrus Limon (Lemon) Fruit Powder
Citrus Limon (Lemon) Fruit Water
Citrus Limon (Lemon) Juice
Citrus Limon (Lemon) Juice Extract
Citrus Limon (Lemon) Juice Powder
Citrus Madurensis Fruit Extract
Citrus Madurensis Fruit Juice
Citrus Medica Vulgaris Fruit Extract
Citrus Nobilis (Mandarin Orange) Fruit Extract
Citrus Nobilis (Mandarin Orange) Fruit Juice
Citrus Paradisi (Grapefruit) Fruit Extract
Citrus Paradisi (Grapefruit) Fruit Water
Citrus Paradisi (Grapefruit) Juice
Citrus Reticulata (Tangerine) Fruit
Citrus Reticulata (Tangerine) Fruit Extract
Citrus Reticulata (Tangerine) Fruit Water
Citrus Shunkokan Fruit Extract
Citrus Sinensis (Orange) Fruit Extract
Citrus Sinensis (Orange) Fruit Water
Citrus Sphaerocarpa Fruit Juice
Citrus Sudachi Fruit Extract
Citrus Sudachi Fruit Juice
Citrus Tachibana/Reticulata Fruit Juice
Citrus Tamurana Fruit Extract
Citrus Tangelo Fruit Juice
Citrus Tangelo Fruit Powder
Citrus Tangerina (Tangerine) Fruit
Citrus Tangerina (Tangerine) Fruit Water
Citrus Tankan Fruit Extract
Citrus Tankan Fruit Water
Citrus Unshiu/Citrus Reticulata/Citrus Iyo Fruit Water
Citrus Unshiu Fruit Extract

Citrus Unshiu Fruit Juice
Citrus Unshiu Fruit Juice Ferment Extract Filtrate
Citrus Unshiu Fruit Oil
Citrus Unshiu Fruit Powder
Citrus Unshiu Fruit Water
Citrus Unshiu/Sinensis/Reticulata Fruit Extract
Defatted Citrus Unshiu Fruit
Hydrolyzed Citrus Aurantium Dulcis Fruit Extract
Microcitrus Australasica Fruit Extract
Microcitrus Australis Fruit Extract

The CIR Expert Panel has reviewed the safety of citrus-derived peel oils and concluded that 14 citrus-derived peel oil 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).[1]

The citrus fruits that are used to derive the ingredients described in this safety assessment are used as food, and daily exposure from food use would result in much larger systemic exposures than from use in cosmetic products. Per 21CFR§170.30(c)(1) and (2) and §170.30(c):

> "… food ingredients of natural biological origin that has been widely consumed for its nutrient properties in the United States prior to January 1, 1958, without known detrimental effects, which is subject only to conventional processing as practiced prior to January 1, 1958, and for which no known safety hazard exists, will ordinarily be regarded as generally recognized as safe (GRAS) without specific inclusion in 21CFR§182, § 184, or §186.1."
>
> Further…"A substance used in food prior to January 1, 1958, may be GRAS through experience based on its common use in food when that use occurred exclusively or primarily outside of the United States if the information about the experience establishes that the use of the substance is safe within the meaning of the act (see §170.3(i)). Common use in food prior to January 1, 1958, that occurred outside of the United States shall be documented by published or other information and shall be corroborated by information from a second, independent source that confirms the history and circumstances of use of the substance. The information used to document and to corroborate the history and circumstances of use of the substance must be generally available; that is, it must be widely available in the country in which the history of use has occurred and readily available to interested qualified experts in this country. Persons claiming GRAS status for a substance based on its common use in food outside of the United States should obtain U.S. Food and Drug Administration concurrence that the use of the substance is GRAS."

Additionally, essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some citrus fruits are GRAS for their intended use in foods for human and animal consumption. Volatile oils of limes, lemons, grapefruits, bitter oranges, oranges, and tangerines are described as flavoring agents in the United States Pharmacopeia (USP) Food Chemicals Codex.[2] Thus, the systemic toxicity potential of citrus fruit-derived ingredients via oral exposure is not addressed further in this report. The primary focus of the safety assessment of these citrus ingredients as used in cosmetics is on the potential for irritation and sensitization from dermal exposure.

The CIR does not review ingredients that function only as fragrance ingredients because, as fragrances, the safety of these ingredients is evaluated by the Research Institute for Fragrance Materials (RIFM). Four of the citrus-derived fruit ingredients in this report function only as fragrance ingredients, according to the *International Cosmetic Ingredient Dictionary and Handbook* (see Table 2).[3] However, according to personal communications with RIFM in March 2015, these ingredients were not included in their review process, thus CIR is reviewing the safety of these ingredients.

Botanicals such as citrus contain 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 fruits. In this assessment, CIR is reviewing the potential toxicity of each of the citrus fruit-derived ingredients 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 fruits from which the ingredient 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 juice). If the substance is clearly a cosmetic ingredient, the International Nomenclature of Cosmetic Ingredients (INCI) name will be used (e.g. "citrus limon (lemon) juice"). Additionally, some inconsistencies were noted in both taxonomic and INCI naming conventions. For example, this report includes the sweet orange ingredient described as citrus aurantium dulcis (orange) in the *International Cosmetic Ingredient Dictionary and Handbook*.[3] In contrast, most of the published literature

and FDA refer to this ingredient as citrus sinensis (sweet orange). Another example of a naming inconsistency is citrus grandis (grapefruit); *Citrus grandis* is generally considered a name for a pummelo, which may also be referred to as *Citrus maxima*. *Citrus paradisi* appears to be the more widely accepted nomenclature for grapefruit. The INCI Committee of the Personal Care Products Council (Council) is working to correct some of these inconsistencies.

CHEMISTRY

The definitions and functions of the citrus fruit-derived ingredients included in this report are provided in Table 1. In some cases, the definition provides insight on the method(s) of manufacture. It should be noted that essential oils are hydrophobic, liquid, volatile aroma compounds from plants. These are typically small molecules, but their chemical structures can vary rather widely. Fixed oils, on the other hand are hydrophobic, nonvolatile, fatty compounds from plants. These are primarily composed of glycerides, and to some extent, free fatty acids. The volatile nature of essential oils makes them more likely to be useful as fragrances, but that does not necessitate that fragrance is their only function. Constituents of these citrus-derived ingredients may include both oil types.

Chemical and Physical Properties

The available chemical and physical properties of some cosmetic-grade citrus fruit extracts are found in Table 3.

Method of Manufacturing

Figures 1 is a generic representation of the method of manufacturing for citrus fruit waters. Figures 2 and 3 are the manufacturing flow charts provided by the suppliers of citrus nobilis (mandarin orange) fruit extract and citrus grandis (grapefruit) fruit extract.

Constituents/Composition

The citrus fruit-derived ingredients are complex botanicals composed of numerous constituents; there is great variation among citrus species and cultivars because of frequent bud mutations, interspecific and intergeneric hybridization, and apoximis (i.e., one or more of several types of asexual reproduction).[4] The composition of citrus fruits will vary based on the location where the plant is grown, the maturity of the plant, and storage conditions.[5] The method of extraction will also affect the compositions of the ingredients. Table 4 lists citrus constituents that are established contact allergens, according the European Commission's Scientific Committee on Consumer Safety (SCCS). Table 5 describes the cosmetics allergens certificates for some citrus fruit waters and fruit extracts. Table 6 presents the constituents, composition, and impurities of some citrus fruit extract products. Table 7 describes general constituent data on citrus fruit (non-cosmetic grade).

USE

Cosmetic

The safety of these cosmetic ingredients is evaluated on the basis of the expected use in cosmetics. The Panel utilizes data received from the FDA and the cosmetics industry in determining the expected cosmetic use. The data received from the FDA are those it collects from manufacturers on the use of individual ingredients in cosmetics by cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP), and those from the cosmetic industry are submitted in response to a survey of the maximum reported use concentrations by category conducted by the Personal Care Products Council (Council).

According to the 2015 VCRP survey data, citrus limon (lemon) fruit extract has the most reported uses of the ingredients in this report in cosmetic products, with a total of 571; more than half of the uses are in leave-on skin care preparations (Table 8).[6] Citrus aurantium amara (bitter orange) fruit extract has the second greatest number of overall uses reported, with a total of 295; more than half of those uses also are in leave-on skin care preparations. The results of the concentration of use survey conducted in 2013 by the Council indicate citrus aurantium dulcis (orange) fruit water has the highest reported maximum concentration of use; it is used at up to 19% in paste masks and mud packs.[7] Citrus grandis (grapefruit) fruit extract had the second highest reported maximum concentration of uses; it is used at up to 15% in face and neck products. Most of the use concentrations that were reported for the other citrus fruit ingredients were much lower than these two ingredients.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided. For example, citrus medica vulgaris fruit extract is reported to be used in 11 formulations, but no use concentration data were available. In other cases, no reported uses were reported to the VCRP, but a maximum use concentration was provided in the industry survey. For example, citrus japonica fruit extract was not reported in the VCRP database to be in use, but the industry survey indicated that it is used in non-coloring hair conditioners at up to 0.0038%. It should be presumed that citrus japonica fruit extract is used in at least one cosmetic formulation.

Table 9 lists all citrus fruit-derived ingredients not indicated to be in use based on the VCRP data or the results of the Council concentration of use survey. A survey is still being conducted on the following ingredients: citrus grandis (grapefruit) fruit/peel water, citrus iyo fruit water, citrus tamurana fruit extract, defatted citrus unshiu fruit, and hydrolyzed citrus aurantium dulcis fruit extract. These data will be incorporated once they are received.

Some of these ingredients may be used in products that can be incidentally ingested or come into contact with mucous membranes. For example, citrus limon (lemon) fruit extract is used at 0.03% in lipstick and citrus aurantifolia (lime) fruit extract is used at 0.2% in personal cleanliness products. Additionally, some of these ingredients were reported to be used in hair sprays and body and hand sprays and could possibly be inhaled. For example, citrus nobilis (mandarin orange) fruit extract was reported to be used in body and hand sprays at a maximum concentration of 0.0075%. 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.[8-11] 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.[9,10]

Under the rules governing cosmetic products in the European Union, citrus-derived ingredients must have a furocoumarin content below 1 mg/kg in sun-protection products and in bronzing products.[12] The International Fragrance Association (IFRA) has issued standards for citrus oils and other furocoumarin-containing essential oils.[13] Finished products that are applied to the skin, excluding rinse-off products like bath preparations and soaps, must not contain more than 0.0015% or 15 ppm 5-MOP. This equates to a level of 0.0075% or 75 ppm in a fragrance compound when used at 20% in a consumer product that is applied to the skin. If the level of 5-MOP has not been determined, limits specified for individual oils should be observed, and when such oils are used in combination with other phototoxic ingredients, the potential for an additive effect should be considered and use levels should be reduced accordingly.

An IFRA standard also has been issued for 7-methoxycoumarin, which is prohibited for use in fragrance compounds.[14] Based on established maximum levels of this substance from commercially-available natural sources (like essential oils, extracts and absolutes), IFRA has determined that exposure to 7-methoxycoumarin from the use of these oils and extracts is acceptable if the level of 7-methoxycoumarin in the finished product does not exceed 100 ppm.

Non-Cosmetic

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

Citrus aurantium amara (bitter orange) and extracts of its dried fruit and peel have been used in traditional Western medicines and in Chinese and Japanese herbal medicines.[15]

TOXICOLOGICAL STUDIES

As noted earlier, the citrus ingredients in this assessment are found in foods, and daily exposures from food use would result in a much larger systemic exposure than those from use in cosmetic products. Essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some citrus fruits are GRAS for their intended use in foods for human and animal consumption according to the FDA. Volatile oils of limes, lemons, grapefruits, bitter oranges, oranges, and tangerines are described as flavoring agents in the USP Food Chemicals Codex.[2] Therefore, the systemic toxicity potential of these ingredients is not addressed further in this report. The primary focus of this safety assessment is on the potential for irritation and sensitization from dermal exposure to these citrus ingredients as used in cosmetic products.

GENOTOXICITY

In Vitro

Citrus nobilis (mandarin orange) fruit extract in dimethyl sulfoxide was analyzed for mutagenic potential in an Ames assay using *Salmonella typhimurium* strains TA97a, TA98, TA100, TA102, and TA1535, with and without S9 metabolic activation.[16] Concentrations tested were 0.05, 0.1, 0.5, 1.0, and 5.0 mg/plate. Positive and negative controls yielded expected results. No sign of mutagenicity was observed with or without S9. The test material was cytotoxic at 5.0 mg/plate. It was concluded that citrus nobilis (mandarin orange) fruit extract was not mutagenic, with or without metabolic activation.

IRRITATION AND SENSITIZATION

Ocular Irritation

Citrus grandis (grapefruit) fruit extract (100% in powder form) was not a ocular irritant in an EpiOcular eye irritation test.[17] Citrus nobilis (mandarin orange) fruit extract was not an ocular irritant when tested up to 100% in a hen egg chorioallantoic membrane assay.[18]

Dermal Irritation and Sensitization

Dermal sensitization studies are presented in Table 10. Citrus grandis (grapefruit) fruit extract (100% in powder form) was not a dermal irritant in an vitro study.[17] Fruit extracts of citrus aurantium bergamia (bergamot) (0.081525%), citrus aurantium dulcis (orange) (1.2%), citrus limon (lemon) (1.2%), citrus nobilis (mandarin orange) (1%), and citrus grandis (grapefruit) (0.16%) and fruit waters of citrus aurantium dulcis (orange) (38%) and citrus limon (lemon) (1%) were not sensitizing in human repeat insult patch tests (HRIPTs).[19-24]

Phototoxicity and Photosensitization

Phototoxicity and photosensitization studies are presented in Table 11. Phytophotodermatitis was observed in rats following exposure to undiluted lemon fruit juice.[25] No reactions were observed in human patients exposed to undiluted pure or extracts of orange mesocarp or fruit.[26]

Case Reports

Case reports describing reactions to citrus-derived ingredients are summarized in Table 12. Phytophotodermatitis was noted in numerous patients exposed to the juices of lemons and limes.[27-39]

SUMMARY

The 79 citrus fruit-derived ingredients described in this report function primarily as skin conditioning agents-miscellaneous and fragrance. Botanicals such as citrus are composed of hundreds of constituents, some of which have the potential to cause toxic effects; for example, bergapten (aka 5-methoxypsoralen or 5-MOP) is a naturally-occurring, photo-toxic furanocoumarin (psoralen) in citrus fruits. Presently, CIR reviewed the information available on the potential toxicity of each of the citrus fruit-derived ingredients as a whole, complex substance; CIR did not review the potential toxicity information on the individual constituents of which the citrus fruit-derived ingredients are comprised.

Citrus limon (lemon) fruit extract has the most reported uses in cosmetic products, with a total of 571; more than half of the uses are in leave-on skin care preparations. The maximum use concentration range for citrus limon (lemon) fruit extract is 0.0001% to 1.2%, with 1.2% reported in night skin care products. Citrus aurantium amara (bitter orange) fruit extract has the second greatest number of overall uses reported, with a total of 295 more than half of those uses are in leave-on skin care preparations. Citrus aurantium amara (bitter orange) fruit extract had a maximum use concentration range of 0.00002% to 0.002%, with 0.002% reported in lipstick and eye makeup preparations. Most of the other use concentrations that were reported had similar ranges. However, maximum use concentrations as high as 19% were reported for citrus aurantium dulcis (orange) fruit water in paste masks and mud packs and as high as 15% for citrus grandis (grapefruit) fruit extract in face and neck products.

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

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

Citrus grandis (grapefruit) fruit extract (100% in powder form) and citrus nobilis (mandarin orange) fruit extract (up to 100%) were not ocular irritants in in vitro studies.

Citrus grandis (grapefruit) fruit extract (100% in powder form) was not a dermal irritant in an vitro study. Fruit extracts of citrus aurantium bergamia (bergamot) (0.081525%), citrus aurantium dulcis (orange) (1.2%), citrus limon (lemon) (1.2%), citrus nobilis (mandarin orange) (1%), and citrus grandis (grapefruit) (0.16%) and fruit waters of citrus aurantium dulcis (orange) (38%) and citrus limon (lemon) (1%) were not sensitizing in HRIPTs.

Phytophotodermatitis was observed in rats following exposure to undiluted lemon fruit juice. No reactions were observed in human patients exposed to 0.081525% citrus aurantium bergamia (bergamot) fruit extract or undiluted pure or

extracts of orange mesocarp or fruit. Phytophotodermatitis was noted in numerous patients exposed to the juices of lemons or limes.

DRAFT DISCUSSION

The citrus ingredients in this assessment are found in foods, and daily exposures from the consumption of foods can be expected to yield much larger systemic exposures to these ingredients than those from the use of cosmetic products. Essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some citrus fruits are GRAS in foods and animal feeds. Additionally, volatile oils of limes, lemons, grapefruits, bitter oranges, oranges, and tangerines are used as flavoring agents. Consequently, the primary focus of this safety assessment is on the potential for irritation and sensitization from dermal exposures to the citrus ingredients.

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients may each contribute to the final concentration of a single constituent. Therefore, when formulating products, manufacturers should avoid reaching levels in final formulation of plant constituents that may cause sensitization or other adverse effects. Specific examples of constituents that could induce adverse effects are limonene, citral, and other monoterpenes, furocoumarins (such as 5- MOP and 7-methoxycoumarin).

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

(Further discussion points to be determined.)

CONCLUSION

To be determined.

FIGURES

Figure 1. Method of manufacturing of fruit waters.[40]

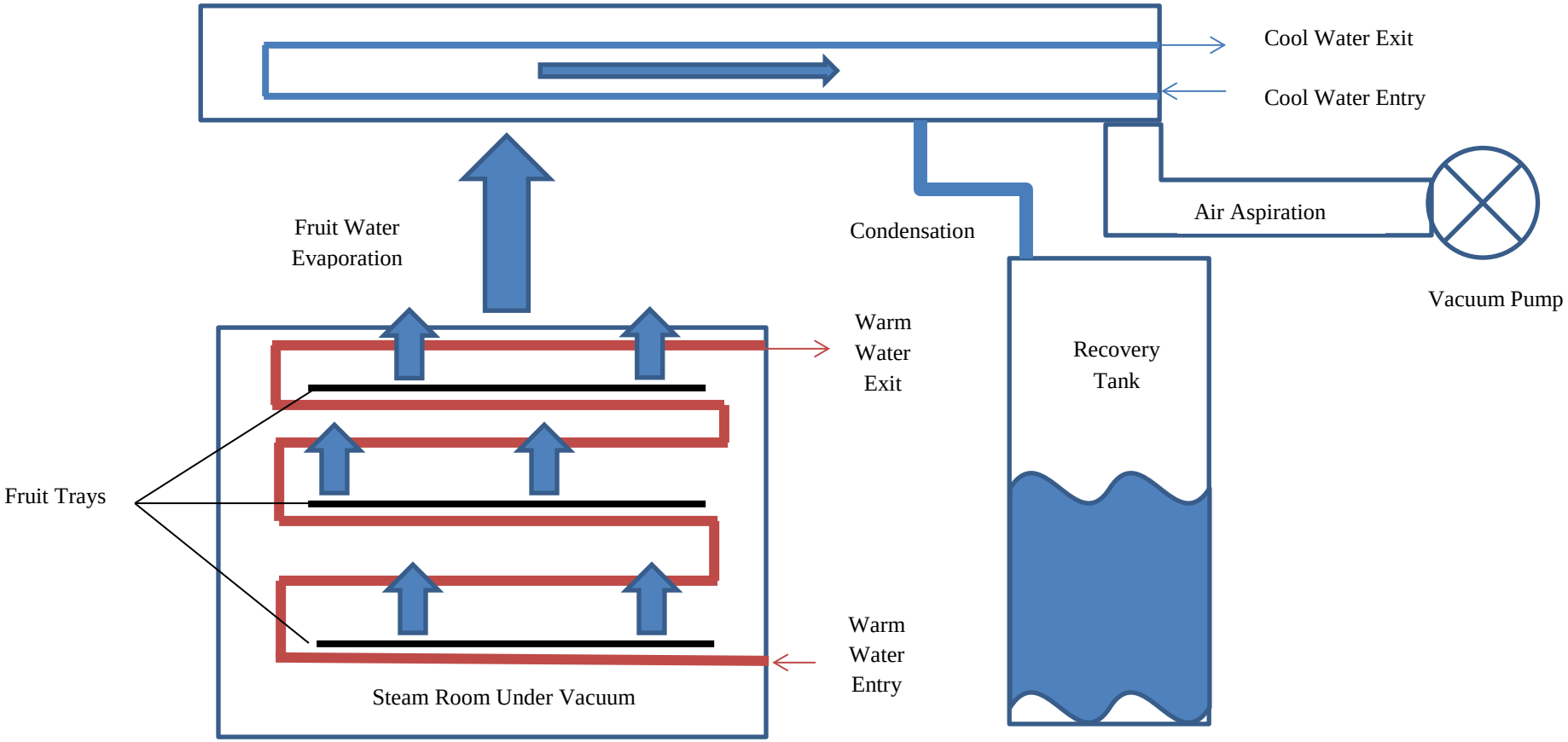


Figure 2. Manufacturing flow chart for citrus nobilis (mandarin orange) fruit extract.[41]

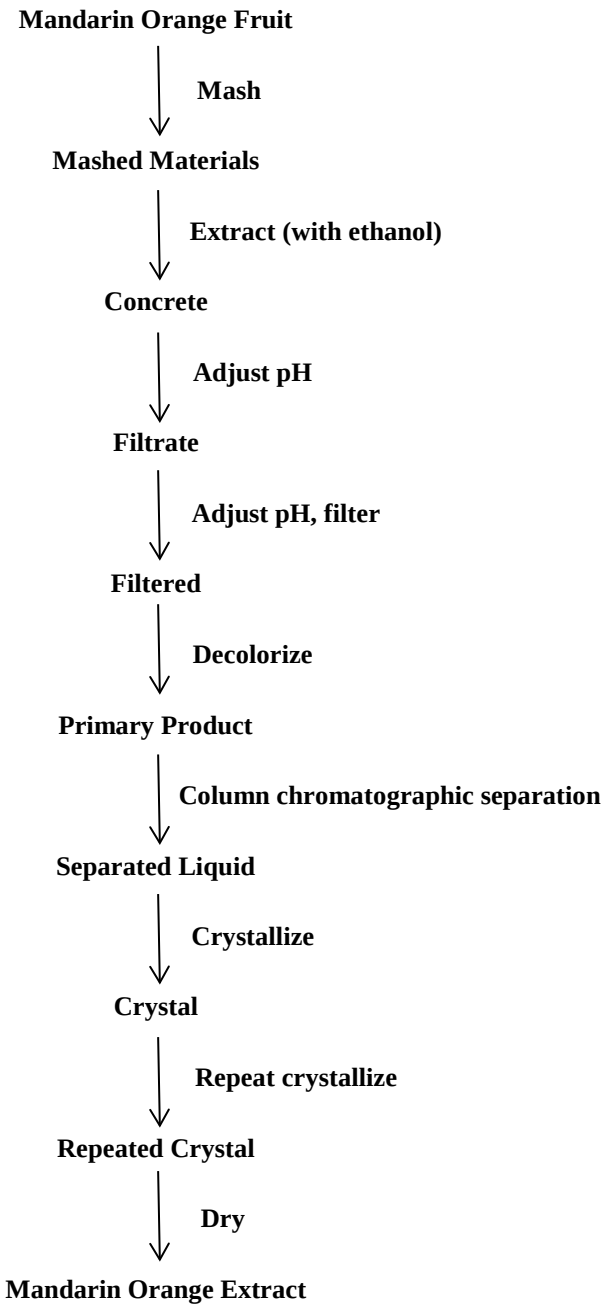
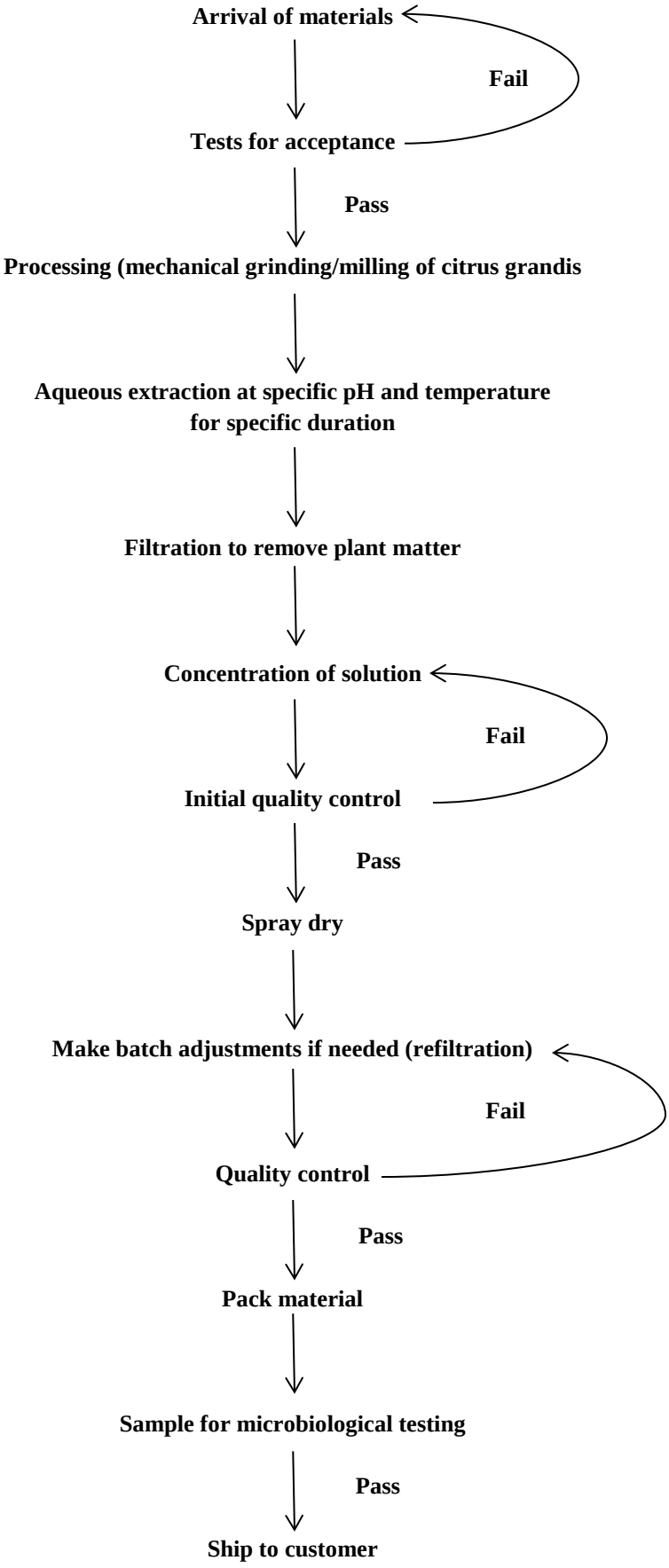


Figure 3. Manufacturing flow chart for citrus grandis (grapefruit) fruit extract – powder form.[42]



TABLES

Table 1. Definitions and functions of Citrus-derived ingredients. [3]

Ingredient	Definition	Function
Citrus Aurantifolia (Lime)/Citrus Limon (Lemon) Fruit Water	Citrus Aurantifolia (Lime)/Citrus Limon (Lemon) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus aurantifolia* and *Citrus limon.*	Skin-Conditioning Agents - Humectant
Citrus Aurantifolia (Lime) Fruit	Citrus Aurantifolia (Lime) Fruit is the fruit of *Citrus aurantifolia.*	Not reported
Citrus Aurantifolia (Lime) Fruit Extract CAS No. 90063-52-8	Citrus Aurantifolia (Lime) Fruit Extract is the extract of the fruit of *Citrus aurantifolia*.	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Fruit Water	Citrus Aurantifolia (Lime) Fruit Water is an aqueous solution of the steam distillates obtained from the fruit of *Citrus aurantifolia*.	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Juice	Citrus Aurantifolia (Lime) Juice is the liquid expressed from the fresh pulp of the lime, *Citrus aurantifolia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Fruit Extract CAS No. 84625-25-2	Citrus Aurantium Amara (Bitter Orange) Fruit Extract is the extract of the fruit of *Citrus aurantium amara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Fruit Juice Extract	Citrus Aurantium Amara (Bitter Orange) Fruit Juice Extract is the extract of the fruit juice of *Citrus aurantium amara.*	Hair Conditioning Agents; Nail Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Bergamia (Bergamot) Fruit Extract CAS No. 89957-91-5	Citrus Aurantium Bergamia (Bergamot) Fruit Extract is the extract of the fruit of *Citrus aurantium bergamia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Bergamia (Bergamot) Fruit Water	Citrus Aurantium Bergamia (Bergamot) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus aurantium bergamia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Fruit Extract CAS No. 84012-28-2	Citrus Aurantium Dulcis (Orange) Fruit Extract is the extract of the fruit of *Citrus aurantium dulcis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Fruit Powder	Citrus Aurantium Dulcis (Orange) Fruit Powder is the powder obtained from the dried, ground fruit of *Citrus aurantium dulcis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Fruit Water	Citrus Aurantium Dulcis (Orange) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of the orange, *Citrus aurantium dulcis.*	Flavoring Agents; Fragrance Ingredients
Citrus Aurantium Dulcis (Orange) Juice	Citrus Aurantium Dulcis (Orange) Juice is the liquid expressed from the pulp of the orange, *Citrus aurantium dulcis.*	Not reported
Citrus Clementina Fruit Extract	Citrus Clementina Fruit Extract is the extract of the fruit of *Citrus clementina.*	Skin-Conditioning Agents - Miscellaneous
Citrus Clementina Juice	Citrus Clementina Juice is the juice expressed from the pulp of *Citrus clementina.*	Skin-Conditioning Agents - Miscellaneous
Citrus Depressa Fruit Extract	Citrus Depressa Fruit Extract is the extract of the fruit of *Citrus depressa*.	Skin-Conditioning Agents - Miscellaneous
Citrus Depressa Fruit Water	Citrus Depressa Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus depressa.*	Skin-Conditioning Agents - Humectant
Citrus Glauca Fruit Extract CAS No. 1174331-62-4	Citrus Glauca Fruit Extract is the extract of the fruit of *Citrus glauca.*	Antistatic Agents; Hair Conditioning Agents; Skin-Conditioning Agents - Humectant
Citrus Grandis (Grapefruit) Fruit Extract	Citrus Grandis (Grapefruit) Fruit Extract is the extract of the fruit of *Citrus grandis.*	Preservatives; Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Fruit/Peel Water	Citrus Grandis (Grapefruit) Fruit/Peel Water is the aqueous solution of the steam distillates obtained from the fruits and peels of the grapefruit, *Citrus grandis*.	Skin-Conditioning Agents - Humectant
Citrus Grandis (Grapefruit) Fruit Water	Citrus Grandis (Grapefruit) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus grandis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Juice	Citrus Grandis (Grapefruit) Juice is the liquid expressed from the fresh pulp of the grapefruit, *Citrus grandis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Grandis/Paradisi Fruit Water	Citrus Grandis/Paradisi Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of the hybrid of *Citrus paradisi* and *Citrus grandis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Hassaku Fruit Extract	Citrus Hassaku Fruit Extract is the extract of the fruit of *Citrus hassaku.*	Skin-Conditioning Agents - Humectant
Citrus Hassaku/Natsudaidai Fruit Juice	Citrus Hassaku/Natsudaidai Fruit Juice is the juice expressed from the fruit of a hybrid of *Citrus hassaku* and *Citrus natsudaidai.*	Skin-Conditioning Agents - Humectant
Citrus Hassaku/Natsudaidai Fruit Powder	Citrus Hassaku/Natsudaidai Fruit Powder is the powder obtained from the dried, ground fruit of a hybrid of *Citrus hassaku* and *Citrus natsudaidai*.	Skin-Conditioning Agents - Emollient
Citrus Iyo Fruit Extract	Citrus Iyo Fruit Extract is the extract of the fruit of *Citrus iyo.*	Skin-Conditioning Agents - Emollient; Skin-Conditioning Agents - Humectant
Citrus Iyo Fruit Water	Citrus Iyo Fruit Water is the aqueous solution of the steam distillates obtained from the fruit of *Citrus iyo*.	Skin-Conditioning Agents - Humectant

Table 1. Definitions and functions of Citrus-derived ingredients. [3]

Ingredient	Definition	Function
Citrus Jabara Juice	Citrus Jabara Juice is the liquid expressed from the fruit of *Citrus jabara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Japonica Fruit Extract	Citrus Japonica Fruit Extract is the extract obtained from the fruit of *Citrus japonica.*	Skin-Conditioning Agents - Miscellaneous
Citrus Junos Fruit Extract	Citrus Junos Fruit Extract is the extract of the fruit of *Citrus junos.*	Skin-Conditioning Agents - Miscellaneous
Citrus Junos Fruit Juice	Citrus Junos Fruit Juice is the juice expressed from the fruit of *Citrus junos.*	Skin-Conditioning Agents - Humectant
Citrus Junos Fruit Oil	Citrus Junos Fruit Oil is the volatile oil obtained from the fruit of *Citrus junos.*	Fragrance Ingredients
Citrus Junos Fruit Powder	Citrus Junos Fruit Powder is the powder obtained from the dried, ground fruit of *Citrus junos.*	Exfoliants
Citrus Junos Fruit Water	Citrus Junos Fruit Water is the aqueous solution of the steam distillates obtained the fruit of *Citrus junos.*	Fragrance Ingredients
Citrus Limon (Lemon) Fruit Extract CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Fruit Extract is the extract of the fruit of *Citrus limon.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous; Skin-Conditioning Agents - Occlusive
Citrus Limon (Lemon) Fruit Oil	Citrus Limon (Lemon) Fruit Oil is the volatile oil obtained from the fruit of *Citrus limon.*	Cosmetic Astringents
Citrus Limon (Lemon) Fruit Powder	Citrus Limon (Lemon) Fruit Powder is the powder obtained from the dried fruit of *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Fruit Water	Citrus Limon (Lemon) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus limon.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Juice CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Juice is the liquid expressed from the fresh pulp of the lemon, *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Juice Extract CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Juice Extract is the extract of the juice of *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Juice Powder CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Juice Powder is the powder obtained from the dried juice of *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Madurensis Fruit Extract	Citrus Madurensis Fruit Extract is the extract of the fruit of *Citrus madurensis.*	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Citrus Madurensis Fruit Juice	Citrus Madurensis Fruit Juice is the juice expressed from the fruit of *Citrus madurensis.*	Flavoring Agents
Citrus Medica Vulgaris Fruit Extract CAS No. 92346-90-2	Citrus Medica Vulgaris Fruit Extract is the extract of the fruit of *Citrus medica vulgaris.*	Antioxidants; Chelating Agents
Citrus Nobilis (Mandarin Orange) Fruit Extract	Citrus Nobilis (Mandarin Orange) Fruit Extract is the extract of the fruit of *Citrus nobilis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Nobilis (Mandarin Orange) Fruit Juice	Citrus Nobilis (Mandarin Orange) Fruit Juice is the liquid expressed from the fruit of the mandarin orange, *Citrus nobilis.*	Bath Soaps and Detergents
Citrus Paradisi (Grapefruit) Fruit Extract CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Fruit Extract is the extract of the fruit of *Citrus paradisi*.	Skin-Conditioning Agents - Miscellaneous
Citrus Paradisi (Grapefruit) Fruit Water CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus paradisi.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Paradisi (Grapefruit) Juice CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Juice is the liquid expressed from the fresh pulp of the grapefruit *Citrus paradisi.*	Skin-Conditioning Agents - Miscellaneous
Citrus Reticulata (Tangerine) Fruit	Citrus Reticulata (Tangerine) Fruit is the fruit of *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Citrus Reticulata (Tangerine) Fruit Extract	Citrus Reticulata (Tangerine) Fruit Extract is the extract of the fruit of *Citrus reticulata.*	Drug Astringents - Skin Protectant Drugs
Citrus Reticulata (Tangerine) Fruit Water	Citrus Reticulata (Tangerine) Fruit Water is the aqueous solution of the steam distillates obtained from the fruit of *Citrus reticulata.*	Fragrance Ingredients
Citrus Shunkokan Fruit Extract	Citrus Shunkokan Fruit Extract is the extract of the fruit of *Citrus shunkokan.*	Antioxidants
Citrus Sinensis (Orange) Fruit Extract	Citrus Sinensis (Orange) Fruit Extract is the extract of the fruit of *Citrus sinensis.*	Antioxidants; Skin-Conditioning Agents - Miscellaneous
Citrus Sinensis (Orange) Fruit Water	Citrus Sinensis (Orange) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus sinensis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Sphaerocarpa Fruit Juice	Citrus Sphaerocarpa Fruit Juice is the juice expressed from the fruit of *Citrus sphaerocarpa.*	Skin-Conditioning Agents - Miscellaneous
Citrus Sudachi Fruit Extract	Citrus Sudachi Fruit Extract is the extract of the fruit of *Citrus sudachi.*	Skin-Conditioning Agents - Humectant
Citrus Sudachi Fruit Juice	Citrus Sudachi Fruit Juice is the juice expressed from the fruit of *Citrus sudachi.*	Skin-Conditioning Agents - Humectant
Citrus Tachibana/Reticulata Fruit Juice	Citrus Tachibana/Reticulata Fruit Juice is the juice expressed from the fruit of a hybrid of *Citrus tachbana* and *Citrus reticulata.*	Flavoring Agents; Skin-Conditioning Agents - Miscellaneous

Table 1. Definitions and functions of Citrus-derived ingredients. [3]

Ingredient	Definition	Function
Citrus Tamurana Fruit Extract	Citrus Tamurana Fruit Extract is the extract of the fruit of *Citrus tamurana.*	Skin-Conditioning Agents - Humectant
Citrus Tangelo Fruit Juice	Citrus Tangelo Fruit Juice is the juice expressed from the fruit of *Citrus tangelo.*	Skin-Conditioning Agents - Humectant
Citrus Tangelo Fruit Powder	Citrus Tangelo Fruit Powder is the powder obtained from the dried, ground fruit, *Citrus tangelo.*	Skin-Conditioning Agents - Emollient
Citrus Tangerina (Tangerine) Fruit	Citrus Tangerina (Tangerine) Fruit is the fruit of *Citrus tangerina*.	Not reported
Citrus Tangerina (Tangerine) Fruit Water	Citrus Tangerina (Tangerine) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus tangerina.*	Skin-Conditioning Agents - Miscellaneous
Citrus Tankan Fruit Extract	Citrus Tankan Fruit Extract is the extract of the fruit of *Citrus tankan.*	Skin-Conditioning Agents - Humectant
Citrus Tankan Fruit Water	Citrus Tankan Fruit Water is the aqueous solution of the steam distillates obtained from the fruit of *Citrus tankan.*	Humectants
Citrus Unshiu/Citrus Reticulata/Citrus Iyo Fruit Water	Citrus Unshiu/Citrus Reticulata/Citrus Iyo Fruit Water is the aqueous solution of the steam distillates obtained from the fruit of *Citrus unshiu, Citrus reticulata* and *Citrus Iyo.*	Fragrance Ingredients
Citrus Unshiu Fruit Extract	Citrus Unshiu Fruit Extract is the extract of the fruit of *Citrus unshiu.*	Antioxidants; Hair Conditioning Agents; Skin Protectants; Skin-Conditioning Agents - Emollient; Sunscreen Agents
Citrus Unshiu Fruit Juice	Citrus Unshiu Fruit Juice is the juice expressed from the fruit of *Citrus unshiu.*	Skin-Conditioning Agents - Humectant
Citrus Unshiu Fruit Juice Ferment Extract Filtrate	Citrus Unshiu Fruit Juice Ferment Extract Filtrate is a filtrate of an extract of the product obtained by the spontaneous fermentation of Citrus Unshiu Fruit Juice (q.v.).	Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu Fruit Oil	Citrus Unshiu Fruit Oil is the volatile oil derived from the fruit of *Citrus unshiu.*	Skin-Conditioning Agents - Emollient
Citrus Unshiu Fruit Powder	Citrus Unshiu Fruit Powder is the powder obtained from the dried, ground fruit of *Citrus unshiu.*	Antioxidants; Exfoliants; Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu Fruit Water	Citrus Unshiu Fruit Water is the aqueous solution of the steam distillates obtained from the fruit of *Citrus unshiu.*	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu/Sinensis/Reticulata Fruit Extract	Citrus Unshiu/Sinensis/Reticulata Fruit Extract is the extract of the fruit of *Citrus unshiu*, *Citrus sinensis*, and *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Defatted Citrus Unshiu Fruit	Defatted Citrus Unshiu Fruit is the dried, defatted fruit of *Citrus unshiu.*	Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Citrus Aurantium Dulcis Fruit Extract	Hydrolyzed Citrus Aurantium Dulcis Fruit Extract is the hydrolysate of Citrus Aurantium Dulcis (Orange) Fruit Extract (q.v.) derived by acid, enzyme or other method of hydrolysis.	Skin Protectants
Microcitrus Australasica Fruit Extract	Microcitrus Australasica Fruit Extract is the extract of the fruit of *Microcitrus australasica.*	Skin-Conditioning Agents - Miscellaneous
Microcitrus Australis Fruit Extract	Microcitrus Australis Fruit Extract is the extract of the fruit of *Microcitrus Australis*.	Skin-Conditioning Agents - Miscellaneous

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

Citrus Junos Fruit Oil
Citrus Junos Fruit Water
Citrus Reticulata (Tangerine) Fruit Water
Citrus Unshiu/Citrus Reticulata/Citrus Iyo Fruit Water

Table 3. Chemical and physical properties

Property	Value	Reference
Citrus limon (lemon) fruit extract		
Physical Form	clear, brownish yellow liquid	43-45
Odor	faint, fruity	43-45
Density (at 20ºC)	1.035-1.240	43-45
Refraction Index (at 20ºC)	1.425-1.460	43-45
pH	3.5-5.0	43-45
Citrus paradisi (grapefruit) fruit extract		
Physical Form	clear, yellowish liquid	46,47
Odor	faint, fruity	46,47
Density (at 20ºC)	1.040-1.215	46,47
Refraction Index (at 20ºC)	1.415-1.455	46,47
pH	4.0-5.0	46,47
Citrus aurantium dulcis (orange) fruit extract		
Physical Form	clear, yellow brown liquid	48,49
Odor	faint, fruity	48,49
Density (at 20ºC)	1.050-1.240	48,49
Refraction Index (at 20ºC)	1.425-1.465	48,49
pH	4.0-5.0	48,49
Citrus grandis (grapefruit) fruit extract		
Physical Form	clear to light yellow liquid or off-white to pale yellow powder	50-52
Odor	characteristic	50-52
Density (at 20ºC)	1.040-1.215	50
Refraction Index (at 25ºC)	1.385-1.400	50
pH	4.0-6.0 (in liquid at25ºC); 2.0-5.0 (in powder at 1% in water)	50-52
Citrus aurantifolia (lime) fruit extract		
Physical Form	clear yellow to light amber liquid	53
Odor	characteristic	53
Specific Gravity	1.000-1.020	53
Boiling Point (ºC)	209	54
Freezing Point (ºC)	-50	54
Refraction Index	1.4350-1.4450	53
pH (at25ºC)		

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

Constituent	**categorized according to number of patients reacting positively and to the number of patients tested (>1000 patients tested, unless indicated as r.t., i.e., rarely tested)** [55]
β-caryophyllene	≤10 (oxidized and non-oxidized)
carvone	≤10 (r.t.)
citral	101 to 1000
citronellol	11-100
coumarin	101 to 1000
farnesol	101 to 1000
geraniol	101 to 1000
linalyl acetate	≤10
α- and β-pinene	11-100
(DL)-limonene	11-100 (non-oxidized); 101 to 1000 (oxidized)
tepineol (mixture of isomers)/α-terpineol	≤10
terpinolene	11-100

Table 5. Cosmetic allergens certificate from a manufacturer of citrus fruit waters and extracts [56-62]

Allergen	Citrus Sinensis (Orange) Fruit Water	Citrus Limon (Lemon) Fruit Water	Citrus Reticulata (Tangerine) Fruit Water	Citrus Paradisi (Grapefruit) Fruit Water	Citrus Aurantifolia (Lime) Fruit Extract	Citrus Grandis (Grapefruit) Fruit Extract
Amyl cinnamal	NP	NP	NP	NP	NP	NP
Benzyl alcohol	NP	NP	NP	NP	NP	NP
Cinnamyl alcohol	NP	NP	NP	NP	NP	NP
Citral	NP	Max. content < 100 ppm	NP	NP	NP	NP
Eugenol	NP	NP	NP	NP	NP	NP
Hydroxycitronellal	NP	NP	NP	NP	NP	NP
Isoeugenol	NP	NP	NP	NP	NP	NP
Amylcinnamyl alcohol	NP	NP	NP	NP	NP	NP
Benzyl salicylate	NP	NP	NP	NP	NP	NP
Cinnamal	NP	NP	NP	NP	NP	NP
Coumarin	NP	NP	NP	NP	NP	NP
Geranlol	NP	Max. content < 100 ppm	NP	NP	NP	NP
Hydroxyisohexyl 3-cyclo hexane carboxaldehyde	NP	NP	NP	NP	NP	NP
Anise alcohol	NP	NP	NP	NP	NP	NP
Benzyl cinnamate	NP	NP	NP	NP	NP	NP
Farnesol	NP	NP	NP	NP	NP	NP
Butylphenyl methylpropional	NP	NP	NP	NP	NP	NP
Linalool	Max. content < 10 ppm	Max. content < 100 ppm	NP	Max. content < 10 ppm	NP	NP
Benyl benzoate	NP	NP	NP	NP	NP	NP
Citronellol	NP	NP	NP	NP	NP	NP
Hexyl cinnamal	NP	NP	NP	NP	NP	NP
Limonene	NP	NP	NP	NP	NP	NP
Methyl 2-octynoate	NP	NP	NP	NP	NP	NP
Alpha-isomethyl ionone	NP	NP	NP	NP	NP	NP
Evernia prunastri	NP	NP	NP	NP	NP	NP
Evernia furfuracea	NP	NP	NP	NP	NP	NP

Detection limit 2 ppm.
ND = unable to be detected by GCSM
NP = not present

Table 6. Constituents, components, and impurities in citrus fruit extract products. [43-49,51,53,63]

Constituent	Citrus Limon (Lemon) Fruit Extract – propylene glycol	Citrus Limon (Lemon) Fruit Extract – glycerin	Citrus Paradisi (Grapefruit) Fruit Extract – propylene glycol	Citrus Paradisi (Grapefruit) Fruit Extract - glycerin	Citrus Aurantium Dulcis (Orange) Fruit Extract – propylene glycol	Citrus Aurantium Dulcis (Orange) Fruit Extract - glycerin	Citrus Nobilis (Mandarin Orange) Fruit Extract-ethanol
fruit extract	50-75% (may have < 0.1% citrus limon (lemon) peel oil	50-75%	10-25%	10-25%	75-100%	25-50%	NR
propylene glycol	75-100%	NR	75-100%	NR	75-100%	NR	NR
glycerin	NR	75-100%	NR	50-75%	NR	75-100%	NR
ethanol	NR	NR	NR	NR	NR	NR	NR
butylene glycol	NR	NR	NR	NR	NR	NR	NR
limonene	0.015-0.03% max.	max. 0.015%	NR	NR	0.016% max.	0.01% max.	NR
citral	0.001- 0.002% max.	max. 0.001%	NR	NR	NR	NR	NR
limonene	NR	NR	0.11% max.	0.11% max.	NR	NR	NR
tangeretin	NR	NR	NR	NR	NR	NR	>70%
furanocoumarins	NR	NR	NR	NR	NR	NR	NR
bactiphen or phenonip (phenoxyethnaol, methylparaben, ethylparaben, propylparaben, butylparaben)	0-0.6%	NR	NR	NR	NR	NR	NR
lactic acid	0.1-1%	0.1-1%	0.1-1%	0.1-1%	0.1-1%	0.1-1%	NR
potassium sorbate	0-0.35%	0.3%	0.35%	0.35%	0.35%	0.4%	NR
sodium benzoate	0-0.35%	0.3%	0.35%	0.35%	0.35%	0.4%	NR
arsenic	NR	NR	NR	NR	NR	NR	limit: not more than 2 ppm
heavy metals	NR	NR	NR	NR	NR	NR	limit: not more than 20 ppm

Constituent	Citrus Aurantifolia (Lime) Fruit Extract – butylene glycol	Citrus Grandis (Grapefruit) Fruit Extract
fruit extract	20.0%	100%
propylene glycol	NR	NR
glycerin	NR	NR
ethanol	NR	NR
butylene glycol	79.5%	NR
limonene	NR	NR
citral	NR	NR
limonene	NR	NR
tangeretin	NR	NR
furanocoumarins	NR	< 1 ppm (limit)
bactiphen or phenonip (phenoxyethnaol, methylparaben, ethylparaben, propylparaben, butylparaben)	0.5%	NR
lactic acid	NR	NR
potassium sorbate	NR	NR
sodium benzoate	NR	NR
arsenic	< 2 ppm	< 2 ppm
heavy metals	< 20 ppm	< 20 ppm

Table 7. Additional constituent data from various citrus fruits.[64]

General Citrus
Carotenoids
Flavonoids as characterized a flavanones, flavones, and 3-hydroxyflavylium
-Flavanones may include: hesperidin, naringin, neohesperidin
-Flavones may include: apigenin, acacetin, luteolin
Limonoids including limonin, nomilin, ichangin, obacunaic acid, photolimonin I, deoxylimonin, obacunone, limonoic acid, limonilic acid, and limonol
Lipids
Inorganic elements (in juice):
-Major include: Ca, P, Fe, Mg, K, Na, CL, and N
-Minor include: Si, Mn, B, Sr, AL, Cu, Li, Ni, Cr, V, Br, Zn, Pb, Sn, Co, As, Ba, Mo, Ag, Zn
Nitrogen content: 0.1-0.2% on net weight for whole citrus fruit, 5-10% on total solids in fruit juice
Organic acids: mainly citric, malic, succinic; also tartaric, benzoic, oxalic, formic, adipic, iso-citric, aconitic, chlorogenic, citramalic, glacturonic, lactic, malonic, phosphoric, quinic, and 2-keto-glutaric.
Polysaccharides, including galacturonan-containing pectic substances, cellulose, glucan, arabinan, xylan, and starch
Simple polyphenolic compounds including phloroglucinol, phenolic acids, and coumarins
-Coumarins common to all species include: umbelliferone, scopoletin, citropten, bergaptol, aurapten, bergamottin, and byakangelicin
Sugars: 40%
Vitamins, including ascorbic acid, biotin, carotenoids, β-carotene, choline, folic acid, inositol, niacin, pantothenic acid, pyridoxine, riboflavin, and thiamine
Volatile flavoring constituents including essence oil, aroma oil, stripper oil, and citrus essences
-Juice oil content is about 0.005%
Grapefruit
Coumarins including aurapten, auraptene, osthaol, auraptenol, bergaptene, herniarin, esulanten
Flavonoids including neohesperidin, rhoifolin, rutin, apigenin 7-β-rutinoside, tangeritin, nobiletin, naringin, poncirin
Lipids (in juice): 75-86 mg/100 ml
-major fatty acids: palmitic (21.7-23.7%), palmitoleic (3.1-4.3%), oleic (23.4-24.4%), linoleic (33.5-35.5%), linolenic (8.2-9.4%), others (5.8-7.2%)
Nitrogen content: total (3.58-6.64 g/l), amino nitrogen (0.218-0.422 g/l), ammonia nitrogen (1.2-2.8 mg/l), nitrates (0.33-0.76 mg/l)
Organic acids: citric (0.42-1.13%), malic (0.03-0.23%), succinic (0.06-0.86%)
Sugars (in juice): 5.0-8.3%, mainly fructose, glucose, and sucrose, as well as traces of other sugars
Vitamins, including 36-45 mg/100 ml ascorbic acid in juice
Lemons
Coumarins including imperatorin, 8-geranoxypsoralen, isopimpinellin, oxypeucedanin hydrate, phellopterin, 5-geranoxy-8-methoxysoralen
Flavonoids including neohesperidin, naringenin, eriocitrin, hesperidin, neohesperidoside, neodiosmin, rutinoside, diosmin
Lipids (in juice): 58-78 mg/100 ml)
-major fatty acids: palmitic (23.0-23.4%), palmitoleic (0.7-0.9%), oleic (9.5-9.5%), linoleic (34.8-36.0%), linolenic (18.8-19.0%), others (12.0-12.4%)
Nitrogen content: total (0.55-5.21 g/l), amino nitrogen (0.027-0.525 g/l), ammonia nitrogen (3.2-7.2 mg/l), nitrates (0.25-0.76 mg/l)
Organic acids: citric (4.00-4.38%), malic (0.07-0.26%)
Sugars (in juice): 0.81-3.70% , mainly fructose, glucose, and sucrose, as well as traces of other sugars
Vitamins, including 39.46 mg/100 g ascorbic acid in juice
Limes
Coumarins including bergaptene, imperatorin, 8-geranoxypsoralen, isopimpinellin, oxypeucedanin hydrate, phellopterin, 5-geranoxy-8-methoxysoralen, 5-isopentoxy-8-methoxypsoralen, 5-geranoxy-7-methoxycoumarin (2.2-3.2%), bergamottin (2.2-2.5%), citropten (0.89-1.70%), and bergapten (0.17-0.33%)
Polysaccharides including 24-30% pectin
Lipids
-major fatty acids: palmitic (21.7-22.3%), palmitoleic (5.4-5.6%), oleic (14.8-15.0%), linoleic (26.9-27.5%), linolenic (13.8-14.4%), others (16.0-16.6%)
Sugars (in juice): 0.76-1.39%, mainly fructose, glucose, and sucrose, as well as traces of other sugars
Mandarin Oranges
Coumarins including aurapten, auraptene, osthaol, auraptenol, and bergaptene
Flavonoids including hesperidin, neohespridin, and permethoxylated flavones
Organic acids: citric (0.86-1.22%), malic (0.08-0.21%)
Vitamins, including 68.39 mg/100 g ascorbic acid in juice
Oranges
Coumarins including aurapten, auraptene, osthaol, auraptenol, and bergaptene
Flavonoids including herperidin, narigenin, isosakuranetin, neohesperidin, naringin, poncirin, neoeriocitrin, rhoifolin, luteolin, neodiosmin, ruin, limoncitrin 3-β-D-glucoside
Lipids (in juice): 84-101 mg/100 ml
-major fatty acids: palmitic (21.2-23.3%), palmitoleic (4.0-4.6%), oleic (24.1-26.7%), linoleic (27.8-35.2%), linolenic (7.9-13.6%), others (5.9-7.1%)
Organic acids: citric (0.17-2.37%), malic (0.06-0.31%), succinic (trace-1.59%)
Sugars (in juice): 5.4-10.5%, mainly fructose, glucose, and sucrose, as well as traces of other sugars
Vitamins, including 35-56 mg/100 ml ascorbic acid in juice

Table 8. Frequency (2015) and concentration of use (2013) according to duration and type of exposure for citrus fruit-derived ingredients.[6,7]

	# 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) Fruit Extract		**Citrus Aurantifolia (Lime) Juice**		**Citrus Aurantium Amara (Bitter Orange) Fruit Extract[d]**		**Citrus Aurantium (Bitter Orange) Fruit Water[e]**	
Totals[†]	**55**	**0.0001-0.2**	**1**	**NR**	**295**	**0.00002-0.002**	**9**	**NR**
Duration of Use								
Leave-On	21	0.0009-0.2	NR	NR	190	0.00002-0.002	6	NR
Rinse Off	32	0.0001-0.2	1	NR	103	0.0001	2	NR
Diluted for (Bath) Use	2	0.002	NR	NR	2	NR	1	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	6	0.0001-0.002	2	NR
Incidental Ingestion	NR	NR	NR	NR	3	0.002	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 13[a]; 3[b]	spray: 0.001 possible: 0.01[a]; 0.0009[b]	NR	NR	spray: 7 possible: 65[a]; 65[b]	NR	spray: NR possible: 2[a]	NR
Incidental Inhalation-Powder	powder: NR possible: 3[b]	0.0009[b]; 0.001-0.2[c]	NR	NR	powder: NR possible: 65[b]	powder: NR possible: 0.00002-0.0002[c]	NR	NR
Dermal Contact	46	0.0001-0.2	NR	NR	256	0.00002-0.002	9	NR
Deodorant (underarm)	NR	NR	NR	NR	spray: NR possible: 3[a]	NR	NR	NR
Hair - Non-Coloring	9	0.0005-0.01	1	NR	33	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	2	NR	NR	NR
Mucous Membrane	17	0.002-0.2	NR	NR	44	0.002	2	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Aurantium Dulcis (Orange) Fruit Extract		**Citrus Aurantium Dulcis (Orange) Fruit Water**		**Citrus Bergamia (Bergamot Orange) Fruit Extract**	
Totals[†]	**7**	**NR**	**23**	**2-19**	**24**	**0.000001-0.82**
Duration of Use						
Leave-On	4	NR	19	2-10	13	0.000001-0.82
Rinse Off	3	NR	4	2-19	11	0.000001-0.0063
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	3	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 1[a]; 2[b]	NR	spray: 1 possible: 3[a]; 6[b]	NR	spray: NR possible: 4[a]; 6[b]	spray: 0.000001
Incidental Inhalation-Powder	powder: NR possible: 2[b]	NR	powder: NR possible: 6[b]	powder: NR possible: 3-10[c]	powder: NR possible: 6[b]	powder: NR possible: 0.0001-0.001
Dermal Contact	7	NR	22	2-19	9	0.0001-0.82
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	15	0.000001-0.0001
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 8. Frequency (2015) and concentration of use (2013) according to duration and type of exposure for citrus fruit-derived ingredients.[6,7]

	# 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 Glauca Fruit Extract		**Citrus Grandis (Grapefruit) Fruit Extract**		**Citrus Grandis (Grapefruit) Fruit Water**		**Citrus Grandis (Grapefruit) Juice**	
Totals[†]	**5**	**0.003-0.0051**	**211**	**0.0000005-15**	**2**	**0.0029**	**15**	**0.01**
Duration of Use								
Leave-On	NR	NR	102	0.0001-15	NR	NR	11	NR
Rinse Off	5	0.003-0.0051	107	0.0000005-8	2	0.0029	4	0.01
Diluted for (Bath) Use	NR	NR	2	0.005-0.01	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	3	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	8	0.01-0.02	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	spray:4 possible: 42[a]; 33[b]	spray: 0.01 possible: 0.005-0.01[a]; 0.0001[b]	NR	NR	spray: NR possible: 4[a]; 7[b]	NR
Incidental Inhalation-Powder	NR	NR	powder: 3 possible: 33[b]	powder: NR possible: 0.0001[b]; 0.0001-15[c]	NR	NR	powder: NR possible: 7[b]	NR
Dermal Contact	NR	NR	134	0.0001-15	2	0.0029	15	0.01
Deodorant (underarm)	NR	NR	spray: NR possible: 1[a]	NR	NR	NR	NR	NR
Hair - Non-Coloring	5	0.003-0.0051	63	0.0000005-0.01	NR	NR	NR	NR
Hair-Coloring	NR	NR	6	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	25	0.001-0.1	2	NR	3	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Japonica Fruit Extract		**Citrus Junos Fruit Extract**		**Citrus Limon (Lemon) Fruit Extract**		**Citrus Limon (Lemon) Juice**	
Totals[†]	**NR**	**0.0038**	**38**	**0.0005-0.002**	**571**	**0.0001-1.2**	**26**	**0.035-1**
Duration of Use								
Leave-On	NR	NR	31	0.0005-0.002	431	0.0001-1.2	13	0.05-1
Rinse Off	NR	0.0038	7	0.0005-0.001	138	0.002-0.5	13	0.035-0.05
Diluted for (Bath) Use	NR	NR	NR	NR	2	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	6	NR	13	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.001	7	0.03	NR	NR
Incidental Inhalation-Spray	NR	NR	spray: 1 possible: 6[a]; 12[b]	spray: 0.0005-0.001	spray: 17 possible: 199[a]; 108[b]	spray: NR possible: 0.001[a]	spray: NR possible: 6[a]; 7[b]	spray: NR possible: 0.05[a]
Incidental Inhalation-Powder	NR	NR	powder: NR possible: 12[b]	powder: NR possible: 0.0005-0.002[c]	powder: NR possible: 108[b]	powder: NR possible: 0.0001-0.5[c]	powder: NR possible: 7[b]	powder: NR possible: 1[c]
Dermal Contact	NR	NR	37	0.0005-0.002	478	0.0001-1.2	17	0.035-1
Deodorant (underarm)	NR	NR	NR	NR	spray: NR possible: 1[a]	NR	NR	NR
Hair - Non-Coloring	NR	0.0038	1	NR	83	0.002-0.005	8	0.05
Hair-Coloring	NR	NR	NR	NR	NR	NR	1	NR
Nail	NR	NR	NR	NR	3	0.0001-0.5	NR	NR
Mucous Membrane	NR	NR	2	0.0005-0.001	44	0.0028-0.04	2	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 8. Frequency (2015) and concentration of use (2013) according to duration and type of exposure for citrus fruit-derived ingredients.[6,7]

	# 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 Madurensis Fruit Extract		**Citrus Medica Limonum (Lemon)Fruit Water**		**Citrus Medica Limonum (Lemon) Juice Extract**		**Citrus Medica Vulgaris Fruit Extract**	
Totals[†]	**NR**	**0.0005**	**3**	**1**	**4**	**0.05-0.2**	**11**	**NR**
Duration of Use								
Leave-On	NR	0.0005	2	NR	2	0.2	6	NR
Rinse Off	NR	NR	1	1	2	0.05	5	NR
Diluted for (Bath) Use	NR	0.0005	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	spray: 1 possible: 1[b]	NR	spray: NR possible: 2[b]	NR	spray: 1 possible: 2[a]; 2[b]	NR
Incidental Inhalation-Powder	NR	powder: NR possible: 0.0005	powder: NR possible: 1[b]	NR	powder: NR possible: 2[b]	powder: NR possible: 0.2[c]	powder: NR possible: 2[b]	NR
Dermal Contact	NR	0.0005	3	1	3	0.05-0.2	8	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	spray: NR possible: 1[a]	NR
Hair - Non-Coloring	NR	NR	NR	NR	1	NR	3	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.0005	1	NR	1	NR	4	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Nobilis (Mandarin Orange) Fruit Extract[f]		**Citrus Paradisi (Grapefruit) Fruit Extract**		**Citrus Paradisi (Grapefruit) Fruit Juice**		**Citrus Reticulata (Tangerine) Fruit Extract**	
Totals[†]	**27**	**0.001-0.04**	**59**	**0.005-1.5**	**2**	**NR**	**5**	**NR**
Duration of Use								
Leave-On	7	0.001-0.04	35	0.05-1.5	1	NR	3	NR
Rinse Off	19	0.001-0.04	24	0.005-0.2	1	NR	1	NR
Diluted for (Bath) Use	1	NR	NR	NR	NR	NR	1	NR
Exposure Type								
Eye Area	NR	NR	2	NR	NR	NR	1	NR
Incidental Ingestion	NR	NR	1	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 4[a]; 2[b]	spray: 0.0075 possible: 0.001-0.01[a]	spray: NR possible: 7[a]; 15[b]	NR	spray: NR possible: 1[b]	NR	spray: NR possible: 1[b]	NR
Incidental Inhalation-Powder	powder: NR possible: 2[b]	powder: NR possible: 0.0018-0.04[c]	powder: NR possible: 15[b]	powder: NR possible: 0.05-1.5[c]	powder: NR possible: 1[b]	NR	powder: NR possible: 1[b]	NR
Dermal Contact	18	0.0018-0.04	52	0.05-1.5	2	NR	5	NR
Deodorant (underarm)	spray: NR possible: 1[a]	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	9	0.001-0.01	6	0.005	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	11	0.002-0.04	5	NR	1	NR	2	NR
Baby Products	NR	NR	1	NR	NR	NR	1	NR

Table 8. Frequency (2015) and concentration of use (2013) according to duration and type of exposure for citrus fruit-derived ingredients.[6,7]

	# 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 Sinensis (Orange) Fiber		**Citrus Sinensis (Orange) Juice**		**Citrus Sinensis (Orange) Powder**		**Citrus Sinensis (Sweet Orange) Fruit Extract**	
Totals†	**3**	**NR**	**1**	**0.000038**	**1**	**NR**	**12**	**0.00003-1.2**
Duration of Use								
Leave-On	3	NR	1	0.000038	1	NR	6	0.00003-1.2
Rinse Off	NR	NR	NR	NR	NR	NR	6	0.00003-0.25
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	0.1
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 3[b]	NR	spray: NR possible: 1[b]	spray: NR possible: 0.000038[a]	spray: NR possible: 1[b]	NR	spray: 1 possible: 1[a]	spray: NR possible: 0.001[a]
Incidental Inhalation-Powder	powder: NR possible: 3[b]	NR	powder: NR possible: 1[b]	NR	powder: NR possible: 1[b]	NR	NR	powder: NR possible: 0.0005-0.32[c]
Dermal Contact	3	NR	1	NR	1	NR	10	0.00003-1.2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.000038	NR	NR	2	0.0007-0.25
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	0.2
Mucous Membrane	NR	NR	NR	NR	NR	NR	3	0.004-0.041
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Sinensis (Sweet Orange) Fruit Water		**Citrus Tangerina (Tangerine) Extract**		**Hydrolyzed Citrus Aurantium Dulcis Fruit Extract**	
Totals†	**4**	**NR**	**16**	**NR**	**15**	**NR**
Duration of Use						
Leave-On	3	NR	4	NR	15	NR
Rinse Off	1	NR	12	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 1[a]; 1[b]	NR	spray: 1 possible: 1[a]; 1[b]	NR	spray:6 possible: 3[a]; 3[b]	NR
Incidental Inhalation-Powder	powder: NR possible: 1[b]	NR	powder: NR possible: 1[b]	NR	powder: NR possible: 3[b]	NR
Dermal Contact	4	NR	5	NR	15	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	11	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	2	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

NR = Not reported.

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

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

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

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

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

[e] Only listed in the VCRP database, not in the INCI dictionary

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

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

Citrus Aurantifolia (Lime)/Citrus Limon (Lemon) Fruit Water
Citrus Aurantifolia (Lime) Fruit
Citrus Aurantifolia (Lime) Fruit Water
Citrus Aurantium Amara (Bitter Orange) Fruit Juice Extract
Citrus Aurantium Bergamia (Bergamot) Fruit Water
Citrus Aurantium Dulcis (Orange) Fruit Powder
Citrus Clementina Fruit Extract
Citrus Clementina Juice
Citrus Depressa Fruit Extract
Citrus Depressa Fruit Water
Citrus Grandis/Paradisi Fruit Water
Citrus Hassaku Fruit Extract
Citrus Hassaku/Natsudaidai Fruit Juice
Citrus Hassaku/Natsudaidai Fruit Powder
Citrus Iyo Fruit Extract
Citrus Jabara Juice
Citrus Junos Fruit Juice
Citrus Junos Fruit Oil
Citrus Junos Fruit Powder
Citrus Junos Fruit Water
Citrus Limon (Lemon) Fruit Oil
Citrus Limon (Lemon) Fruit Powder
Citrus Limon (Lemon) Juice Powder
Citrus Madurensis Fruit Juice
Citrus Paradisi (Grapefruit) Fruit Water
Citrus Paradisi (Grapefruit) Juice
Citrus Reticulata (Tangerine) Fruit
Citrus Reticulata (Tangerine) Fruit Water
Citrus Shunkokan Fruit Extract
Citrus Sphaerocarpa Fruit Juice
Citrus Sudachi Fruit Extract
Citrus Sudachi Fruit Juice
Citrus Tachibana/Reticulata Fruit Juice
Citrus Tangelo Fruit Juice
Citrus Tangelo Fruit Powder
Citrus Tangerina (Tangerine) Fruit
Citrus Tangerina (Tangerine) Fruit Water
Citrus Tankan Fruit Extract
Citrus Tankan Fruit Water
Citrus Unshiu/Citrus Reticulata/Citrus Iyo Fruit Water
Citrus Unshiu Fruit Extract
Citrus Unshiu Fruit Juice
Citrus Unshiu Fruit Oil
Citrus Unshiu Fruit Powder
Citrus Unshiu Fruit Water
Citrus Unshiu/Sinensis/Reticulata Fruit Extract
Microcitrus Australasica Fruit Extract
Microcitrus Australis Fruit Extract

Table 10 . Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			DERMAL IRRITATION - ALTERNATIVE STUDIES		
Citrus grandis (grapefruit) fruit extract	100% in powder form	reconstructed human epidermal model	EpiDerm dermal irritation test	-non-irritating	17
			DERMAL SENSITIZATION – HUMAN STUDIES		
citrus aurantium bergamia (bergamot) fruit extract	0.081525% in a white lotion	105 subjects	-modified Draize HRIPT -during induction phase, 0.2 ml test material was applied for 24 h to skin sites on the scapular back with an occlusive Webril patch -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the same dose was applied during the challenge phase to naïve sites via occlusive patch -patches were removed after 24 h and sites were evaluated at 48 and 72 h post-application	-test material did not induce irritation or sensitization	21
citrus aurantium dulcis (orange) fruit extract and citrus limon (lemon) fruit extract	1.2% each in a night moisturizer	100 subjects	-modified Draize HRIPT -product was tested neat, not occluded -during the induction phase, test material was applied to the back and allowed to air dry -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the test material was applied to naïve sites and the sites were scored 24 and 48 h post-application	-test material did not induce irritation or sensitization	23
citrus aurantium dulcis (orange) fruit water	38% in an eye gel	214 subjects	-HRIPT -0.2 g test material applied by a 2 cm^2 Webril patch to back or upper arm and occluded -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the test material was applied for 24 h to naïve sites and the sites were scored 48 and 72 h post-application	-test material did not induce sensitization -1 subject experienced erythema during induction, but no reactions were observed when subject received test material on a new test site	22
citrus nobilis (mandarin orange) fruit extract	1% in dioctyl adipate/octyl palmitate/octyl stearate	107 subjects	-HRIPT -0.2 ml test material applied by a 1 in^2 patch to upper back and semi-occluded -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the test material was applied to naïve sites and the sites were scored 24 and 72 h post-application	-test material did not induce irritation or sensitization	19
citrus limon (lemon) fruit water	1% in a skin cleansing product	102 subjects	-HRIPT -0.2 ml test material applied by a 3/4 in^2 patch to upper back and semi-occluded -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the test material was applied to naïve sites and the sites were scored 24 and 72 h post-application	-test material did not induce sensitization -2 subjects experienced mild to moderate erythema during the induction phase, but did not have sensitivity reactions	20
citrus grandis (grapefruit) fruit extract	0.16% in a toner	206 subjects	-HRIPT -0.15 ml test material applied by 2 cm^2 patch to back and occluded -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the test material was applied for 24 h to naïve sites and the sites were scored 24, 48, and 72 h post-application	-test material did not induce irritation or sensitization	24

Table 11. Photosensitization and phototoxicity studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
lemon fruit juice and lemon peel juice (Tahitian and Sicilian varieties)	undiluted; liberally applied	3 adult rats (strain not specified) per group	-rats were painted with fresh lemon fruit juice or lemon peel juice from 2 lemon varieties on depilated skin on the right back; left side was negative control with only sunlight exposure -rats were placed in plastic tubes with eight orifices to allow natural sunlight through - exposure to sunlight was 2.5, 5 , 7.5, or 10 min -experiment repeated with Tahitian variety lemon peel juice with sun block SPF 45, UVA and UVB -biopsies performed for each time period for histopathological studies and photodocumentation	-phytophotodermatitis observed after 48 h after exposure to both types of peel juice -no reactions observed to peel juice without sun exposure or to sun exposure alone -minimum exposure time of 2.5 min sufficient to induce phototoxic reaction, with longer exposures causes more intense reactions -histopathological studies showed epithelial time-dependent vacuolar degeneration -sunblock diminished reaction intensity, but did not prevent it	[25]
			HUMAN		
sweet orange peel, mesocarp, and fruit and alcohol extractions of all 3	undiluted	3 subjects with type I skin and 1 subject with type II skin	-in duplicate Finn Chambers, peel, mesocarp, or fruit were applied directly to skin or as alcohol extract solutions (0.2 g/0.2 ml) at 20 µl on paper discs -closed patches were 1 h in duration - 48 h after dosing, subjects were exposed to sunlight for 30 min, a Phillips blacklight TL 20W/09 (320-440 nm) that delivered a total dose of 2.5 J/cm^2 - test sites were examined 8, 24, 48, 72, and 96 h after irradiation	-strong erythema (++) observed in 2 subjects with type 1 skin and strong erythema and infiltration (+++) observed in 1 subject with type I skin 48 h after irradiation and exposure to pure peel and peel extract -slight erythema observed in all 3 type I subjects after exposure to pure peel and peel extract with no sun exposure after 48 h -no reactions observed to mesocarp or fruit, either pure or extract -no reactions induced in the type II skin subject	[26]
citrus aurantium bergamia (bergamot) fruit extract	0.081525% in a white lotion	20 subjects with type I to type III skin	-patches of ¾ in^2 area containing 0.2 ml test material that volatilized for at least 30 min were applied to test site and occluded -patches were removed after 24 h and the test sites were irradiated with 0.5 MED of UVB light followed by 20 J of UVA -light source was a 150 W xenon arc lamp with WG-320 and UG-11 filters, emission spectrum for UVA and UVB ranges was 290-400 nm -test sites were examined at 24 and 48 h after irradiation	-no contact dermal phototoxic responses observed	[65]

Table 12. Case reports

Mode of Contact	Patient(s)	Presentation	Reference
limeade made from the juice of Mexican limes; exposure to lime juice was at least 15 min in duration; minimal sunlight exposure for 1 h while swimming outdoors	6-year-old boy	-initial presentation was marked symmetric, painful erythema of both hands that abruptly stopped at the wrists; skin had a wrinkled appearance similar of an early second-degree burn or severe contact allergy -8 h later, dramatic bullae developed over the dorsum of both hands	[27]
fresh limes used in an arts-and-crafts activity at a summer camp	12 children initially	-skin eruptions consistent with phototoxic dermatitis confined to hands, wrists, and forearms -eruptions observed as discreet and confluent polymorphous patches and linear streaks -eruptions were also macular, hyperpigmented, and nonpruritic -clinical examination of 622 children, 104 counselors, and 57 adult staff at the camp found 97 (16%) of the children, 7 of the counselors (7%), and none of the adult staff with a similar rash	[28]
fresh limes and lime juice while making salsa on vacation in the Bahamas	28-year-old male active duty sailor	-hyperpigmented macules on the dorsa of both hand and right forearm; macules were uniformly brown in color and well demarcated with minimal erythema -lesions were observed near the knuckles and between the thumb and forefinger, with guttate macules scattered along the radial right forearm -large bullous lesion also developed on the dorsum of the patient's left hand -no reactions were observed on the palms and there were no other related cutaneous mucosal lesions -based on physical examination and patient history, the patient was diagnosed with phytophotodermatitis.	[29]
fresh limes used to wash clothing and scrubbed directly on the skin during travel to beaches in Mexico, Belize, and Guatemala	22-year-old female	-painful, streaky, hyperpigmented rash on lateral surface of right thigh, with an associated area of blistering and erythema -similar rash on the dorsal aspect of both hands -rash started with painful burning erythema and progressed to blister formation in linear pattern -rash began shortly after the patient started washing her clothes in freshly squeezed lime juice and after spending time in the sun -patient was diagnosed with phytophotodermatitis from psoralen and UV light exposure	[30]
fresh lemon that was accidentally mixed with sunscreen	3-year-old girl	-erythema, hyperpigmentation, and ulcerated areas on the trunk except on areas that had been covered with a bathing suit -child's mother had similar hypercromic patches on her hand -mother had been eating seafood with lemon prior to applying sunscreen on the child -diagnosis was phytophotodermatitis	[31]
fresh lime in gin and tonic	52-year-old female	-patient presented with a 4-month history of an eczematous rash on the side of the mouth and lips -initially diagnosed as angular chelitis by general practitioner -months prior to medical examination, the patient had begun sucking on limes from gin and tonics for up to 1 min -patient also had a history of mild hand eczema and eyelid dermatitis -dermatological examination showed an eczematous eruption on the lips, left corner of the mouth, left chin and eyelids -patch test to the British Contact Dermatitis Society extended standard series, cosmetics, balsams and perfumes, hairdressers series, lemon and lime peel yielded positive reactions to *Myroxylon pereirae*, fragrance mix, santolite resin, geraniol 2%, geranium oil, rose oil Bulgarian, and lime peel on days 2 and 4	[32]

Table 12. Case reports

Mode of Contact	Patient(s)	Presentation	Reference
fresh lemon	13-year-old female	-patient with a history of psoriasis and sports-related musculosketal injuries presented with a week-long painless erythematous rash on right thigh -rash began while on a beach vacation following exposure to lemons -physical examination showed erythematous, hyperpigmented streaks on thigh and 3 well-demarcated erosion on distal thigh that were in the shape of her hand -diagnosis was phytophotodermatitis from exposure to psoralens and UVA light	[33]
liniment containing lime juice	26-year-old female	-patient presented with a residual maculopapular rash on right thigh and several hyperpigmented linear track on right leg -two weeks prior, the patient was thought to have been stung by a jellyfish while surfing and had treated the skin with a liniment containing turmeric, vinegar, and lime juice -3 days after treatment, several pigmented linear tracks appeared on right leg, some extending down to knee and 2 reaching down to the lateral part of the right foot -diagnosis was phytophotodermatitis and not jellyfish envenomation based on delayed reaction and hyperpigmented skin lesions	[34]
lime juice	6-year-old girl	-5 days after squeezing limes, patient presented with large blisters on the dorsum of both hands and thighs with some visible streaking equivalent to a superficial burn surface area of 4% -lime juice exposure was followed by exposure to the sun -diagnosis was phytophotodermatitis	[35]
lime juice	11-year-old girl	-5 days after squeezing limes, patient presented with large blisters to the dorsum of both hands, equivalent to a superficial burn surface area of 2.5% -lime juice exposure was followed by exposure to the sun -diagnosis was phytophotodermatitis	[35]
lime juice	14-year-old girl	-5 days after preparing limes, patient presented with apparent superficial burns to the dorsum of both hands, equivalent to a burn surface area of 1% -lime juice exposure was followed by exposure to the sun -diagnosis was phytophotodermatitis	[35]
key lime juice	24-year-old female	-patient presented with irregularly shaped but well demarcated rash on hands and wrists. Rash had erythematous patches and plaques and was tender with noted edema on the dorsum of the hands -rash developed 2 days prior with tender erythema and swelling, with some vesicle and blister formation -several hours before the development of the lesions, the patient had made a key lime pie from scratch, including hand squeezing limes, and then walked outside on a sunny day -diagnosis was lime phytophotodermatitis	[36]

Table 12. Case reports

Mode of Contact	Patient(s)	Presentation	Reference
limes	23-year-old female	-patient presented with a 3-day history of painful, erythematous, blistering rash on sun-exposed skin -prior to the onset of the rash, patient had spent 2 days at the beach where she had prepared mojitos with limes -in the subsequent 24 h, a burning erythema developed and later blistered -physical examination found tender skin with vesicles and tense bullae atop erythematous, edematous plaques on her dorsal hands, forearms, and chest. Symmetric, discrete, erythematous patches studded with tiny vesicles were found on her back -diagnosis was phytophotodermatitis	[37]
lime juice	32-year-old female	-patient presented with a linear eruption consisting of erythema and hyperpigmentation over the chest, abdomen, and legs. The eruption was only mildly painful and showed no pruritus or blistering -eruption occurred during the final days of a cruise where the patient had inserted limes into bottles of Mexican beer and sprayed the beer and lime juice over lower trunk and legs -diagnosis was lime phytophotodermatitis	[38]
lime juice	24-year-old female	-patient presented with a linear array of hyperpigmentation on the left side of the neck and in a fingerprint smudge pattern on the right side of the neck -five days prior, the patient had been drinking Mexican beer with limes at a festival and had splashed lime juice on her neck -diagnosis was lime phytophotodermatitis	[38]
limes	21-year-old female	-patient developed a raised, pruritic, 10 cm x 30 cm lesion on right lateral chest wall during a vacation in Florida, initially thought to be having an allergic reaction -five days after returning home, rash was diagnosed with herpes zoster due to multiple vesicles in dermatomal distribution on right side of torso -four days later, patient presented to primary care physician due to continuation of occurrence of hyperpigmentation around mouth, chin, upper chest, breasts, thighs, and forearms. Original lesions on right lateral thorax had dried, crusted, and was peeling -while on vacation, the patient was exposed to the sun and had consumed citrus beverages and fresh limes -final diagnosis was phytophotodermatitis	[39]

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2015 FDA VCRP Raw Data

02A - Bath Oils, Tablets, and Salts	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	1
02B - Bubble Baths	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	1
05A - Hair Conditioner	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	4
05F - Shampoos (non-coloring)	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	1
05H - Wave Sets	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	7
10E - Other Personal Cleanliness Products	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	8
12A - Cleansing	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	8
12C - Face and Neck (exc shave)	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	2
12D - Body and Hand (exc shave)	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	1
12F - Moisturizing	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	11
12H - Paste Masks (mud packs)	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	1
12I - Skin Fresheners	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	1
12J - Other Skin Care Preps	CITRUS AURANTIIFOLIA (LIME) FRUIT EXTRACT	5
05A - Hair Conditioner	CITRUS AURANTIIFOLIA (LIME) JUICE	1
02B - Bubble Baths	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	1
02D - Other Bath Preparations	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	1
03D - Eye Lotion	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	2
03F - Mascara	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	1
03G - Other Eye Makeup Preparations	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	3
04E - Other Fragrance Preparation	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	7
05A - Hair Conditioner	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	12
05F - Shampoos (non-coloring)	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	11
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	8
05I - Other Hair Preparations	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	2
07C - Foundations	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	2
07E - Lipstick	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	3
07I - Other Makeup Preparations	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	3
08B - Cuticle Softeners	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	2

10A - Bath Soaps and Detergents	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	16
10B - Deodorants (underarm)	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	3
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	23
12A - Cleansing	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	35
12C - Face and Neck (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	40
12D - Body and Hand (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	23
12E - Foot Powders and Sprays	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	2
12F - Moisturizing	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	49
12G - Night	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	5
12H - Paste Masks (mud packs)	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	6
12I - Skin Fresheners	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	4
12J - Other Skin Care Preps	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	28
13A - Suntan Gels, Creams, and Liquids	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	1
13B - Indoor Tanning Preparations	CITRUS AURANTIUM (BITTER ORANGE) FRUIT EXTRACT	2
02D - Other Bath Preparations	CITRUS AURANTIUM (BITTER ORANGE) FRUIT WATER	1
03E - Eye Makeup Remover	CITRUS AURANTIUM (BITTER ORANGE) FRUIT WATER	1
03G - Other Eye Makeup Preparations	CITRUS AURANTIUM (BITTER ORANGE) FRUIT WATER	1
10A - Bath Soaps and Detergents	CITRUS AURANTIUM (BITTER ORANGE) FRUIT WATER	1
12F - Moisturizing	CITRUS AURANTIUM (BITTER ORANGE) FRUIT WATER	2
12J - Other Skin Care Preps	CITRUS AURANTIUM (BITTER ORANGE) FRUIT WATER	3
03F - Mascara	CITRUS AURANTIUM DULCIS (ORANGE) FRUIT WATER	1
03G - Other Eye Makeup Preparations	CITRUS AURANTIUM DULCIS (ORANGE) FRUIT WATER	2
04A - Cologne and Toilet waters	CITRUS AURANTIUM DULCIS (ORANGE) FRUIT WATER	1
07C - Foundations	CITRUS AURANTIUM DULCIS (ORANGE) FRUIT WATER	1
07I - Other Makeup Preparations	CITRUS AURANTIUM DULCIS (ORANGE) FRUIT WATER	1
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM DULCIS (ORANGE) FRUIT WATER	1

12A - Cleansing	CITRUS AURANTIUM DULCIS (ORANGE) FRUIT WATER	3
12C - Face and Neck (exc shave)	CITRUS AURANTIUM DULCIS (ORANGE) FRUIT WATER	6
12F - Moisturizing	CITRUS AURANTIUM DULCIS (ORANGE) FRUIT WATER	3
12J - Other Skin Care Preps	CITRUS AURANTIUM DULCIS (ORANGE) FRUIT WATER	4

10A - Bath Soaps and Detergents	CITRUS AURANTIUM DULCIS(ORANGE)FRUIT EXTRACT	1
12A - Cleansing	CITRUS AURANTIUM DULCIS(ORANGE)FRUIT EXTRACT	2
12C - Face and Neck (exc shave)	CITRUS AURANTIUM DULCIS(ORANGE)FRUIT EXTRACT	1
12D - Body and Hand (exc shave)	CITRUS AURANTIUM DULCIS(ORANGE)FRUIT EXTRACT	1
12G - Night	CITRUS AURANTIUM DULCIS(ORANGE)FRUIT EXTRACT	1
12J - Other Skin Care Preps	CITRUS AURANTIUM DULCIS(ORANGE)FRUIT EXTRACT	1

05A - Hair Conditioner	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT EXTRACT	5
05F - Shampoos (non-coloring)	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT EXTRACT	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT EXTRACT	3
05I - Other Hair Preparations	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT EXTRACT	3
10E - Other Personal Cleanliness Products	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT EXTRACT	1
12A - Cleansing	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT EXTRACT	1
12C - Face and Neck (exc shave)	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT EXTRACT	5
12D - Body and Hand (exc shave)	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT EXTRACT	1
12F - Moisturizing	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT EXTRACT	1

01A - Baby Shampoos	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	3
01B - Baby Lotions, Oils, Powders, and Creams	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	1
02A - Bath Oils, Tablets, and Salts	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	2
05A - Hair Conditioner	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	3
05C - Hair Straighteners	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	1
05F - Shampoos (non-coloring)	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	4
05G - Tonics, Dressings, and	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT	1

Other Hair Grooming Aids	OIL	
10A - Bath Soaps and Detergents	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	1
10E - Other Personal Cleanliness Products	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	1
11D - Preshave Lotions (all types)	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	1
12A - Cleansing	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	3
12C - Face and Neck (exc shave)	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	3
12D - Body and Hand (exc shave)	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	1
12F - Moisturizing	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	5
12H - Paste Masks (mud packs)	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	1
12I - Skin Fresheners	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	1
12J - Other Skin Care Preps	CITRUS BERGAMIA (BERGAMOT ORANGE) FRUIT OIL	2
05A - Hair Conditioner	CITRUS GLAUCA FRUIT EXTRACT	2
05F - Shampoos (non-coloring)	CITRUS GLAUCA FRUIT EXTRACT	3
02A - Bath Oils, Tablets, and Salts	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
02D - Other Bath Preparations	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
03E - Eye Makeup Remover	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	2
03G - Other Eye Makeup Preparations	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
04A - Cologne and Toilet waters	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	2
04C - Powders (dusting and talcum, excluding aftershave talc)	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
04E - Other Fragrance Preparation	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
05A - Hair Conditioner	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	16
05B - Hair Spray (aerosol fixatives)	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
05F - Shampoos (non-coloring)	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	26
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	15
05H - Wave Sets	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	2
05I - Other Hair Preparations	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	3
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	2
06C - Hair Rinses (coloring)	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
06D - Hair Shampoos (coloring)	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
06H - Other Hair Coloring Preparation	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	2
07B - Face Powders	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	2

07E - Lipstick	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	5
09B - Mouthwashes and Breath Fresheners	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	3
10A - Bath Soaps and Detergents	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	12
10B - Deodorants (underarm)	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
10E - Other Personal Cleanliness Products	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	3
11B - Beard Softeners	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
12A - Cleansing	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	32
12C - Face and Neck (exc shave)	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	21
12D - Body and Hand (exc shave)	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	12
12F - Moisturizing	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	19
12G - Night	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	1
12H - Paste Masks (mud packs)	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	5
12I - Skin Fresheners	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	4
12J - Other Skin Care Preps	CITRUS GRANDIS (GRAPEFRUIT) FRUIT EXTRACT	12
10E - Other Personal Cleanliness Products	CITRUS GRANDIS (GRAPEFRUIT) FRUIT WATER	2
10A - Bath Soaps and Detergents	CITRUS GRANDIS (GRAPEFRUIT) JUICE	2
10E - Other Personal Cleanliness Products	CITRUS GRANDIS (GRAPEFRUIT) JUICE	1
12C - Face and Neck (exc shave)	CITRUS GRANDIS (GRAPEFRUIT) JUICE	5
12D - Body and Hand (exc shave)	CITRUS GRANDIS (GRAPEFRUIT) JUICE	2
12F - Moisturizing	CITRUS GRANDIS (GRAPEFRUIT) JUICE	4
12H - Paste Masks (mud packs)	CITRUS GRANDIS (GRAPEFRUIT) JUICE	1
03D - Eye Lotion	CITRUS JUNOS FRUIT EXTRACT	6
04A - Cologne and Toilet waters	CITRUS JUNOS FRUIT EXTRACT	1
05F - Shampoos (non-coloring)	CITRUS JUNOS FRUIT EXTRACT	1
07I - Other Makeup Preparations	CITRUS JUNOS FRUIT EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS JUNOS FRUIT EXTRACT	2
12A - Cleansing	CITRUS JUNOS FRUIT EXTRACT	2
12C - Face and Neck (exc shave)	CITRUS JUNOS FRUIT EXTRACT	10
12D - Body and Hand (exc shave)	CITRUS JUNOS FRUIT EXTRACT	2
12F - Moisturizing	CITRUS JUNOS FRUIT EXTRACT	6
12H - Paste Masks (mud packs)	CITRUS JUNOS FRUIT EXTRACT	2
12J - Other Skin Care Preps	CITRUS JUNOS FRUIT EXTRACT	5
02B - Bubble Baths	CITRUS LIMON (LEMON) FRUIT EXTRACT	2
03D - Eye Lotion	CITRUS LIMON (LEMON) FRUIT EXTRACT	7

03E - Eye Makeup Remover	CITRUS LIMON (LEMON) FRUIT EXTRACT	1
03G - Other Eye Makeup Preparations	CITRUS LIMON (LEMON) FRUIT EXTRACT	5
04E - Other Fragrance Preparation	CITRUS LIMON (LEMON) FRUIT EXTRACT	11
05A - Hair Conditioner	CITRUS LIMON (LEMON) FRUIT EXTRACT	18
05B - Hair Spray (aerosol fixatives)	CITRUS LIMON (LEMON) FRUIT EXTRACT	6
05F - Shampoos (non-coloring)	CITRUS LIMON (LEMON) FRUIT EXTRACT	19
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS LIMON (LEMON) FRUIT EXTRACT	5
05I - Other Hair Preparations	CITRUS LIMON (LEMON) FRUIT EXTRACT	35
07C - Foundations	CITRUS LIMON (LEMON) FRUIT EXTRACT	5
07E - Lipstick	CITRUS LIMON (LEMON) FRUIT EXTRACT	5
07F - Makeup Bases	CITRUS LIMON (LEMON) FRUIT EXTRACT	1
07I - Other Makeup Preparations	CITRUS LIMON (LEMON) FRUIT EXTRACT	5
08A - Basecoats and Undercoats	CITRUS LIMON (LEMON) FRUIT EXTRACT	1
08B - Cuticle Softeners	CITRUS LIMON (LEMON) FRUIT EXTRACT	1
08G - Other Manicuring Preparations	CITRUS LIMON (LEMON) FRUIT EXTRACT	1
09B - Mouthwashes and Breath Fresheners	CITRUS LIMON (LEMON) FRUIT EXTRACT	1
09C - Other Oral Hygiene Products	CITRUS LIMON (LEMON) FRUIT EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS LIMON (LEMON) FRUIT EXTRACT	15
10B - Deodorants (underarm)	CITRUS LIMON (LEMON) FRUIT EXTRACT	1
10E - Other Personal Cleanliness Products	CITRUS LIMON (LEMON) FRUIT EXTRACT	20
11A - Aftershave Lotion	CITRUS LIMON (LEMON) FRUIT EXTRACT	4
11G - Other Shaving Preparation Products	CITRUS LIMON (LEMON) FRUIT EXTRACT	2
12A - Cleansing	CITRUS LIMON (LEMON) FRUIT EXTRACT	49
12C - Face and Neck (exc shave)	CITRUS LIMON (LEMON) FRUIT EXTRACT	54
12D - Body and Hand (exc shave)	CITRUS LIMON (LEMON) FRUIT EXTRACT	52
12E - Foot Powders and Sprays	CITRUS LIMON (LEMON) FRUIT EXTRACT	2
12F - Moisturizing	CITRUS LIMON (LEMON) FRUIT EXTRACT	172
12G - Night	CITRUS LIMON (LEMON) FRUIT EXTRACT	9
12H - Paste Masks (mud packs)	CITRUS LIMON (LEMON) FRUIT EXTRACT	12
12I - Skin Fresheners	CITRUS LIMON (LEMON) FRUIT EXTRACT	7
12J - Other Skin Care Preps	CITRUS LIMON (LEMON) FRUIT EXTRACT	37
13B - Indoor Tanning Preparations	CITRUS LIMON (LEMON) FRUIT EXTRACT	5

05A - Hair Conditioner	CITRUS LIMON (LEMON) JUICE	1
05F - Shampoos (non-coloring)	CITRUS LIMON (LEMON) JUICE	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS LIMON (LEMON) JUICE	1
06D - Hair Shampoos (coloring)	CITRUS LIMON (LEMON) JUICE	1

10A - Bath Soaps and Detergents	CITRUS LIMON (LEMON) JUICE	1
10E - Other Personal Cleanliness Products	CITRUS LIMON (LEMON) JUICE	1
12B - Depilatories	CITRUS LIMON (LEMON) JUICE	1
12C - Face and Neck (exc shave)	CITRUS LIMON (LEMON) JUICE	3
12D - Body and Hand (exc shave)	CITRUS LIMON (LEMON) JUICE	4
12F - Moisturizing	CITRUS LIMON (LEMON) JUICE	4
12H - Paste Masks (mud packs)	CITRUS LIMON (LEMON) JUICE	2
12I - Skin Fresheners	CITRUS LIMON (LEMON) JUICE	1
04A - Cologne and Toilet waters	CITRUS MEDICA LIMONUM (LEMON) FRUIT WATER	1
10E - Other Personal Cleanliness Products	CITRUS MEDICA LIMONUM (LEMON) FRUIT WATER	1
12C - Face and Neck (exc shave)	CITRUS MEDICA LIMONUM (LEMON) FRUIT WATER	1
05A - Hair Conditioner	CITRUS MEDICA LIMONUM (LEMON) JUICE EXTRACT	1
10E - Other Personal Cleanliness Products	CITRUS MEDICA LIMONUM (LEMON) JUICE EXTRACT	1
12C - Face and Neck (exc shave)	CITRUS MEDICA LIMONUM (LEMON) JUICE EXTRACT	2
04A - Cologne and Toilet waters	CITRUS MEDICA VULGARIS FRUIT EXTRACT	1
05F - Shampoos (non-coloring)	CITRUS MEDICA VULGARIS FRUIT EXTRACT	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS MEDICA VULGARIS FRUIT EXTRACT	2
10A - Bath Soaps and Detergents	CITRUS MEDICA VULGARIS FRUIT EXTRACT	2
10B - Deodorants (underarm)	CITRUS MEDICA VULGARIS FRUIT EXTRACT	1
10E - Other Personal Cleanliness Products	CITRUS MEDICA VULGARIS FRUIT EXTRACT	2
12D - Body and Hand (exc shave)	CITRUS MEDICA VULGARIS FRUIT EXTRACT	2
01A - Baby Shampoos	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	1
03D - Eye Lotion	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	2
05F - Shampoos (non-coloring)	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	5
07E - Lipstick	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	1
07F - Makeup Bases	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	3
10E - Other Personal Cleanliness Products	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	1
12A - Cleansing	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	3
12C - Face and Neck (exc shave)	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	7
12D - Body and Hand (exc	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	8

shave)		
12F - Moisturizing	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	6
12H - Paste Masks (mud packs)	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	11
12J - Other Skin Care Preps	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	9
13B - Indoor Tanning Preparations	CITRUS PARADISI (GRAPEFRUIT) FRUIT EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS PARADISI (GRAPEFRUIT) FRUIT JUICE	1
12D - Body and Hand (exc shave)	CITRUS PARADISI (GRAPEFRUIT) FRUIT JUICE	1
02B - Bubble Baths	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	1
05A - Hair Conditioner	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	2
05F - Shampoos (non-coloring)	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	5
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	2
10A - Bath Soaps and Detergents	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	3
10B - Deodorants (underarm)	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	1
10E - Other Personal Cleanliness Products	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	7
12A - Cleansing	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	1
12C - Face and Neck (exc shave)	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	2
12F - Moisturizing	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	1
12G - Night	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	1
12H - Paste Masks (mud packs)	CITRUS RETICULATA (MANDARIN ORANGE) FRUIT EXTRACT	1
01C - Other Baby Products	CITRUS RETICULATA (TANGERINE) FRUIT EXTRACT	1
02B - Bubble Baths	CITRUS RETICULATA (TANGERINE) FRUIT EXTRACT	1
03D - Eye Lotion	CITRUS RETICULATA (TANGERINE) FRUIT EXTRACT	1
10E - Other Personal Cleanliness Products	CITRUS RETICULATA (TANGERINE) FRUIT EXTRACT	1
12D - Body and Hand (exc shave)	CITRUS RETICULATA (TANGERINE) FRUIT EXTRACT	1
12C - Face and Neck (exc shave)	CITRUS SINENSIS (ORANGE) FIBER	3
12C - Face and Neck (exc shave)	CITRUS SINENSIS (ORANGE) JUICE	1

12C - Face and Neck (exc shave)	CITRUS SINENSIS (ORANGE) POWDER	1

05B - Hair Spray (aerosol fixatives)	CITRUS SINENSIS (SWEET ORANGE) FRUIT EXTRACT	1
05F - Shampoos (non-coloring)	CITRUS SINENSIS (SWEET ORANGE) FRUIT EXTRACT	1
10A - Bath Soaps and Detergents	CITRUS SINENSIS (SWEET ORANGE) FRUIT EXTRACT	3
11A - Aftershave Lotion	CITRUS SINENSIS (SWEET ORANGE) FRUIT EXTRACT	4
12A - Cleansing	CITRUS SINENSIS (SWEET ORANGE) FRUIT EXTRACT	1
12H - Paste Masks (mud packs)	CITRUS SINENSIS (SWEET ORANGE) FRUIT EXTRACT	1
12I - Skin Fresheners	CITRUS SINENSIS (SWEET ORANGE) FRUIT EXTRACT	1

03D - Eye Lotion	CITRUS SINENSIS (SWEET ORANGE) FRUIT WATER	1
12A - Cleansing	CITRUS SINENSIS (SWEET ORANGE) FRUIT WATER	1
12D - Body and Hand (exc shave)	CITRUS SINENSIS (SWEET ORANGE) FRUIT WATER	1
12G - Night	CITRUS SINENSIS (SWEET ORANGE) FRUIT WATER	1

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
12D - Body and Hand (exc shave)	CITRUS TANGERINA (TANGERINE) EXTRACT	1
12J - Other Skin Care Preps	CITRUS TANGERINA (TANGERINE) EXTRACT	1

04E - Other Fragrance Preparation	HYDROLYZED CITRUS AURANTIUM DULCIS FRUIT EXTRACT	6
07C - Foundations	HYDROLYZED CITRUS AURANTIUM DULCIS FRUIT EXTRACT	1
12C - Face and Neck (exc shave)	HYDROLYZED CITRUS AURANTIUM DULCIS FRUIT EXTRACT	3
12F - Moisturizing	HYDROLYZED CITRUS AURANTIUM DULCIS FRUIT EXTRACT	1
12J - Other Skin Care Preps	HYDROLYZED CITRUS AURANTIUM DULCIS FRUIT EXTRACT	2
13B - Indoor Tanning Preparations	HYDROLYZED CITRUS AURANTIUM DULCIS FRUIT EXTRACT	2

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 26, 2015

SUBJECT: Citrus Fruit Extracts: Product Specifications

Grau Aromatics GmbH & Co. KG. 2013. Lemon extract HS 2364 G (propylene glycol extract).

Grau Aromatics GmbH & Co. KG. 2014. Lemon extract HS (propylene glycol extract).

Grau Aromatics GmbH & Co. KG. 2013. Lemon extract HS (glycerin extract).

Grau Aromatics GmbH & Co. KG. 2013. Grapefruit extract HS (propylene glycol extract).

Grau Aromatics GmbH & Co. KG. 2013. Grapefruit extract HS (glycerin extract).

Grau Aromatics GmbH & Co. KG. 2013. Orange extract HS (propylene glycol extract).

Grau Aromatics GmbH & Co. KG. 2013. Orange extract HS (glycerin extract).

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GRAU AROMATICS GmbH & Co. KG
Chemische Fabrik • Schwäbisch Gmünd

LEMON EXTRACT HS 2364 G

1. Product number

521 163

2. Botanicals

Botanical name:	Citrus limon	
INCI name (EU/USA) :	Propylene Glycol	75 – 100 %
	Citrus Limon (Lemon) Fruit Extract	75 – 100 %
	Citrus Limon (Lemon) Peel Oil	< 0,1%
Allergens:	Limonene	max. 0,03 %
	Citral	max. 0,002 %
Parts used:	Fruit without peel	

Plant composition:

- Essential oil	- Flavoinoids	- Vitamins	- Sugars
- α-Hydroxy acids	- Amino acids	- Phytosterols	- Pectin
- Coumarins	- Stachydrine	- Phenylpropanoid glycosides	
- Bitter principle (Limonin)	- Inositol		

Plant properties:

- free radical scavenger	- anti-ageing	- refreshing	- tonic
- AHA-effect	- antiseptic	- astringent	- bleaching
- microvessel protectant	- antioedema	- anti-itching	- purifying

References:

"Drogenkunde", H.A. Hoppe, Band 1, 8. Auflage, Verlag WdeG
"Plants in cosmetics", Vol. 2, Council of Europe Publishing
"Pflanzliche Wirkstoffe für Kosmetika", H. Eggensperger, Melcher-Verlag
"Das große Rezeptbuch der Haut- und Körperpflegemittel", K. Rothemann, Hüthig-Verlag

3. Manufacturing

Solvent of extraction:	1,2 – Propylene glycol
Ratio of Extract to Botanical:	1 : 1,2
Preservatives:	0,6 % Bactiphen 2506 G (Phenoxyethanol 75-100 % and Methylparaben 10-25 % and Ethylparaben 1-5 % and Propylparaben 1-5 % and Butylparaben 1-5 %)
Incidental ingredients:	0,1 – 1 % Lactic acid (pH-regulation if necessary)
Process:	The plant material is extracted at considerate temperatures during a fixed time and sterile filtered at the end of the fabrication.
Origin:	Produced in Germany.

4. Toxicological data (Solvent)

see MSDS

5. Regulatory Information

All components are in compliance with the actual European Cosmetic Law regulation.

April 2013

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GRAU AROMATICS GmbH & Co. KG
Chemische Fabrik • Schwäbisch Gmünd

LEMON EXTRACT HS 2364 G

6. Analytical data

Aspect:	clear, brownish yellow coloured liquid	
Odour:	faint fruity odour	
pH-value:	4,0 – 5,0	
Proof of identity.	HPLC	
Bacteriological control:	max. 100 germs / ml	
Refraction index:	1,425 – 1,445	(20 °C)
Density:	1,040 – 1,060	(20 °C)
Colour number:	max. 10	(Lovibond)
	This is a natural product which can change in colour during age.	
Solubility:	in water clear soluble	
Further information:	see MSDS	

7. Other relevant data

Animal testing:	has not been tested until today on animals and will also not be tested on animals in the future
BSE / TSE:	is processed without using any animal ingredients or animal related ingredients; it therefore exists no danger of BSE / TSE
CMR:	contains no detectable quantities of CMR-substances
GMO:	contains no genetically modified organisms and we are also not using any genetically modified processing aids
Pesticides (Solvent):	expected to be below detection limits according to European Pharmacopoeia
Heavy metals (Solvent):	the chemical materials: Pb, Zn, Cd, Hg, Cr, Sn are neither used during the manufacturing process nor in the formulation of this product ; however, this product has not been tested for these chemical materials
Pesticides/Heavy metals (plant material):	corresponds to the existing actual legal status (random sample tests)
Residual solvents:	not expected
Reach Status:	all components are in compliance with the actual reach regulation
Status SVHC:	(substance very high concern) not relevant – no dangerous substance
Status VOC:	boiling point solvent Propylene glycol: 185 – 190 °C (1013 hPa)

8. Dosage / Use

1 – 10 % in cosmetic products. Not for use in food.

9. Shelf life / Storage

Shelf life:	At least 30 months. All our extracts are filtered clear after fabrication. It is generally accepted, that a longer period of storage may cause sediments. These, however, influence neither the quality nor the usability of the extract and are no reason for complaints.
Storage:	In closed containers, a temperature of 10-25 °C should be maintained, protected from light.

10. Legal status

CAS no.:	84929-31-7
EINECS no.:	284-515-8

This information are given to the best of our knowledge, as an advice for our customers, and without any legal liability. We reserve the right to make any changes according to technological progress or further development.

April 2013

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GRAU AROMATICS GmbH & Co. KG
Chemische Fabrik • Schwäbisch Gmünd

LEMON EXTRACT HS

1. Product number

EX2081021

2. Botanicals

Botanical name:	Citrus limon	
INCI name (EU/USA) :	Propylene Glycol	75 – 100 %
	Citrus Limon (Lemon) Fruit Extract	50 – 75 %
Allergens:	Limonene	max. 0,015 %
	Citral	max. 0,001 %
Parts used:	Fruit without peel	

Plant composition:

- Essential oil
- Flavoinoids
- Vitamins
- Sugars
- α-Hydroxy acids
- Amino acids
- Phytosterols
- Pectin
- Coumarins
- Stachydrine
- Phenylpropanoid glycosides
- Bitter principle (Limonin)
- Inositol

Plant properties:

- free radical scavenger
- anti-ageing
- refreshing
- tonic
- AHA-effect
- antiseptic
- astringent
- bleaching
- microvessel protectant
- antioedema
- anti-itching
- purifying

References:

"Drogenkunde", H.A. Hoppe, Band 1, 8. Auflage, Verlag WdeG
"Plants in cosmetics", Vol. 2, Council of Europe Publishing
"Pflanzliche Wirkstoffe für Kosmetika", H. Eggensperger, Melcher-Verlag
"Das große Rezeptbuch der Haut- und Körperpflegemittel", K. Rothemann, Hüthig-Verlag

3. Manufacturing

Solvent of extraction:	1,2 – Propylene glycol
Preservatives:	0,35 % Potassium sorbate 0,35 % Sodium benzoate
Incidental ingredients:	0,1 – 1 % Lactic acid (pH-regulation)
Process:	The plant material is extracted at considerate temperatures during a fixed time and sterile filtered at the end of the fabrication.
Origin:	Produced in Germany.

4. Toxicological data (Solvent)

see MSDS

5. Regulatory information

All components are in compliance with the actual European Cosmetic Law regulation.

September 2014

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Chemische Fabrik • Schwäbisch Gmünd

LEMON EXTRACT HS

6. Analytical data

Aspect:	clear, yellow brown coloured liquid	
Odour:	faint fruity odour	
pH-value:	4,0 – 5,0	
Proof of identity.	HPLC	
Bacteriological control:	max. 100 germs / ml	
Refraction index:	1,425 – 1,445	(20°C)
Density:	1,035 – 1,055	(20°C)
Colour number:	1 – 8	(Lovibond)
	This is a natural product which can change in colour during age.	
Solubility:	in water clear soluble	
Further information:	see MSDS	

7. Other relevant data

Animal testing:	has not been tested until today on animals and will also not be tested on animals in the future
BSE / TSE:	is processed without using any animal ingredients or animal related ingredients; it therefore exists no danger of BSE / TSE
CMR:	contains no detectable quantities of CMR-substances
GMO:	contains no genetically modified organisms and we are also not using any genetically modified processing aids
Pesticides (Solvent):	expected to be below detection limits according to European Pharmacopoeia
Heavy metals (Solvent):	the chemical materials: Pb, Zn, Cd, Hg, Cr, Sn are neither used during the manufacturing process nor in the formulation of this product ; however, this product has not been tested for these chemical materials
Pesticides/Heavy metals (plant material):	corresponds to the existing actual legal status (random sample tests)
Residual solvents:	not expected
Reach Status:	all components are in compliance with the actual reach regulation
Status SVHC:	(substance very high concern) not relevant – no dangerous substance
Status VOC:	boiling point solvent Propylene glycol: 185 – 190°C (1013 hPa)

8. Dosage / Use

1 – 10 % in cosmetic products. Not for use in food.

9. Shelf life / Storage

Shelf life:	At least 18 months. All our extracts are filtered clear after fabrication. It is generally accepted, that a longer period of storage may cause sediments. These, however, influence neither the quality nor the usability of the extract and are no reason for complaints.
Storage:	In closed containers, a temperature of 10-25 °C should be maintained, protected from light.

10. Legal status

CAS no.:	84929-31-7
EINECS no.:	284-515-8

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September 2014

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GRAU AROMATICS GmbH & Co. KG
Chemische Fabrik • Schwäbisch Gmünd

LEMON EXTRACT HS

1. Product number

EX0071011

2. Botanicals

Botanical name:	Citrus limon			
INCI name (EU/USA):	Glycerin			75 – 100 %
	Aqua (Water)			10 – 25 %
	Citrus Limon (Lemon) Fruit Extract			50 – 75 %
Allergens:	Limonene			max. 0,015 %
	Citral			max. 0,001 %
Parts used:	Fruit without peel			
Plant composition:	- Essential oil	- Flavoinoids	- Vitamins	- Sugars
	- α-Hydroxy acids	- Amino acids	- Phytosterols	- Pectin
	- Coumarins	- Stachydrine	- Phenylpropanoid glycosides	
	- Bitter principle (Limonin)	- Inositol		
Plant properties:	- free radical scavenger	- anti-ageing	- refreshing	- tonic
	- AHA-effect	- antiseptic	- astringent	- bleaching
	- microvessel protectant	- antioedema	- anti-itching	- purifying

References:

"Drogenkunde", H.A. Hoppe, Band 1, 8. Auflage, Verlag WdeG
"Plants in cosmetics", Vol. 2, Council of Europe Publishing
"Pflanzliche Wirkstoffe für Kosmetika", H. Eggensperger, Melcher-Verlag
"Das große Rezeptbuch der Haut- und Körperpflegemittel", K. Rothemann, Hüthig-Verlag

3. Manufacturing

Solvent of extraction:	Glycerin (vegetable origin)
Preservatives:	0,3 % Potassium sorbate 0,3 % Sodium benzoate
Incidental ingredients:	0,1 – 1 % Lactic acid (pH-regulation)
Process:	The plant material is extracted at considerate temperatures during a fixed time and sterile filtered at the end of the fabrication.
Origin:	Produced in Germany.

4. Toxicological data (Solvent)

see MSDS

5. Regulatory information

All components are in compliance with the actual European Cosmetic Law regulation.

April 2013

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LEMON EXTRACT HS

6. Analytical data

Aspect:	clear, yellow to brown coloured liquid	
Odour:	faint fruity odour	
pH-value:	3,5 – 4,5	
Proof of identity.	HPLC	
Bacteriological control:	max. 100 germs / ml	
Refraction index:	1,440 – 1,460	(20 °C)
Density:	1,220 – 1,240	(20 °C)
Colour number:	max. 8	(Lovibond)
	This is a natural product which can change in colour during age.	
Solubility:	in water clear soluble	
Further information:	see MSDS	

7. Other relevant data

Animal testing:	has not been tested until today on animals and will also not be tested on animals in the future
BSE / TSE:	is processed without using any animal ingredients or animal related ingredients; it therefore exists no danger of BSE / TSE
CMR:	contains no detectable quantities of CMR-substances
GMO:	contains no genetically modified organisms and we are also not using any genetically modified processing aids
Pesticides (Solvent):	expected to be below detection limits according to European Pharmacopoeia
Heavy metals (Solvent):	total heavy metals (as PB): ≤5 ppm
Pesticides/Heavy metals (plant material):	corresponds to the existing actual legal status (random sample tests)
Residual solvents:	not expected
Reach Status:	all components are in compliance with the actual reach regulation
Status SVHC:	(substance very high concern) not relevant – no dangerous substance
Status VOC:	boiling point solvent Glycerin: >130 °C

8. Dosage / Use

1 – 10 % in cosmetic products. Not for use in food.

9. Shelf life / Storage

Shelf life:	At least 18 months. All our extracts are filtered clear after fabrication. It is generally accepted, that a longer period of storage may cause sediments. These, however, influence neither the quality nor the usability of the extract and are no reason for complaints.
Storage:	In closed containers, a temperature of 10-25 °C should be maintained, protected from light.

10. Legal status

CAS no.:	84929-31-7
EINECS no.:	284-515-8

This information are given to the best of our knowledge, as an advice for our customers, and without any legal liability. We reserve the right to make any changes according to technological progress or further development.

April 2013

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GRAU AROMATICS GmbH & Co. KG
Chemische Fabrik • Schwäbisch Gmünd

GRAPEFRUIT EXTRACT HS

1. Product number

EX1051081

2. Botanicals

Botanical name:	Citrus decumana / Citrus paradisi				
INCI name (EU/USA) :	Propylene Glycol				75 – 100 %
	Citrus Paradisi (Grapefruit) Fruit Extract				10 – 25 %
Allergens:	Limonen				max. 0,11 %
Fresh fruits	Fresh fruits				
Plant composition:	- Carbohydrates	- Essential oil	- Vitamins	- Proteins	
	- Bitter substances	- Flavonoids	- Fruit acids		
Plant properties:	- AHA-Effect	- refreshing			
References:	"Drogenkunde", H.A. Hoppe, Band 1, 8. Auflage, Verlag WdeG				
	"Römpp Chemielexikon" 9. Auflage, Thieme-Verlag				
	"Pflanzliche Wirkstoffe für Kosmetika", H. Eggensperger, Melcher-Verlag				

3. Manufacturing

Solvent of extraction:	1,2 – Propylene glycol
Preservatives:	0,35 % Potassium sorbate 0,35 % Sodium benzoate
Incidental ingredients:	0,1 – 1 % Lactic acid (pH-regulation)
Process:	The plant material is extracted at considerate temperatures during a fixed time and sterile filtered at the end of the fabrication.
Origin:	Produced in Germany.

4. Toxicological data (Solvent)

see MSDS

5. Regulatory information

All components are in compliance with the actual European Cosmetic Law regulation.

November 2013

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GRAPEFRUIT EXTRACT HS

6. Analytical data

Aspect:	clear, yellowish coloured liquid	
Odour:	faint fruity odour	
pH-value:	4,0 – 5,0	
Proof of identity.	HPLC	
Bacteriological control:	max. 100 germs / ml	
Refraction index:	1,415 – 1,435	(20 °C)
Density:	1,040 – 1,060	(20 °C)
Colour number:	1 - 3	(Lovibond)
	This is a natural product which can change in colour during age.	
Solubility:	in water clear soluble	
Further information:	see MSDS	

7. Other relevant data

Animal testing:	has not been tested until today on animals and will also not be tested on animals in the future
BSE / TSE:	is processed without using any animal ingredients or animal related ingredients; it therefore exists no danger of BSE / TSE
CMR:	contains no detectable quantities of CMR-substances
GMO:	we are not using any genetically modified processing aids (plant material is food-grade, GMO-certificate not available)
Pesticides (Solvent):	expected to be below detection limits according to European Pharmacopoeia
Heavy metals (Solvent):	the chemical materials: Pb, Zn, Cd, Hg, Cr, Sn are neither used during the manufacturing process nor in the formulation of this product ; however, this product has not been tested for these chemical materials
Pesticides/Heavy metals (plant material):	corresponds to the existing actual legal status
Residual solvents:	not expected
Reach Status:	all components are in compliance with the actual reach regulation
Status SVHC:	(substance very high concern) not relevant – no dangerous substance
Status VOC:	boiling point solvent Propylene glycol: 185 – 190 °C (1013 hPa)

8. Dosage / Use

1 – 10 % in cosmetic products. Not for use in food.

9. Shelf life / Storage

Shelf life:	At least 18 months. All our extracts are filtered clear after fabrication. It is generally accepted, that a longer period of storage may cause sediments. These, however, influence neither the quality nor the usability of the extract and are no reason for complaints.
Storage:	In closed containers, a temperature of 10-25 °C should be maintained, protected from light.

10. Legal status

CAS no.:	90045-43-5
EINECS no.:	289-904-6

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November 2013

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GRAU AROMATICS GmbH & Co. KG
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GRAPEFRUIT EXTRACT HS

1. Product number

EX1051082

2. Botanicals

Botanical name:	Citrus decumana / Citrus paradisi			
INCI name (EU/USA):	Glycerin			50 – 75 %
	Aqua (Water)			10 – 25 %
	Citrus Paradisi (Grapefruit) Fruit Extract			10 – 25 %
Allergens:	Limonen			max. 0,11 %
Parts used:	Fresh fruits			
Plant composition:	- Carbohydrates	- Essential oil	- Vitamins	- Proteins
	- Bitter substances	- Flavonoids	- Fruit acids	
Plant properties:	- AHA-Effect	- refreshing		
References:	"Drogenkunde", H.A. Hoppe, Band 1, 8. Auflage, Verlag WdeG			
	"Römpp Chemielexikon" 9. Auflage, Thieme-Verlag			
	"Pflanzliche Wirkstoffe für Kosmetika", H. Eggensperger, Melcher-Verlag			

3. Manufacturing

Solvent of extraction:	Glycerin (vegetable origin)
Preservatives:	0,35 % Potassium sorbate
	0,35 % Sodium benzoate
Incidental ingredients:	0,1 – 1 % Lactic acid (pH-regulation)
Process:	The plant material is extracted at considerate temperatures during a fixed time and sterile filtered at the end of the fabrication.
Origin:	Produced in Germany.

4. Toxicological data (Solvent)

see MSDS

5. Regulatory Information

All components are in compliance with the actual European Cosmetic Law regulation.

November 2013

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GRAPEFRUIT EXTRACT HS

6. Analytical data

Aspect:	clear, yellowish coloured liquid	
Odour:	faint fruity odour	
pH-value:	4,0 – 5,0	
Proof of identity.	HPLC	
Bacteriological control:	max. 100 germs / ml	
Refraction index:	1,435 – 1,455	(20°C)
Density:	1,195 – 1,215	(20°C)
Colour number:	1 - 3	(Lovibond)
	This is a natural product which can change in colour during age.	
Solubility:	in water clear soluble	
Further information:	see MSDS	

7. Other relevant data

Animal testing:	has not been tested until today on animals and will also not be tested on animals in the future
BSE / TSE:	is processed without using any animal ingredients or animal related ingredients; it therefore exists no danger of BSE / TSE
CMR:	contains no detectable quantities of CMR-substances
GMO:	we are not using any genetically modified processing aids (plant material is food-grade, GMO-certificate not available)
Pesticides (Solvent):	expected to be below detection limits according to European Pharmacopoeia
Heavy metals (Solvent):	total heavy metals (as PB): ≤5 ppm
Pesticides/Heavy metals (plant material):	corresponds to the existing actual legal status
Residual solvents:	not expected
Reach Status:	all components are in compliance with the actual reach regulation
Status SVHC:	(substance very high concern) not relevant – no dangerous substance
Status VOC:	boiling point solvent Glycerin: >130°C

8. Dosage / Use

1 – 10 % in cosmetic products. Not for use in food.

9. Shelf life / Storage

Shelf life:	At least 18 months. All our extracts are filtered clear after fabrication. It is generally accepted, that a longer period of storage may cause sediments. These, however, influence neither the quality nor the usability of the extract and are no reason for complaints.
Storage:	In closed containers, a temperature of 10-25 °C should be maintained, protected from light.

10. Legal status

CAS no.:	90045-43-5
EINECS no.:	289-904-6

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November 2013

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GRAU AROMATICS GmbH & Co. KG
Chemische Fabrik • Schwäbisch Gmünd

ORANGE EXTRACT HS

1. Product number

EX2061011

2. Botanicals

Botanical name:	Citrus sinensis			
INCI name (EU/USA) :	Propylene Glycol			75 – 100 %
	Citrus Aurantium Dulcis (Orange) Fruit Extract			75 – 100 %
Allergens:	Limonene			max. 0,016 %
Parts used:	Fruits			
Plant composition:	- Essential oil	- Proteins	- Coumarins	- Sugars
	- Phytosterol and esters	- Phenol acids	- Flavonoids	- Diterpenes
	- Bitter substances	- Vitamins	- Organic acids	- Citrantin
	- Carbohydrates	- Mineral salts	- Carotenoids	- Pectins
Plant properties:	- free radical scavenger	- vasoprotector	- moisturising	- cheratolitic
	- anti-inflammatory	- dermopurifying	- antimicrobial	- tonic

References:

"Drogenkunde", H.A. Hoppe, Bd. 1, 8. Aufl., Verlag WdeG
"Plants in cosmetics", Vol. 2, Council of Europe Publishing
"Römpps Chemielexikon", 9. Aufl., Thieme-Verlag
"Kosmetik International", 12/84

3. Manufacturing

Solvent of extraction:	1,2 – Propylene glycol
Preservatives:	0,35 % Potassium sorbate 0,35 % Sodium benzoate
Incidental ingredients:	0,1 – 1 % Lactic acid (pH-regulation)
Process:	The plant material is extracted at considerate temperatures during a fixed time and sterile filtered at the end of the fabrication.
Origin:	Produced in Germany.

4. Toxicological data (Solvent)

see MSDS

5. Regulatory information

All components are in compliance with the actual European Cosmetic Law regulation.

March 2013

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GRAU AROMATICS GmbH & Co. KG
Chemische Fabrik • Schwäbisch Gmünd

ORANGE EXTRACT HS

6. Analytical data

Aspect:	clear, yellow brown coloured liquid	
Odour:	faint fruity odour	
pH-value:	4,0 – 5,0	
Proof of identity.	HPLC	
Bacteriological control:	max. 100 germs / ml	
Refraction index:	1,425 – 1,445	(20°C)
Density:	1,050 – 1,070	(20°C)
Colour number:	max. 10	(Lovibond)
	This is a natural product which can change in colour during age.	
Solubility:	in water clear soluble	
Further information:	see MSDS	

7. Other relevant data

Animal testing:	has not been tested until today on animals and will also not be tested on animals in the future
BSE / TSE:	is processed without using any animal ingredients or animal related ingredients; it therefore exists no danger of BSE / TSE
CMR:	contains no detectable quantities of CMR-substances
GMO:	contains no genetically modified organisms and we are also not using any genetically modified processing aids
Pesticides (Solvent):	expected to be below detection limits according to European Pharmacopoeia
Heavy metals (Solvent):	the chemical materials: Pb, Zn, Cd, Hg, Cr, Sn are neither used during the manufacturing process nor in the formulation of this product ; however, this product has not been tested for these chemical materials
Pesticides/Heavy metals (plant material):	corresponds to the existing actual legal status (random sample tests)
Residual solvents:	not expected
Reach Status:	all components are in compliance with the actual reach regulation
Status SVHC:	(substance very high concern) not relevant – no dangerous substance
Status VOC:	boiling point solvent Propylene glycol: 185 – 190°C (1013 hPa)

8. Dosage / Use

1 – 10 % in cosmetic products. Not for use in food.

9. Shelf life / Storage

Shelf life:	At least 18 months. All our extracts are filtered clear after fabrication. It is generally accepted, that a longer period of storage may cause sediments. These, however, influence neither the quality nor the usability of the extract and are no reason for complaints.
Storage:	In closed containers, a temperature of 10-25 °C should be maintained, protected from light.

10. Legal status

CAS no.:	8028-48-6
EINECS no.:	232-433-8

This information are given to the best of our knowledge, as an advice for our customers, and without any legal liability. We reserve the right to make any changes according to technological progress or further development.

March 2013

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GRAU AROMATICS GmbH & Co. KG
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ORANGE EXTRACT HS 3331 G/A

1. Product number

529 812

2. Botanicals

Botanical name:	Citrus sinensis	
INCI name (EU/USA):	Glycerin	75 – 100 %
	Aqua (Water)	10 – 25 %
	Citrus Aurantium Dulcis (Orange) Fruit Extract	25 – 50 %
Allergens:	Limonene	max. 0,01 %
Parts used:	Fruits	

Plant composition:

- Essential oil	- Proteins	- Coumarins	- Sugars
- Phytosterol and esters	- Phenol acids	- Flavonoids	- Diterpenes
- Bitter substances	- Vitamins	- Organic acids	- Citrantin
- Carbohydrates	- Mineral salts	- Carotenoids	- Pectins

Plant properties:

- free radical scavenger	- vasoprotector	- moisturising	- cheratolitic
- anti-inflammatory	- dermopurifying	- antimicrobial	- tonic

References:

"Drogenkunde", H.A. Hoppe, Bd. 1, 8. Aufl., Verlag WdeG
"Plants in cosmetics", Vol. 2, Council of Europe Publishing
"Römpps Chemielexikon", 9. Aufl., Thieme-Verlag
"Kosmetik International", 12/84

3. Manufacturing

Solvent of extraction:	Glycerin (vegetable origin)
Preservatives:	0,4 % Potassium sorbate 0,4 % Sodium benzoate
Incidental ingredients:	0,1 – 1 % Lactic acid (pH-regulation)
Process:	The plant material is extracted at considerate temperatures during a fixed time and sterile filtered at the end of the fabrication.
Origin:	Produced in Germany.

4. Toxicological data (Solvent)

see MSDS

5. Regulatory information

All components are in compliance with the actual European Cosmetic Law regulation.

March 2013

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e-mail: info@grau-aromatics.de internet: www.grau-aromatics.de

GRAU AROMATICS GmbH & Co. KG
Chemische Fabrik • Schwäbisch Gmünd

ORANGE EXTRACT HS 3331 G/A

6. Analytical data

Aspect:	clear, yellow coloured liquid	
Odour:	faint fruity odour	
pH-value:	4,0 – 5,0	
Proof of identity.	HPLC	
Bacteriological control:	max. 100 germs / ml	
Refraction index:	1,445 – 1,465	(20°C)
Density:	1,220 – 1,240	(20°C)
Colour number:	max. 6	(Lovibond)
	This is a natural product which can change in colour during age.	
Solubility:	in water clear soluble	
Further information:	see MSDS	

7. Other relevant data

Animal testing:	has not been tested until today on animals and will also not be tested on animals in the future
BSE / TSE:	is processed without using any animal ingredients or animal related ingredients; it therefore exists no danger of BSE / TSE
CMR:	contains no detectable quantities of CMR-substances
GMO:	contains no genetically modified organisms and we are also not using any genetically modified processing aids
Pesticides (Solvent):	expected to be below detection limits according to European Pharmacopoeia
Heavy metals (Solvent):	total heavy metals (as PB): ≤5 ppm
Pesticides/Heavy metals (plant material):	corresponds to the existing actual legal status (random sample tests)
Residual solvents:	not expected
Reach Status:	all components are in compliance with the actual reach regulation
Status SVHC:	(substance very high concern) not relevant – no dangerous substance
Status VOC:	boiling point solvent Glycerin: >130°C

8. Dosage / Use

1 – 10 % in cosmetic products. Not for use in food.

9. Shelf life / Storage

Shelf life:	At least 18 months. All our extracts are filtered clear after fabrication. It is generally accepted, that a longer period of storage may cause sediments. These, however, influence neither the quality nor the usability of the extract and are no reason for complaints.
Storage:	In closed containers, a temperature of 10-25 °C should be maintained, protected from light.

10. Legal status

CAS no.:	8028-48-6
EINECS no.:	232-433-8

This information are given to the best of our knowledge, as an advice for our customers, and without any legal liability. We reserve the right to make any changes according to technological progress or further development.

March 2013

Grau Aromatics GmbH & Co. KG • Bismarckstrasse 4 • D - 73525 Schwaebisch Gmuend • Germany
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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 26, 2015

SUBJECT: Products Containing Citrus Aurantium Bergamia (Bergamot) Fruit Extract

Consumer Product Testing. 2004. Summary of a phototoxicity test of a white lotion containing 0.081525% Citrus Aurantium Bergamia (Bergamot) Fruit Extract.

TKL Research Inc. 2004. Summary of a repeated insult patch study (humans) of a white lotion containing 0.081525% Citrus Aurantium Bergamia (Bergamot) Fruit Extract.

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EXECUTIVE SUMMARY

Product(s):	SPF25 white lotion
Name of Protocol:	Phototoxicity Test
Research Institution:	Consumer Product Testing (CPT) Fairfield, NJ 07004-2514 USA
Investigating Physician:	None
CPT Ref. No.:	S04-1374.03
Experimental Start Date:	November 30, 2004
Requesting Company Study No.:	2122
Test Material Description:	2122.0.01 White Lotion

Contains 0.081525% Citrus Aurantium Bergamia (Bergamot) Fruit Extract

OBJECTIVE

This study was conducted to evaluate the potential of the test article (Sample 2122.01) to induce a phototoxic response in human subjects.

METHODOLOGY

Twenty subjects, age 18 through 65, were placed on test.

Subject Selection Criteria

1. Must be fair-skinned subjects of the following types:
   - Type I: Always burns easily; never tans
   - Type II: Always burns easily; tans minimally
   - Type III: Burns moderately; tans gradually
2. Must have completed Medical History Form and the understanding and signing of an Informed Consent form
3. Must not exhibit any visible skin disease which might be confused with a skin reaction from the test material
4. Panelist must not be taking any medication which may influence test results or have experienced any adverse reactions to sunlight attributed to a phototoxic/photoallergic response

5. Considered dependable and capable of following directions
6. Must not be in ill health
7. Must not be pregnant or nursing
8. Must not have a history of adverse reactions to cosmetics, sunscreens, or other personal care products
9. Must not be regular users of UVA sun-tanning beds

The Xenon Arc Solar Simulator (Solar Light Company, Philadelphia, PA), consisting of a 150-watt xenon arc lamp with WG-320 and UG-11 filters, was used as the UV light source. The induction phase of the study, the instrument produced a continuous emission spectrum in the UVA and UVB range (290-400 nanometers). During the Challenge phase, a Schott WG 345 filter was used to block out sunburning UVB wavelengths (290-320 nanometers), allowing delivery of only UVA wavelengths (320-400 nanometers). UVA irradiation was delivered for a total dose of 20 joules).

Patches (¾" x ¾" gauze portion of an adhesive dressing manufactured by Trumed Technologies Inc.), containing approximately 0.2 ml of the test material, were allowed to volatilized for at least 30 minutes and then applied to treatment site of each subject under occlusive conditions.

Twenty-four hours after application, the patches were removed and the test sites were irradiated with 0.5 MED of UVB irradiation followed by 20 joules of UVA irradiation. All test materials and control sites were examined at twenty-four (24) hours and forty-eight (48) hours following irradiation.

The test sites were evaluated for irritation according to the following scale:

Response Evaluation Scale

0	No visible reaction
0.5	Barely perceptible or spotty erythema
1	Mild erythema covering most of the test site
2	Moderate erythema, possible presence of mild edema
3	Marked erythema, possible edema
4	Severe erythema, possible edema, vesiculation, bullae, and/or ulceration

The criteria for a positive (phototoxic) reaction is based upon interpretation of erythemal responses as follows:

If the degree of erythema/tanning noted on the treated, irradiated site is significantly greater than that observed on the non-treated, irradiated control site, the test material may be judged phototoxic.

RESULTS

Twenty (20) subjects completed the study; no subject discontinued from the study. No reactions were observed on either the irradiated or non-irradiated test sites with the test material. Similarly, there no reactions were exhibited on the irradiated control sites (no test material applied).

CONCLUSION

In conclusion, under the conditions of the study, test article (Sample 2122.01) did not induce a contact dermal phototoxic response in human subjects.

EXECUTIVE SUMMARY

Product(s):	SPF25 white lotion
Name of Protocol:	Repeated Insult Patch Study (Humans)
Research Institution:	TKL Research, Inc. (TKL) Paramus, NJ 07652
Investigating Physician:	Jonathan S. Dosik, M.D. Board-Certified Dermatologist
TKL Panel No.:	DS107104
Experimental Start Date:	November 3, 2004
Requesting Company Study No.:	2106
Test Material Description:	2106.01 White Lotion contains 0.081525% Citrus Aurantium Bergamia (Bergamot) Fruit Extract

OBJECTIVE

This study was conducted to evaluate the potential of the test article (sample no. 2106.01 to induce irritation and/or sensitization in normal, adult volunteers following repeated applications under occlusive patch test conditions.

METHODOLOGY

The study was conducted under the supervision of a board-certified dermatologist. One hundred and eight (108) subjects were enrolled in the study.

Subject Selection Criteria

1. Must be 18 years of age or older
2. Must be free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would interfere with the study results or increase the risk of adverse reactions
3. May be of any skin type or race providing the skin pigmentation will allow discernment of erythema
4. Must complete a patch study Medical Screening form as well as a Medical/Personal History form
5. Must read, understand, sign, and date an informed consent agreement

6. Must not have any visible skin disease at the evaluation site which, in the opinion of the investigative personnel, would interfere with the evaluation
7. Must not be receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would interfere with the study results
8. Must not have psoriasis and/or active atopic dermatitis/eczema
9. Must not be pregnant, planning to become pregnant during the study, or breast-feeding a child
10. Must not have a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated

A modified Draize assay consisting of an Induction (insult) Phase followed by a Challenge (elicitation) Phase was used. For the Induction Phase, the test product (0.2 ml) was applied to skin sites on the scapular back by means of an occlusive, Webril® patch. The same dose was maintained for the Challenge Phase. A total of nine Induction patches were completed over a period of three weeks. Twenty-four hours after application, the patches were removed, and twenty-four to forty-eight hours after patch removal, the test sites were evaluated for irritation according to the scale below:

Response Evaluation Scale

-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation

During the Challenge Phase, after a rest period of approximately two weeks (no patch application), the test article was applied to a naive site, not previously exposed, via an occlusive patch. The patches were removed twenty-four hours after application, and the test sites were evaluated forty-eight and seventy-two hours after patch application.

RESULTS

One hundred and five (105) subjects completed the study. Three subjects discontinued prior to the completion of the study due to reasons unrelated to the test material. No reactions were exhibited during the Induction Phase. and no reactions were exhibited during the Challenge Phase.

CONCLUSION

In conclusion, under the conditions of this study, test article (sample no. 2106.01, formula # white lotion did not induce irritant contact dermatitis or allergic contact dermatitis in human subjects.

The results of this study serve as support for the claims "clinically tested for skin irritancy and allergy" and "dermatologist tested" for the test article.

Personal Care Products Council
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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: March 30, 2015

SUBJECT: HRIPT: Product Containing Orange and Lemon Fruit Extracts

AMA Laboratories, Inc. 2012. Summary of an HRIPT on a night product containing 1.2% Citrus Aurantium Dulcis (Orange) Fruit Extract and 1.2% Citrus Limon (Lemon) Fruit Extract.

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Citrus aurantium dulcis (Orange) Fruit Extract
Citrus limon (Lemon) Fruit Extract

Summary of HRIPT

A night moisturizer containing a blend of 1.2% *Citrus aurantium dulcis* (Orange) Fruit Extract and 1.2% *Citrus limon* (Lemon) Fruit Extract was tested using Modified Draize Human Repeated Insult Patch Test (HRIPT) procedure to determine the potential of this product to induce irritation and contact sensitization. The product was tested neat, "open patch".

The HRIPT consisted of three phases: induction phase, rest phase and challenge phase. During the induction phase, test material was applied directly on the subject's back and allowed to air dry. The test material was applied at the same site 3 times a week for 3 consecutive weeks for a total of 9 applications. A trained examiner scored skin responses before each application. Following the 9th application, a rest period of 10-14 days elapsed after which a challenge phase started. During challenge phase the test material was applied to adjacent virgin sites and test site was scored at 24 and 48 hours after application.

A total of 100 subjects satisfactorily completed the study. Under the conditions of a Modified Draize HRIPT procedure, the tested product containing 1.2% *Citrus aurantium dulcis* (Orange) Fruit Extract and 1.2% *Citrus limon* (Lemon) Fruit Extract was not associated with skin irritation or allergic contact dermatitis.

This study was conducted by AMA Laboratories, Inc. New City, NY from January 18 to February 24, 2012 in accordance with the spirit of Good Clinical Practice regulations described in 21 CFR, Part 50 (Protection of Human Subjects-Informed Consent).

Personal Care Products Council
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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: March 31, 2015

SUBJECT: Citrus Grandis (Grapefruit) Fruit Extract

New Age Botanical, Inc. 2015. Product information Extract Grapefruit BG (Citrus Grandis (Grapefruit) Fruit Extract.

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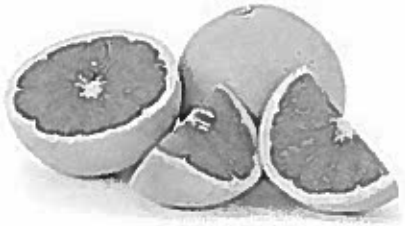
2015

NEW AGE BOTANICAL inc



Product Name: Extract Grapefruit BG
Product Code: NAE0186-02
INCI Name: Butylene Glycol, Water and Grapefruit Extract Citrus Grandis (Grapefruit) Fruit Extract
Preservative: Phenonip
Other Common Names: Pomelo, Chinese Grapefruit
Family Name: Rutaceae
CAS Number: 90045-43-5
EINECS / ELINCS Number: 289-904-6
Composition Breakdown by Percentage: Butylene Glycol 39.5%, Water 39.5%, Grapefruit Extract 20% and Phenonip 1%
Additives Statement:
There are no other agents, anti-oxidants, or additives included in this blend. To the best of our knowledge there are no heavy metals, impurities, or residual solvents in this extract.
Impurities, Heavy Metals, Residual Solvents:
To the best of our knowledge there are no impurities, heavy metals, residual solvents in this extract.
Animal testing Statement: NEW AGE BOTANICAL Inc. products are not subject to animal testing or retesting for cosmetic purposes by or on behalf of this company. We do however participate in the Chemical Industry's efforts in ensuring the protection of human health and the environment.

NOT TESTED ON ANIMALS

Allergen Statement: To the best of our knowledge this product is free of any known allergens and contains no food glutens of any type.
SOURCE / BSE / GMO Statement:
This product was made with chemicals and plant. There are not BSE or GMOs added to or around this extract.
Country of Origin: Butylene Glycol (USA); Grapefruit (USA)
REACH Compliance: The following extracts are listed as either Pre-Registered substances on the REACH-ECHA list of acceptable substances. All items in the extract were searched by their common synonym or CAS number at the following site: http://apps.echa.europa.eu/preregistered/pre-registered-sub.aspx#rowsCOunt
Butylene Glycol – Is on the list of pre-registered substances. Searched by CAS#: 107-88-0
Citrus Grandis, Extract – Is on the list of pre-registered substances. Searched by CAS #: NA

Shelf Life: 2 years from the date of manufacture noted on the Certificate of Analysis.

11630 Chairman Drive, Dallas, TX 75243-5204
Phone: (214) 341-0582 Fax: (214) 341-3723
E-mail: sales@newagebotanical.com
Web Site: www.newagebotanical.com

NEW AGE BOTANICAL INC

Conditions & Storage:
Do not freeze – store at room temperature.
Suppiler and Manufacturer: NEW AGE BOTANICAL, inc.

	Specification Test:
Appearance:	CLEAR
Color:	CLEAR TO LIGHT YELLOW
Odor:	CHARACTERISTIC
Ph:	4.0-6.0 AT 25°C
Refractive Index:	1.3850-1.4000 AT 25°C
Microbial Count:	<200 ORGANISMS PER GRAM

Test Methods and Products Used

PH Testing: Metrohm 744ph Meter at 25°C
Refractive: Vista C10 Abbe Refractometer at 25°C
Micro Testing: A sample of the product is swabbed and plated to three (*listed*) Petrie dishes for 72 hours in a stasis oven set to 25°C. They are then removed and checked for growth signs of bacterial spore, pathogens, and foreign organisms.

Plates used:

Plate 1: Potato Dextrose Plate – for cultures of molds and yeasts.
Plate 2: Lechithin & Tween 80 Plate – for the inactivate preservatives and provide a better medium for damaged or slow-growing cells, which grow in colonies when present.
Plate 3: Levine EMB Plate- is used as a selective and differential medium for the isolation of gram-negative bacilli (including coli form organisms and enteric pathogens).

Constituents:

- 0.3-2% volatile oil (including bisabolol);
- bitter glycosides (anthemic acid);
- flavone glycosides (anthemidin),
- coumarins (including umbelliferon and herniarin),
- phenolic carboxylic acids,
- polysaccharides,
- mucilage,
- choline,
- amino acids,
- tannins,
- Malic acid.

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Phone: (214) 341-0582 Fax: (214) 341-3723
E-mail: sales@newagebotanical.com
Web Site: www.newagebotanical.com

NEW AGE BOTANICAL Inc.

Uses:

Skin care (Facial care, Facial cleansing, Body care, Baby care)
Hair care (Shampoos, Conditioners & Styling)
Decorative cosmetics / Make-up.

Usage Levels:

Recommended 0.10-3% in skin and hair care products.
*For external use only. *Not for drug use.

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Phone: (214) 341-0582 Fax: (214) 341-3723
E-mail: sales@newagebotanical.com
Web Site: www.newagebotanical.com

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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: March 30, 2015

SUBJECT: Citrus Nobilis (Mandarin Orange) Fruit Extract

Premier Specialties, Inc. 2007. Manufacturing flow chart Premier Mandarin Orange Extract (Tangeretin 70%).

Premier Specialties, Inc. 2015. Specification sheet Premier Mandarin Orange Extract (70% Tangeretin).

Consumer Product Testing Co. 2007. Bacterial reverse mutation assay: Mandarin Orange Extract (Tangeretin 70%).

MB Research Laboratories. 2008. Chorioallantoic membrane vascular assay: Mandarin Orange Extract (Tangeretin 70%).

Consumer Product Testing Co. 2007. Repeated insult patch test: 1% Mandarin Orange Extract (Tangeretin 70%) in Wickenol 161.

Note: Wickenol 161 is Dioctyl Adipate/Octyl Palmitate/Octyl Stearate (see: http://www.alzointernational.com/esters.php)

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PREMIER

Manufacturing Flow Chart

Premier Mandarin Orange Extract (Tangeretin 70%) 441350

Mandarin Orange Fruit

↓ Mash

Mashed Materials

↓ Extract (extraction solvent = ethanol)

Concrete

↓ Adjust PH

Filtrate

↓ Adjust PH, Filter

Filtered

↓ Decolorize

Primary Product

↓ Column Chromatographic Separation

Separated Liquid

↓ Crystallize

Crystal

↓ Repeat Crystallize

Repeated Crystal

↓ Dry

Premier Mandarin Orange Extract
(Tangeretin 70%) 441350

236 Blackford Avenue
Middlesex, NJ 08846
Tel. (732) 469-6615
Fax. (732) 469-6772

Premier Specialties, Inc.

Specification Sheet

Premier Mandarin Orange Extract (70% Tangeretin)

Product Code: 441350
INCI Name: Citrus Nobilis (Mandarin Orange) Fruit Extract
EINECS No: 284-521-0
CAS No: 84929-38-4
Country of Origin: China

Appearance:	Off White Powder
Tangeritin:	> 70%
Loss on Drying:	Limit: Not more than 5.0%
Residue on Ignition:	Limit: Not more than 5.0%
Heavy Metals:	Limit: Not more than 20 ppm
Arsenic:	Limit: Not more than 2 ppm
Residual Solvents:	Negative
Sieve test (passes through) -80 mesh	100%
Microbiological Profile	
-Total Microbial Count:	Limit: Not more than 1000 cfu/g
-Yeast and Mold:	Limit: Not more than 100 cfu/g
-E. Coli:	Negative
-Salmonella:	Negative

Storage: Store in a cool & dry place.

Shelf Life: 2 years from manufacturing date.

The information contained in this spec sheet is to the best of our knowledge true and correct. No warranties, expressed or implied, are made.

Cosmetic, Flavor & Fragrance Innovation

Consumer Product Testing Co.

EST. 1975

BACTERIAL REVERSE MUTATION ASSAY

FINAL REPORT

STUDY NUMBER: M07-4429

SPONSOR: Premier Specialties, Inc.
236 Blackford, Avenue
Middlesex, NJ 08846

SPONSOR'S REPRESENTATIVE: Roger Rich

TESTING FACILITY: Consumer Product Testing Company, Inc.
70 New Dutch Lane
Fairfield, NJ 07004
PH: (973) 808-7111 Ext. 202
FX: (973) 244-7517
Email: kgoins@cptclabs.com

STUDY DIRECTOR: D. Keith Goins, Ph.D.
Director, Microbiology

STUDY INITIATION: September 18, 2007

STUDY COMPLETION: September 24, 2007

APPROVED BY: Keith Goins 9/24/07
D. Keith Goins, Ph.D. Date
Director, Microbiology

REVIEWED BY: P Patel 9-24-07
Quality Assurance Date

1.0 STUDY PURPOSE

The purpose of this study was to evaluate if the test samples would induce a mutagenic response in five different strains of *Salmonella typhimurium*, namely TA97a, TA 98, TA 100, TA102, and TA 1535. Test samples were screened at different dose levels by plating them with the tester strains both with and without Aroclor™ 1254 induced rat liver microsomes (S9). The test sample was considered mutagenic if it caused an increase in revertant colonies above the spontaneous background (i.e. no test sample) level.

2.0 TEST SAMPLES

The test sample below was received from the sponsor on 09/10/07 and assigned the test sample number M07-4429.01 and stored as indicated by the client-supplied storage conditions until testing commenced.

Name: Mandarin Orange Extract (Tangeretin 70%), Sample #07-0179S Code # 441350
Lot No.: 17839
Storage conditions: Room temperature
CPTC ID No.: M07-4429.01

3.0 TEST SYSTEM:

The test systems used for the Bacterial Reverse Mutation Assay were :

Salmonella typhimurium TA 97a
Salmonella typhimurium TA 98
Salmonella typhimurium TA100
Salmonella typhimurium TA 102
Salmonella typhimurium TA1535

4.0 TEST SYSTEM JUSTIFICATION:

The Bacterial Reverse Mutation Assay is widely used to evaluate the mutagenic properties of chemicals.The test is based on the work of Dr. Bruce Ames and his coworkers and is commonly referred to as the Ames Test. Their studies involved the development of select histidine auxotrophs of *S. typhimurium* that are normally growth arrested due to mutations in a gene needed to produce the essential amino acid Histidine. In the absence of an external histidine source, the cells cannot grow to form colonies unless a reversion of the mutation occurs which allows the production of histidine to be resumed. As might be expected, spontaneous reversions occur with each of the strains. However, chemical agents can induce a mutagenic response so that the number of revertant colonies is substantially higher than the spontaneous background reversion level. The test involves the analysis of the number of revertant colonies that are obtained with each strain in the presence and absence of the test sample. Since the mutagenic response of a formulation could vary with the concentration, test samples are routinely dosed over an appropriate concentration range. In this study, a complete set of positive and negative controls was included with each assay, and was plated routinely with all of the tester strains. Aroclor™ 1254 induced rat liver microsomes were included to mimic the *in vivo* activity of the liver enzymes in activating some pro-mutagens to mutagenic status.

5.0 PROCEDURE:

All testing was conducted in accordance with non-GLP Protocol EDCZ01-001_2006-08-10_AMES (See attachment A)

5.1 SOLUBILITY

The solubility of the test sample was tested in different solvents at 50 mg/mL concentration. Test sample M07-4429.01 was found to be completely soluble in DMSO.. This solvent was used to dissolve the test sample in this study.

5.2 BACTERIAL REVERSE MUTATION (AMES MUTAGENICITY) ASSAY

The bacterial reverse mutation assay was used to evaluate the mutagenic potential of the test sample at 5 concentrations of the test sample: 5.0, 1.0, 0.5, 0.1 and 0.05 mg. Testing was done with the appropriate solvent control and positive controls were plated with overnight cultures of the test systems (TA 97a, TA 98, TA 100, TA102, TA 1535) on selective minimal agar in the presence and absence of Aroclor-induced rat liver S9. All dose levels of the test samples, solvent controls and positive controls were plated in triplicate. (Refer to attachment A: Protocol EDCZ01-001_2006-08-10_AMES for detailed test procedure).

6.0 RESULTS

Results for the mutagenicity test for test materials M07-4429.01 are presented in the following Tables:

Table 1: Ames Mutagenicity (w/o S9 Activation) for Mandarin Orange Extract (Tangeretin 70%)

Table 2: Ames Mutagenicity (w/ S9 Activation) for Mandarin Orange Extract (Tangeretin 70%)

Ames Mutagenicity Test Results.

Table # 1: Number of revertants without S-9 activation.

Sponsor: Premier Specialties, Inc. Study # M07-4429.01
Sample: Mandarin Orange Extract (Tangeritin 70%) Lot# 17839
Concentration tested at : 5.0, 1.0, 0.5, 0.1 and 0.05 mg/plate.
Solvent used = DMSO

Test Strain #		Solvent Control	Positive Control Est. #	5.0 mg sample	1.0 mg sample	0.5 mg sample	0.1 mg sample	0.05 mg sample
TA 97a	1-	66	1311	23	63	58	62	66
	2-	62	1297	18	65	66	65	63
	3-	60	1325	18	64	65	68	61
Average =		63	1311	20	64	63	65	63
Std. Deviation =		3.06	14.00	2.89	1.00	4.36	3.00	2.52

Test Strain #		Solvent Control	Positive Control Est. #	5.0 mg sample	1.0 mg sample	0.5 mg sample	0.1 mg sample	0.05 mg sample
TA 98	1-	24	941	16	21	22	24	23
	2-	21	969	13	23	22	23	26
	3-	23	955	15	22	23	26	26
Average =		23	955	15	22	22	24	25
Std. Deviation =		1.53	14.00	1.53	1.00	0.58	1.53	1.73

Test Strain #		Solvent Control	Positive Control Est. #	5.0 mg sample	1.0 mg sample	0.5 mg sample	0.1 mg sample	0.05 mg sample
TA 100	1-	88	1026	63	86	88	87	88
	2-	86	1055	62	90	90	89	85
	3-	84	1040	68	87	88	86	89
Average =		86	1040	64	88	89	87	87
Std. Deviation =		2.00	14.50	3.21	2.08	1.15	1.53	2.08

Test Strain #		Solvent Control	Positive Control Est. #	5.0 mg sample	1.0 mg sample	0.5 mg sample	0.1 mg sample	0.05 mg sample
TA 102	1-	225	2109	130	216	230	221	231
	2-	221	2052	158	220	223	227	226
	3-	219	2066	160	221	220	229	223
Average =		222	2076	149	219	224	226	227
Std. Deviation =		3.06	29.70	16.77	2.65	5.13	4.16	4.04

Test Strain #		Solvent Control	Positive Control Est. #	5.0 mg sample	1.0 mg sample	0.5 mg sample	0.1 mg sample	0.05 mg sample
TA 1535	1-	11	570	9	12	13	12	10
	2-	14	599	7	12	11	14	16
	3-	12	613	8	13	14	10	14
Average =		12	594	8	12	13	12	13
Std. Deviation =		1.53	21.93	1.00	0.58	1.53	2.00	3.06

Ames Mutagenicity Test Results.

Table # 2: Number of revertants with S-9 activation.

Sponsor: Premier Specialties, Inc. **Study #** M07-4429.01
Sample: Mandarin Orange Extract (Tangeritin 70%) **Lot#** 17839
Concentration tested at : 5.0, 1.0, 0.5, 0.1 and 0.05 mg/plate.
Solvent used = DMSO

Test Strain #		Solvent Control	Positive Control Est. #	5.0 mg sample	1.0 mg sample	0.5 mg sample	0.1 mg sample	0.05 mg sample
TA 97a	1-	73	1325	22	68	72	74	75
	2-	75	1354	27	75	77	73	74
	3-	70	1340	29	73	76	72	76
Average =		73	1340	26	72	75	73	75
Std. Deviation =		2.52	14.50	3.61	3.61	2.65	1.00	1.00

Test Strain #		Solvent Control	Positive Control Est. #	5.0 mg sample	1.0 mg sample	0.5 mg sample	0.1 mg sample	0.05 mg sample
TA 98	1-	24	969	15	25	23	23	24
	2-	25	983	15	21	24	24	26
	3-	24	955	14	25	25	24	27
Average =		24	969	15	24	24	24	26
Std. Deviation =		0.58	14.00	0.58	2.31	1.00	0.58	1.53

Test Strain #		Solvent Control	Positive Control Est. #	5.0 mg sample	1.0 mg sample	0.5 mg sample	0.1 mg sample	0.05 mg sample
TA 100	1-	82	998	63	84	83	79	83
	2-	85	1026	59	85	85	87	88
	3-	87	1012	61	80	86	88	89
Average =		85	1012	61	83	85	85	87
Std. Deviation =		2.52	14.00	2.00	2.65	1.53	4.93	3.21

Test Strain #		Solvent Control	Positive Control Est. #	5.0 mg sample	1.0 mg sample	0.5 mg sample	0.1 mg sample	0.05 mg sample
TA 102	1-	243	2451	158	238	239	243	253
	2-	239	2437	160	243	246	250	247
	3-	245	2493	168	240	244	239	246
Average =		242	2460	162	240	243	244	249
Std. Deviation =		3.06	29.14	5.29	2.52	3.61	5.57	3.79

Test Strain #		Solvent Control	Positive Control Est. #	5.0 mg sample	1.0 mg sample	0.5 mg sample	0.1 mg sample	0.05 mg sample
TA 1535	1-	12	584	5	10	11	12	12
	2-	13	613	5	11	15	11	12
	3-	10	627	7	14	12	13	11
Average =		12	608	6	12	13	12	12
Std. Deviation =		1.53	21.93	1.15	2.08	2.08	1.00	0.58

7.0 PROTOCOL DEVIATIONS/AMENDMENTS

There were no protocol deviations or amendments for the listed test samples.

8.0 CONCLUSION/DISCUSSION

The results in Tables 1 and 2 show that the test strains were sensitive to the positive control mutagens and had a spontaneous reversion rate well within the accepted values of each strain, indicating that under the test conditions, the strains were sensitive to the detection of potentially genotoxic agents. The test sample was partially cytotoxic/inhibitory at the 5.0 mg concentration to the test system but was not cytotoxic at the remaining concentrations (1.0, 0.5, 0.1, 0.05 mg).

The metabolic activation using the S9 activation mixture shows an active microsomal preparation.

Using the same test conditions, there was no detectable genotoxic activity associated with the four non-cytotoxic concentrations (1.0, 0.5, 0.1, 0.05 mg) of test sample M07-4429.01 (Mandarin Orange Extract (Tangeretin 70%), Sample # 07-0179S, Code#441350: Tables 1 and 2) either in the presence or absence of S9 enzyme activation.

9.0 RECORDS AND RETENTION

All materials and data pertinent to this study will be stored in the Archive Facilities at 70 New Dutch Lane, Fairfield, New Jersey, 07004, or 69 Bassett Highway, Dover, NJ 07801, unless specified otherwise in writing by the Sponsor.

MB Research Laboratories

1765 Wentz Road
P.O. Box 178
Spinnerstown, PA 18968
phone (215) 536-4110
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VOLUME I

Study Title	:	Chorioallantoic Membrane Vascular Assay (CAMVA-14 Day)
Test Article	:	Mandarin Orange Extract (Tangeretin 70%), Lot/batch #17839
Author	:	Alison L. Ball, B.S., Study Director
Study Completed On	:	February 1, 2008
Performing Laboratory	:	MB Research Laboratories 1765 Wentz Road P.O. Box 178 Spinnerstown, PA 18968
MB Research Project #	:	MB 07-16320.09
MB Research Protocol #	:	439-03
Sponsor	:	Premier Specialties, Inc. 236 Blackford Avenue Middlesex, NJ 08846
Citation	:	Alison L. Ball, B.S. (2007) Unpublished Report by MB Research Laboratories

Study Title : **CAMVA**
Project # : **MB 07-16320.09**
Test Article : **Mandarin Orange Extract (Tangeretin 70%), Lot/batch #17839**
Protocol : **439-03**

GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT

This study was conducted in accordance with the Good Laboratory Practices regulations of the FDA (21 CFR Part 58), with the following exception:

Prior to study initiation, test article characterization was provided, but did not include strength, composition or uniformity.

STUDY DIRECTOR REVIEWED: Alison L. Ball 2/1/08

Alison L. Ball, B.S. Date
MB RESEARCH LABORATORIES

1765 wentz road, post office box 178, spinnerstown, pa 18968
phone: (215) 536-4110 fax: (215) 536-1816

PROJECT NUMBER	:	**MB 07-16320.09**
TEST ARTICLE	:	**Mandarin Orange Extract (Tangeretin 70%), Lot/batch #17839**
SPONSOR	:	**Premier Specialties, Inc.**
TITLE	:	**Chorioallantoic Membrane Vascular Assay (CAMVA-14 Day)**
PROTOCOL #	:	**439-03**

A B S T R A C T

Objective: To determine the potential for ocular irritation using an alternative to the Draize methodology. The methodology is based on that described in An Improved CAM Method for Predicting Ocular Irritation, Bagley, D.M., Rizvi, P.Y., Kong, B.M., and De Salva, S.J. (1988), Alternative Methods in Toxicology, Vol. 6, Progress in *In Vitro* Toxicology, pp. 131-138.

Method Synopsis: Based on the results of a preliminary screen, the chorioallantoic membrane (CAM) of twenty White Leghorn eggs, incubated for 14 days, was dosed with 40 µl or 40 mg of Mandarin Orange Extract (Tangeretin 70%), Lot/batch #17839. A total of two concentrations were used, one per group. The dosed eggs were then incubated for another 30 ± 5 minutes after which the CAM was observed for signs of vascular hemorrhage, capillary injection, or ghost vessels. The RC_{50} was determined.

Summary: There were no positive responses to the one dilution in distilled water or the undiluted test article.

Concentration (%)	# of Eggs	# of Positive Responses
50	10	0/10
100	10	0/10

Conclusion: The RC_{50} is >100%.

Study Title : CAMVA
Project # : MB 07-16320.09
Test Article : Mandarin Orange Extract (Tangeretin 70%), Lot/batch #17839
Protocol : 439-03

OBJECTIVE

To determine the potential for ocular irritation using an alternative to the Draize methodology. The methodology is based on that described in An Improved CAM Method for Predicting Ocular Irritation, Bagley, D.M., Rizvi, P.Y., Kong, B.M., and De Salva, S.J. (1988), Alternative Methods in Toxicology, Vol. 6, Progress in *In Vitro* Toxicology, pp. 131-138.

TEST ARTICLE

Identity	:	Mandarin Orange Extract (Tangeretin 70%), Lot/batch #17839
Test Article Characterization	:	See Appendix A for Test Article Characterization
Stability	:	The test article is stable according to the Test Article Characterization (See Appendix A).
Date Received	:	09/10/07
Supplied By	:	PREMIER SPECIALTIES, INC.
Storage	:	The test article was stored at room temperature and humidity.
Description	:	Off-white powder
Sample Preparation	:	The test article was used as received and diluted in distilled water to a 50% concentration.

TEST DATES

Study Initiation:	(date protocol signed)	:	10/10/07
Experimental Start Date	(1st exposure to test substance)	:	10/11/07
Experimental Term Date	(last date data collected)	:	10/11/07
Draft Report Signed	(if applicable)	:	10/23/07
Final Report Signed	(study completion)	:	02/01/08

Study Title : CAMVA
Project # : MB 07-16320.09
Test Article : Mandarin Orange Extract (Tangeretin 70%), Lot/batch #17839
Protocol : 439-03

EXPERIMENTAL DESIGN

Test System

Fertile, White Leghorn eggs (twenty) were selected for use from a larger group received on 09/27/07 from Moyer's Chicks, Quakertown, PA.

Pre-dose Procedures

Upon receipt the eggs were placed in a commercial incubator for 14 days. During this 14-day period, the positioning of the egg trays within the incubator was rotated daily to ensure even atmospheric exposure.

On day 4 of the incubation period, the eggs were removed from the incubator and candled to determine the location of the embryo. After determining the presence and location of the embryo, a small hole was drilled into the narrow end of each egg and approximately 2.5 ml of albumen was removed using a needle and syringe. The hole was sealed with collodion adhesive. A rectangular window was cut in the shell directly over the developing embryo. All cutting was performed using a Dremel® drill with a diamond wheel bit. The rectangular window was removed with forceps, the opening covered with transparent tape and the egg returned to the incubator.

On day 14 the eggs were removed from the incubator, the tape peeled back and the chorioallantoic membrane (CAM) examined for any abnormalities. Any egg with improperly developed membranes, undeveloped membranes or any other abnormality was discarded.

Dosing

Following the pre-dose examination, a Teflon ring was gently placed on the CAM and 40 µl of the test article concentration (50% dilution) was pipetted into the ring and 40 mg of test article was placed in the ring for dosing. The window was re-sealed, the egg numbered and returned to the incubator.

Type and Frequency of Observations

After 30 ± 5 minutes additional incubation, the eggs were removed and the CAM exposed by removing the tape and portions of the surrounding shell. The condition of the CAM within the Teflon ring was examined and recorded. Vascular hemorrhage, capillary injection and/or presence of ghost vessels are considered positive responses. If any abnormalities were noted outside the ring, the egg was not included in the calculations.

EXPERIMENTAL DESIGN (continued)

Analysis of Data

The test article was considered to be a non-irritant if the RC_{50} was greater than 3%.

Retention of Data

Upon signing the final report, all raw data, supporting documentation and reports are submitted to the Archivist by the Study Director. The raw data is filed at MB Research by project number. The final report is filed at MB Research by sponsor name and MB project number.

The test article will be returned following submission of the report.

Amendment to the Protocol

There were no amendments to the protocol.

Deviation to the Good Laboratory Practices

Although full test article characterization was not provided to the study director prior to study initiation, information on storage, identity, purity, and stability was provided. The information provided should be adequate for the intents and purposes of this study.

Study Title : **CAMVA**
Project # : **MB 07-16320.09**
Test Article : **Mandarin Orange Extract (Tangeretin 70%), Lot/batch #17839**
Protocol : **439-03**

RESULTS

CONCENTRATION: 50%[a]	*EGG NUMBER*									
OBSERVATIONS	111	112	113	114	115	116	117	118	119	120
Normal	X	X	X	X	X	X	X	X	X	X

CONCENTRATION: 100%[b]	*EGG NUMBER*									
OBSERVATIONS	101	102	103	104	105	106	107	108	109	110
Normal	X	X	X	X	X	X	X	X	X	X

a = Test Article physically removed from CAM
b = CAM washed with distilled water

Study Title : **CAMVA**
Project # : **MB 07-16320.09**
Test Article : **Mandarin Orange Extract (Tangeretin 70%), Lot/batch #17839**
Protocol : **439-03**

DISCUSSION

There were no positive responses to the one dilution in distilled water or the undiluted test article.

Concentration (%)	# of Eggs	# of Positive Responses
50	10	0/10
100	10	0/10

CONCLUSION

The RC_{50} is >100%.

FINAL REPORT

Approved by: Alison L. Ball 2/11/08

Alison L. Ball, B.S. Date
Study Director

MB Research Laboratories

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TEST ARTICLE CHARACTERIZATION INFORMATION

In compliance with Good Laboratory Practice (GLP) regulations, a characterization of the test article is required and should include identity, strength, purity, composition, stability and uniformity. This data must be reviewed by the Study Director prior to study initiation and will be included in the final report. (EPA 40 CFR 160.105 and 792.105; FDA 21 CFR 58.105, OECD 6.2).

In addition, the test article characterization should be performed in compliance with the Good Laboratory Practices.

Any exceptions to the GLP requirements will be indicated in the Compliance Statement of the final report.

Accordingly, please supply the following information for each test article submitted:

Test Article Identity : Premier MANDARIN ORANGE EXTRACT (Tangeretin 70%)

Strength : Not a mixture, Botanical Extract.

Purity : 100% Botanical Extract

Composition : Not Applicable.

Stability : Stable.

Uniformity : Not Applicable

☐ This characterization was conducted under GLPs *(or)*

☒ This characterization was not conducted under GLPs

BY: _____ (signature) FOR: PREMIER SPECIALTIES INC (company)

9/12/2007 (date)

MB Research Laboratories

Study Title : **CAMVA**
Project # : **MB 07-16320.09**
Test Article : **Mandarin Orange Extract (Tangeretin 70%), Lot/batch #17839**
Protocol : **439-03**

QUALITY ASSURANCE EVALUATION

The Quality Assurance Unit has inspected an in-life phase of this study, audited the raw data and the report and determined that the methods and results contained herein accurately reflect the raw data. No changes/modifications from the approved protocol or Standard Operating Procedures were made without proper authorization and documentation. A summary of the compliance inspections is presented below.

Date of Inspection	Phase	Performed By	Date Findings Reported to Mgmt.	Sty. Dir.
10/11/07	Dose administration	William J. Kintigh	01/30/08	02/01/08
10/16/07	Raw data audit	William J. Kintigh	01/30/08	02/01/08
10/22/07	Draft report audit	Erin Range	01/30/08	02/01/08
01/30/08	Final report audit	Erin Range	01/30/08	02/01/08

E Range 2/4/08

Erin Range, B.S., LATG — Date
Quality Assurance Unit

Consumer Product Testing Co.

EST. 1975

FINAL REPORT

CLIENT: Premier Specialties, Inc.
236 Blackford Avenue
Middlesex, New Jersey 08846

ATTENTION: Roger Rich

TEST: Repeated Insult Patch Test
Protocol No.: 1.01

TEST MATERIAL: Mandarin Orange Extract (Tangeretin 70%) 1% Wickenol 161 Code # 690475 Lot # LG090707

EXPERIMENT REFERENCE NUMBER: C07-4428.01

Richard R. Eisenberg, M.D.
Board Certified Dermatologist

Joy Frank, R.N.
Executive Vice President, Clinical Evaluations

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

Consumer Product Testing Co.
EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: C07-4428.01

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of clinical laboratory studies. These studies have been performed with adherence to the applicable ICH Guideline E6 for Good Clinical Practice and requirements provided for in 21 CFR parts 50 and 56 and in accordance to standard operating procedures and applicable protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study. All data pertinent to this study will be stored in the Consumer Product Testing Company archive, unless specified otherwise, in writing by the Sponsor.

Quality Assurance personnel involved:

Quality Assurance

11-2-07
Date

The representative signature of the Quality Assurance Unit signifies that this study has been performed in accordance with standard operating procedures and study protocol as well as government regulations regarding such procedures and protocols.

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234
Clinical • Toxicology • Analytical Chemistry • Microbiology

Objective: To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.

Participants: One hundred twelve (112) qualified subjects, male and female, ranging in age from 17 to 77 years, were selected for this evaluation. One hundred seven (107) subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

a. Male and female subjects, age 16[a] and over.
b. Absence of any visible skin disease which might be confused with a skin reaction from the test material.
c. Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.
d. Completion of a Medical History form and the understanding and signing of an Informed Consent form.
e. Considered reliable and capable of following directions.

Exclusion Criteria:

a. Ill health.
b. Under a doctor's care or taking medication(s) which could influence the outcome of the study.
c. Females who are pregnant or nursing.
d. A history of adverse reactions to cosmetics or other personal care products.

Test Material: Mandarin Orange Extract (Tangeretin 70%) 1% Wickenol 161 Code # 690475 Lot # LG090707

Study Schedule:

Panel #	Initiation Date	Completion Date
20070315	September 17, 2007	October 25, 2007
20070319	September 17, 2007	October 26, 2007

[a]With parental or guardian consent

Methodology:

The upper back between the scapulae served as the treatment area. Approximately 0.2 ml of the test material, or an amount sufficient to cover the contact surface, was applied to the 1" x 1" absorbent pad portion of a clear adhesive dressing* and allowed to volatilize for several minutes. This was then applied to the appropriate treatment site to form a semi-occlusive patch.

Induction Phase:

Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period.

With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications were discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted.

Rest periods consisted of twenty-four hours following each Tuesday and Thursday removal, and forty-eight hours following each Saturday removal.

Challenge Phase:

Approximately two (2) weeks after the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic twenty-four and seventy-two hours post-application.

*Manufactured by TruMed Technologies, Inc., Burnsville, MN

Methodology (continued):

Evaluation Criteria (Erythema and additional Dermal Sequelae):

0	=	No visible skin reaction	E	=	Edema
0.5 / +	=	Barely perceptible	D	=	Dryness
1	=	Mild	S	=	Staining
2	=	Moderate	P	=	Papules
3	=	Marked	V	=	Vesicles
4	=	Severe	B	=	Bullae
			U	=	Ulceration
			Sp	=	Spreading

Erythema was scored numerically according to this key. If present, additional Dermal Sequelae were indicated by the appropriate letter code and a numerical value for severity.

Results:

The results of each participant are appended (Table 1).

Observations remained negative throughout the test interval.

Subject demographics are presented in Table 2.

Summary:

Under the conditions of this study, test material, Mandarin Orange Extract (Tangeretin 70%) 1% Wickenol 161 Code # 690475 Lot # LG090707, did not indicate a potential for dermal irritation or allergic contact sensitization.

Table 1
Panel #20070315

Individual Results

Mandarin Orange Extract (Tangeretin 70%) 1% Wickenol 161 Code # 690475 Lot # LG090707

Subject Number	24*hr	Induction Phase									Virgin Challenge Site	
		1	2	3	4	5	6	7	8	9	24*hr	72 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	----------DID NOT COMPLETE STUDY----------										
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	----------DID NOT COMPLETE STUDY----------										
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch

Table 1
(continued)
Panel #20070315

Individual Results

Mandarin Orange Extract (Tangeretin 70%) 1% Wickenol 161 Code # 690475 Lot # LG090707

Subject Number	Induction Phase									Virgin Challenge Site	
	24*hr	1	2	3	4	5	6	7	8	9	24*hr	72 hr
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0[m]	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
m = Additional makeup day granted at the discretion of the clinic supervisor

Table 1
(continued)
Panel #20070319

Individual Results

Mandarin Orange Extract (Tangeretin 70%) 1% Wickenol 161 Code # 690475 Lot # LG090707

Subject Number	Induction Phase									Virgin Challenge Site	
	24*hr	1	2	3	4	5	6	7	8	9	24*hr	72 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	DID NOT COMPLETE STUDY											
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch

Table 1
(continued)
Panel #20070319

Individual Results

Mandarin Orange Extract (Tangeretin 70%) 1% Wickenol 161 Code # 690475 Lot # LG090707

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	DID NOT COMPLETE STUDY										
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	DID NOT COMPLETE STUDY									
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch

Table 2
Panel #20070315

Subject Data

Subject Number	Initials	Age	Sex
1	RM	43	F
2	RR	48	M
3	FA	36	F
4	KR	42	F
5	JK	73	M
6	DC	44	M
7	DS	77	M
8	JR	67	M
9	HS	64	F
10	MR	44	F
11	AT	68	F
12	NT	71	F
13	LT	76	M
14	LV	68	F
15	VW	57	F
16	AL	56	F
17	BA	40	F
18	SL	65	F
19	JM	22	F
20	MC	47	M
21	MH	44	F
22	SR	50	M
23	KM	22	F
24	CP	45	M
25	BR	48	F
26	LF	44	F
27	LV	27	F
28	RG	34	M
29	BA	54	F

Table 2
(continued)
Panel #20070315

Subject Data

Subject Number	Initials	Age	Sex
30	RC	39	F
31	NM	59	F
32	KR	46	M
33	ES	55	F
34	RO	77	F
35	AM	41	M
36	DB	62	F
37	AC	26	M
38	ND	19	F
39	MP	50	F
40	FC	46	M
41	LN	48	F
42	CK	51	F
43	YB	40	F
44	MC	41	F
45	TP	62	F
46	TM	54	F
47	JL	22	F
48	RR	21	M
49	OR	33	F
50	DP	49	M
51	SC	23	F
52	JS	61	F
53	LC	26	M
54	CM	26	M
55	MP	40	F
56	WH	47	M

Table 2
(continued)
Panel #20070319

Subject Data

Subject Number	Initials	Age	Sex
1	MF	47	M
2	MR	42	F
3	RF	37	F
4	MV	21	F
5	RV	29	F
6	JP	26	F
7	LA	41	M
8	AK	47	F
9	CO	44	F
10	JF	25	M
11	JS	22	F
12	BC	22	F
13	SC	42	F
14	HF	44	M
15	CK	67	M
16	AA	60	F
17	ED	77	F
18	JH	22	F
19	NV	59	F
20	TS	17	F
21	YD	35	F
22	LZ	46	F
23	PD	44	F
24	LU	53	F
25	GB	54	F
26	ES	48	F
27	DC	66	F
28	LR	54	F
29	NP	58	F

Table 2
(continued)
Panel #20070319

Subject Data

Subject Number	Initials	Age	Sex
30	EM	61	F
31	LR	31	F
32	AN	57	F
33	ML	36	M
34	BL	45	F
35	DO	41	F
36	JL	60	F
37	LP	41	F
38	DS	66	F
39	AM	41	F
40	SH	19	F
41	MK	40	F
42	NP	34	F
43	NE	18	F
44	MB	58	F
45	DC	21	F
46	TM	41	F
47	JM	18	M
48	RD	55	M
49	KK	51	M
50	DE	52	F
51	RE	54	M
52	KW	32	F
53	ES	21	M
54	LK	31	F
55	MK	50	F
56	AD	56	M

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 1, 2015

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

Active Concepts. 2015. Compositional breakdown ABS Lime Extract BG (Citrus Aurantifolia (Lime) Fruit Extract).

Active Concepts. 2015. Product specification ABS Lime Extract BG (Citrus Aurantifolia (Lime) Fruit Extract).

Active Concepts. 2015. Safety data sheet: ABS Lime Extract BG (Citrus Aurantifolia (Lime) Fruit Extract).

Active Concepts. 2011. Manufacturing flow chart: ABS Grapefruit Powder (Citrus Grandis (Grapefruit) Extract).

Active Concepts. 2014. Compositional breakdown: ABS Grapefruit Powder (Citrus Grandis (Grapefruit) Extract).

Active Concepts. 2014. Product specification: ABS Grapefruit Powder (Citrus Grandis (Grapefruit) Extract).

Active Concepts. 2014. Dermal and ocular irritation tests: ABS Grapefruit Powder (Citrus Grandis (Grapefruit) Extract).

Active Concepts. 2015. Safety data sheet: ABS Grapefruit Powder (Citrus Grandis (Grapefruit) Extract).

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Compositional Breakdown

ABS Lime Extract BG
Code: 10319

Compositional Breakdown:

Ingredient	%
Butylene Glycol	79.50
Citrus Aurantifolia (Lime) Fruit Extract	20.00
Phenonip	0.50

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Compositional Breakdown

This is to certify that the following allergens were not detected in ABS Lime Extract BG:

ALLERGENS Dir 2003 15 CEE	
INCI NAME	CAS NUMBER
Alpha-IsoMethyl Ionone	127-51-5
Amyl Cinnamal	122-40-7
Anise Alcohol	105-13-5
Benzyl Alcohol	100-51-69
Benzyl Benzoate	120-51-4
Benzyl Cinnamate	103-41-3
Benzyl Salicylate	118-58-1
Butylphenyl Methylpropional	80-54-6
Cinnamal	104-55-2
Cinnamyl Alcohol	104-54-1
Citral	5392-40-5
Citronellol	106-22-9
Coumarin	91-64-5
Eugenol	97-53-0
Farnesol	4602-84-0
Geraniol	106-24-1
Hexyl Cinnamal	101-86-0
Hydroxycitronellal	107-75-5
Hydroxymethylpentyl 3-Cyclohexene carboxaldehyde	31906-04-4
Isoeugenol	97-54-1
Limonene	5989-27-5
Linalool	78-70-6
Methyl 2 Octynoate	111-12-6
Evernia prunastri	90028-68-5
Evernia furfuracea	90028-67-4
Amylcinnamyl Alcohol	101-85-9

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Product Specification

Product Name: ABS Lime Extract BG
Code Number: 10319
CAS #'s: 107-88-0 & 90063-52-8
EINECS #'s: 203-529-7 & 290-010-3
INCI Name: Butylene Glycol & Citrus Aurantifolia (Lime) Fruit Extract
Status: Conforms

Specification	Parameter
Appearance	Clear Yellow to Light Amber Liquid
Odor	Characteristic
Specific Gravity	1.000 – 1.020
Refractive Index	1.4350 – 1.4450
Heavy Metals	< 20 ppm
Arsenic	< 2 ppm
Microbial Content	< 100 opg No pathogens

May Sediment upon Standing; Mix Well Prior to Use

Safety Data Sheet

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SECTION 1. IDENTIFICATION

Product Name/Identifier	ABS Lime Extract BG
Product Code	10319
Recommended Use	Topical Cosmetic Use
Restrictions on Use	Refer to the detailed list of labeling/restrictions (Section 15 Regulatory Information)
Supplier/Manufacturing Site	Active Concepts, LLC
Address	107 Technology Drive Lincolnton, NC 28092, USA
Telephone No. (24hrs)	1-704-276-7100
Fax No.	1-704-276-7101
Emergency Telephone #	1-704-276-7100 (Mon-Fri: 8:00AM – 5:00PM EST)

SECTION 2. HAZARD(S) IDENTIFICATION

Classification:

GHS / CLP
Basis for Classification: Based on present data no classification and labeling is required according to GHS, taking into account the national implementation (United Nations version 2011)

USA
OSHA Regulatory Status: This material is non-hazardous as defined by the American OSHA Hazard Communication Standard (29 CFR 1910.1200).

Europe
Basis for Classification:
-According to present data no classification and labeling is required according to Directives 67/548/EEC or 1999/45/EC.
-This product is not classified as hazardous to health or environment according to the CLP regulation.

Labeling Elements:

Pictograph: No hazard symbol expected

Hazard statements/Signal Word: Not applicable

Precautionary statements:
P233: Keep container tightly closed
P281: Use personal protective equipment as required
P402: Store in a dry place
P404: Store in a closed container
P410: Protect from sunlight
P411: Store at temperatures not exceeding 25°C

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Other hazards which do not result in classification:

No particular fire or explosion hazard.
By mechanical effect: No particular hazards.
By hydroscopic effect: No particular hazards.

US NFPA 704 (National Fire Protection Association) Hazard Rating System:

Health hazard: Rating 0; Normal Material
Flammability: Rating 0, Will Not Burn
Reactivity: Rating 0, Stable
Other Hazard Information: None

Results of PBT and vPvB assessment:

-PBT: Not applicable
-vPvB: Not applicable

SECTION 3. COMPOSITION / INFORMATION ON INGREDIENTS

Common Chemical Name: Butylene Glycol & Citrus Aurantifolia (Lime) Fruit Extract

Generic name:

Chemical Family: Extract

Description: Mixture: consisting of the following components. This section describes all components of the mixture

Substance	CAS Numbers	EC Numbers	Percentage
Butylene Glycol	107-88-0	203-529-7	79.50%
Citrus Aurantifolia (Lime) Fruit Extract	90063-52-8	290-010-3	20.00%
Phenoxyethanol	122-99-6	204-589-7	0.362%
Methylparaben	99-76-3	202-785-7	0.078%
Ethylparaben	120-47-8	204-399-4	0.02%
Butylparaben	94-26-8	202-318-7	0.02%
Propylparaben	94-13-3	202-307-7	0.01%
Isobutylparaben	4247-02-3	224-208-8	0.01%

Formula: Not applicable

SECTION 4. FIRST-AID MEASURES

General: In all cases of doubt, or when symptoms persist, seek medical attention.

Inhalation: Move to fresh air from exposure area. Get medical attention for any breathing difficulty.

Skin contact: Rinse with soap and water. Get medical advice if irritation develops.

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Eye contact:	Immediately rinse with plenty of water for at least 15 minutes, while keeping the eyes wide open. Consult with a physician.
Ingestion:	Consult with a physician.
Protection of first-aiders:	No special protection required.

SECTION 5. FIRE-FIGHTING MEASURES

Fire and explosion hazards:	Not considered to be a fire and explosion hazard
Extinguishing media:	
Suitable:	Water, dry chemicals, foam and carbon dioxide
Not suitable:	None known
Fire fighting:	Move container from fire area if it can be done without risk. Avoid inhalation of material or combustion by-products. Stay upwind and keep out of low area
Protection for fire-fighters:	Boots, gloves, goggles.

SECTION 6. ACCIDENTAL RELEASE MEASURES

Personal precautions:	Avoid contact with eyes. Personal Protective Equipment: -Protective goggles
Environmental precautions:	Prevent entry into sewers and waterways. Do not allow material to contaminate ground water system
Methods for cleaning up:	
Recovery:	Pick up free liquid for recycling or disposal. Residual liquid can be absorbed on an inert material.
Cleaning/Decontamination:	Wash non-recoverable remainder with water.
Disposal:	For disposal of residues refer to sections 8 & 13.

SECTION 7. HANDLING AND STORAGE

Handling	
Technical measures:	Labeling: Keep out of the reach of children.
Measures:	For industrial use, only as directed.
Safe handling advice:	Wash hands after use. Avoid storage near feed or food stuff.

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Storage

Technical measures:	Keep container closed.
Recommended Storage Conditions:	Store in a cool, dry place. This material must be stored at room temperature (23 - 25°C). It should not be exposed to excessive heat or cold. Do not freeze.
Incompatible products:	Avoid contact with strong oxidizers. Refer to the detailed list of incompatible materials (Section 10 Stability/Reactivity)
Packaging:	Product may be packaged in normal commercial packaging.
Packaging materials:	Recommended - Polypropylene & High Density Polyethylene

SECTION 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Precautionary statements: Ensure adequate ventilation

Control parameters

Occupational exposure Limits:

France:	Not Determined
ACGIH:	Not Determined
Korea:	Not Determined
UK:	Not Determined
Surveillance procedures:	Not Determined
Engineering measures:	Not Determined

Personal Protective Equipment:

Respiratory protection:	Local exhaust
Hand protection:	Protective gloves made of rubber or neoprene.
Eye protection:	Safety glasses.
Collective emergency equipment:	Eye fountain.
Skin and Body Protection:	Suitable protective clothing
Hygiene measures:	Handle in accordance with good industrial hygiene and safety practice.
Measures related to the Environment:	No particular measures.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance:	Clear yellow to light amber liquid
Odor:	Characteristic
Specific Gravity:	1.000 – 1.020
Refractive Index:	1.4350 – 1.4450

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Heavy Metals:	< 20 ppm
Arsenic:	< 2 ppm
Microbial Content:	< 100 CFU/g No pathogens
Vapor density:	Not applicable
Boiling Point:	209°C
Freezing Point:	-50°C
Melting point:	Not applicable
Flash point:	> 200°F
Oxidizing properties:	Non oxidizing material according to EC criteria.
Solubility:	
In water:	Soluble
In organic solvents:	Not determined
Log P:	Not determined

SECTION 10. STABILITY AND REACTIVITY

Stability:	Stable under ordinary conditions of use and storage up to one year then re-test to full product specifications to extend shelf life
Hazardous reactions:	None known
Conditions to avoid:	No dangerous reactions known under use of normal conditions. Avoid extreme heat.
Materials to avoid:	No dangerous reaction known with common products.

Hazardous decomposition products: None known

SECTION 11. TOXICOLOGICAL INFORMATION

Ingestion:	Not Determined
Dermal:	Not Determined
Ocular:	Not Determined
Inhalation:	Not Determined
Acute toxicity data:	Not Determined
Sensitization:	Non-Primary Sensitizers
Repeated dose toxicity:	No known effects
Subacute to chronic toxicity:	Not Determined

Additional Toxicological Information: This product is not subject to classification according to the calculation method of the General EU Classification Guidelines for Preparations as issued in the latest version.

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Specific effects:

Carcinogenicity:	No known effects
Mutagenicity:	No known effects
Reproductive toxicity:	No known effects
Neuro-toxicity:	No known effects

For more information: Does not present any particular risk on handling under normal conditions of good occupational hygiene practice.

This product has not been tested for the following:
-Primary cutaneous and corrosive irritation
-Acute oral toxicity
-Mutagenicity/genotoxicity

SECTION 12. ECOLOGICAL INFORMATION

Ecotoxicity
Effects on the aquatic environment: Not Determined

Biodegradability:
Persistence: Not Determined

Bioaccumulation:
Octanol / water partition coefficient: Not Determined

Mobility:
Precipitation:
Expected behavior of the product: Ultimate destination of the product: Soil & sediment.

Other Adverse Effects: None known

SECTION 13. DISPOSAL CONSIDERATIONS

Residues from product

Prohibition:	Do not allow the product to be released into the Environment.
Destruction/Disposal:	Dispose of in accordance with relevant local regulations

Contaminated packaging

Decontamination/cleaning:	Cleaning is not required prior to disposal.
Destruction/Disposal:	

Note: Take all necessary precautions when disposing of this product according to local regulations.

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SECTION 14. TRANSPORT INFORMATION

UN Number:	None
UN Shipping Name:	None
Transport Hazard Class:	Not classified as dangerous for transport
Land (rail/road):	Material is not restrictive for land transport and is not regulated by ADR/RID
Sea:	Material is not restrictive for sea transport and is not regulated by IMO/IMDG
Air:	Material is not restrictive for land transport and is not regulated by ICA/IATA
Marine Pollutant:	No
Transport/Additional Information:	Not regulated for US DOT Transport in non-bulk containers This material is not dangerous or hazardous
Special Precautions for User:	None known

The above regulatory prescriptions are those valid on the date of publication of this sheet. However, given the possible evolution of transport regulations for hazardous materials and in the event of the MSDS in your possession dating back more than 12 months, it is advisable to check their validity with your sales office.

SECTION 15. REGULATORY INFORMATION

Labelling:

EC regulations:	This product does not need to be labeled in accordance with EC Directives or respective national laws
Restrictions:	Methyl- and Ethyl- esters can be used up to 0.40% (as acid) for 1 ester or 0.80% for mixtures of substances of Methyl- and Ethyl- esters & Butyl- and Propyl- parabens, where the sum of the individual concentrations of butyl- and Propylparaben and their salts do not exceed 0.14% Isobutylparaben is banned by Commission Regulation (EU) No 358/2014

Further regulations

United Kingdom:	Handle in accordance with relevant British regulation: control of substance Hazardous to Health Regulations Environmental Hygiene Guidance: EH40 Workplace Exposure Limits (revised annually)
Korea regulations:	Industrial safety and hygiene regulation: No Hazardous material control regulation: No Fire prevention regulation: No

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Other regulations:

EINECS inventory status:	Butylene Glycol:	203-529-7
	Citrus Aurantifolia Fruit Extract:	290-010-3
	Phenoxyethanol:	204-589-7
	Methylparaben:	202-785-7
	Ethylparaben:	204-399-4
	Butylparaben:	202-318-7
	Propylparaben:	202-307-7
	Not Allowed: Isobutylparaben:	224-208-8
TSCA inventory status:	Exempt	
AICS inventory status:	107-88-0 & 90063-52-8 & 122-99-6 & 99-76-3 & 120-47-8 & 94-26-8 & 94-13-3 & 4247-02-3	
Canadian (CEPA DSL) inventory status:	Listed as 1,3-Butanediol (DSL) & Lime (Citrus Aurantifolia), ext. (DSL) & Ethanol, 2-phenoxy- (DSL) & Benzoic acid, 4-hydroxy-, methyl ester (DSL) & Benzoic acid, 4-hydroxy-, ethyl ester (DSL) & Benzoic acid, 4-hydroxy-, butyl ester (DSL) & Benzoic acid, 4-hydroxy-, propyl ester (DSL) & Benzoic acid, 4-hydroxy-, 2-methylpropyl ester (DSL)	
Japan (MITI list):	Butylene Glycol & Citrus Aurantifolia (Lime) Fruit Extract & Phenoxyethanol & Methylparaben & Ethylparaben & Butylparaben & Propylparaben & Isobutylparaben	
Korea:	Butylene Glycol & Citrus Aurantifolia (Lime) Fruit Extract & Phenoxyethanol & Methylparaben & Ethylparaben & Butylparaben & Propylparaben & Isobutylparaben	
China inventory status:	Butylene Glycol & Citrus Aurantifolia (Lime) Fruit Extract & Phenoxyethanol & Methylparaben & Ethylparaben & Butylparaben & Propylparaben & Isobutylparaben	
Philippines inventory status:	Not Listed: Isobutylparaben (4247-02-3) Listed as 1,3-Butanediol & Lime (Citrus Aurantifolia), ext. & Ethanol, 2-phenoxy- & Benzoic acid, 4-hydroxy-, methyl ester & Benzoic acid, 4-hydroxy-, ethyl ester & Benzoic acid, 4-hydroxy-, butyl ester & Benzoic acid, 4-hydroxy-, propyl ester	

*Listed on 2010 INCI Standard Chinese Name Directory

Note: The regulatory information given above only indicates the principal regulations specifically applicable to the products described in this sheet. The user's attention is drawn to the possible existence of additional provision which complete these regulations. Please refer to all applicable international, national and local regulations and provisions

SECTION 16. OTHER INFORMATION

Prohibited uses:	For specific uses, food industry, ask the manufacturer for more information.
Last Revision Date:	1/30/2014
Preparation Date:	3/30/2015

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MSDS summary of changes - Added Precautionary Statements - Section 2 (Hazards Identification), Added Heavy Metals & Arsenic – Section 9 (Physical & Chemical Properties), Updated Transport Information – Section 14 (Transport Information) & Updated EU Regulations – Section 15 (Regulatory Information)

The information given is based on our knowledge of this product, at the time of publication in good faith. The attention of the user is drawn to the possible risks incurred by using the product for any other purpose other than which it was intended. This is not in any way excuse the user from knowing and applying all the regulations governing their activity. It is sole responsibility of the user to take all precautions required in handling the product. The purpose of mandatory regulation mentioned is to help the user to fulfill his obligations regarding the use of products. This information is not exhaustive, this is not exonerate the user from ensuring that legal obligations other than those mentioned, relating to the use and storage.

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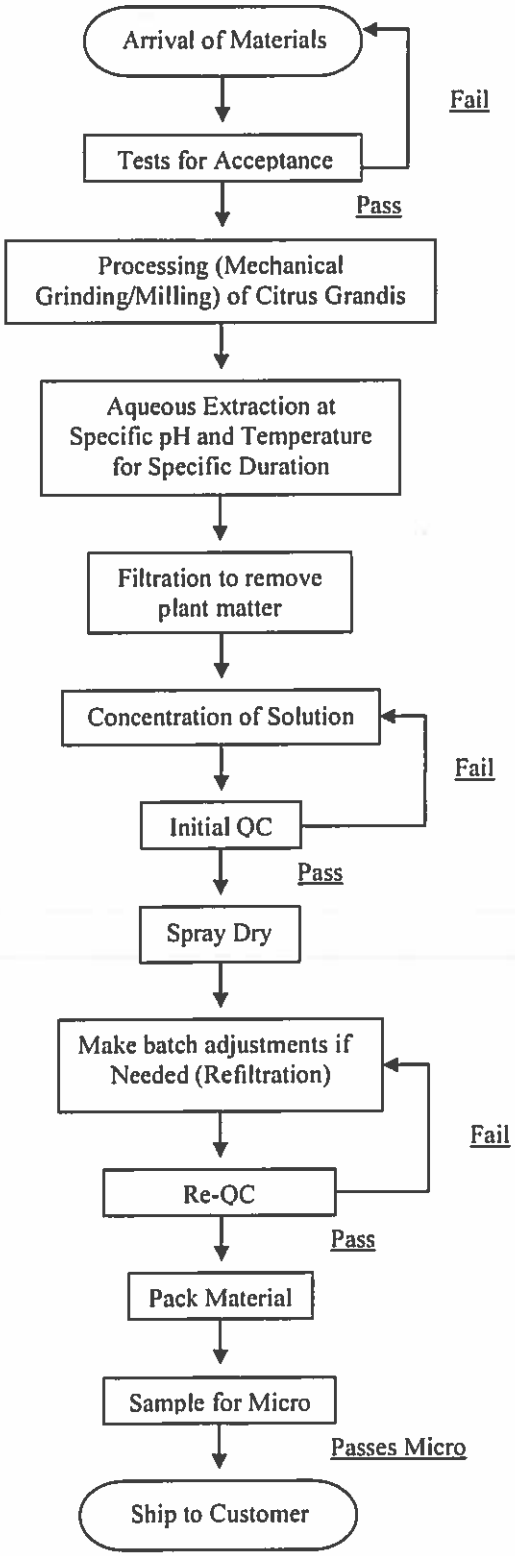
10252-ABS Grapefruit Powder- Manufacturing Flow Chart



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Compositional Breakdown

ABS Grapefruit Powder
Code: 10252

Compositional Breakdown:

Ingredient	%
Citrus Grandis (Grapefruit) Fruit Extract	100.00

- **The above material is free of furanocoumarins to a level of <1 ppm.**

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Compositional Breakdown

This is to certify that the following allergens were not detected in ABS Grapefruit Powder:

ALLERGENS Dir 2003 15 CEE	
INCI NAME	CAS NUMBER
Alpha-IsoMethyl Ionone	127-51-5
Amyl Cinnamal	122-40-7
Anise Alcohol	105-13-5
Benzyl Alcohol	100-51-69
Benzyl Benzoate	120-51-4
Benzyl Cinnamate	103-41-3
Benzyl Salicylate	118-58-1
Butylphenyl Methylpropional	80-54-6
Cinnamal	104-55-2
Cinnamyl Alcohol	104-54-1
Citral	5392-40-5
Citronellol	106-22-9
Coumarin	91-64-5
Eugenol	97-53-0
Farnesol	4602-84-0
Geraniol	106-24-1
Hexyl Cinnamal	101-86-0
Hydroxycitronellal	107-75-5
Hydroxymethylpentyl 3-Cyclohexene carboxaldehyde	31906-04-4
Isoeugenol	97-54-1
Limonene	5989-27-5
Linalool	78-70-6
Methyl 2 Octynoate	111-12-6
Evernia prunastri	90028-68-5
Evernia furfuracea	90028-67-4
Amylcinnamyl Alcohol	101-85-9

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Product Specification

Product Name: ABS Grapefruit Powder
Code Number: 10252
CAS #'s: 90045-43-5
EINECS #'s: 289-904-6
INCI Name: Citrus Grandis (Grapefruit) Fruit Extract
Status: Approved

Specification	Parameter
Appearance	Off-White to Pale Yellow Powder
Odor	Characteristic
pH (1% in Water)	2.0 – 5.0
Loss on Drying (1g-1hr-105°C)	10.0% Maximum
Heavy Metals	< 20 ppm
Arsenic	< 2 ppm
Microbial Content	< 100 opg No pathogens

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Dermal and Ocular Irritation Tests

Tradename: ABS Grapefruit Powder

Code: 10252

CAS #: 90045-43-5

Test Request Form #: 1186

Lot #: 37808P

Sponsor: *Active Concepts, LLC; 107 Technology Drive Lincolnton, NC 28092*
Study Director: *Erica Segura*
Principle Investigator: *Meghan Darley*

Test Performed:
In Vitro EpiDerm™ Dermal Irritation Test (EPI-200-SIT)
EpiOcular™ Eye Irritation Test (OCL-200-EIT)

SUMMARY

In vitro dermal and ocular irritation studies were conducted to evaluate whether ABS Grapefruit Powder would induce dermal or ocular irritation in the EpiDerm™ and EpiOcular™ model assays.

The product was tested according to the manufacture's protocol. The test article solution was found to be a **non-irritant**. Reconstructed human epidermis and cornea epithelial model were incubated in growth media overnight to allow for tissue equilibration after shipping from MatTek Corporation, Ashland, MA. Test substances were applied to the tissue inserts and incubated for 60 minutes for liquid and solid substances in the EpiDerm™ assay and 30 minutes for liquid substances and 90 minutes for solid substances in the EpiOcular™ assay at 37◦C, 5% CO_2, and 95% relative humidity (RH). Tissue inserts were thoroughly washed and transferred to fresh plates with growth media. After post substance dosing incubation is complete, the cell viability test begins. Cell viability is measured by dehydrogenase conversion of MTT [(*3-4,5-dimethyl thiazole 2-yl*)], present in the cell mitochondria, into blue formazan salt that is measured after extraction from the tissue. The irritation potential of the test chemical is dictated by the reduction in tissue viability of exposed tissues compared to the negative control.

Under the conditions of this assay, the test article was considered to be **non-irritating**. The negative and positive controls performed as anticipated.

I. Introduction

A. Purpose

In vitro dermal and ocular irritation studies were conducted to evaluate whether a test article would induce dermal or ocular irritation in the EpiDerm™ and EpiOcular™ model assays. MatTek Corporation's reconstructed human epidermal and human ocular models are becoming a standard in determining the irritancy potential of test substances. They are able to discriminate between irritants and non-irritants. The EpiDerm™ assay has accuracy for the prediction of UN GHS R38 skin irritating and no-label (non-skin irritating) test substances. The EpiOcular™ assay can differentiate chemicals that have been classified as R36 or R41 from the EU classifications based on Dangerous Substances Directive (DSD) or between the UN GHS Cat 1 and Cat 2 classifications.

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Dermal and Ocular Irritation Tests

II. Materials

A. Incubation Conditions:	37°C at 5% CO_2 and 95% relative humidity
B. Equipment:	Forma humidified incubator, ESCO biosafety laminar flow hood, Synergy HT Microplate reader; Pipettes
C. Media/Buffers:	DMEM based medium; DPBS; sterile deionized H_2O
D. Preparation:	Pre-incubate (37°C) tissue inserts in assay medium; Place assay medium and MTT diluent at 4°C, MTT concentrate at -20°C, and record lot numbers of kit components
E. Tissue Culture Plates:	Falcon flat bottom 96-well, 24-well, 12-well, and 6-well tissue culture plates
F. Reagents:	MTT (1.0mg/mL); Extraction Solution (Isopropanol); SDS (5%); Methyl Acetate
G. Other:	Nylon Mesh Circles (EPI-MESH); Cotton tip swabs; 1mL tuberculin syringes; Ted Pella micro-spatula; 220mL specimen containers; sterile disposable pipette tips; Parafilm

III. Test Assay

A. Test System

The reconstructed human epidermal model, EpiDerm™, and cornea epithelial model, EpiOcular™, consist of normal human-derived epidermal keratinocytes which have been cultured to form a multilayer, highly differentiated model of the human epidermis and cornea epithelium. These models consist of organized basal, spinous, and granular layers, and the EpiDerm™ systems also contains a multilayer stratum corneum containing intercellular lamellar lipid layers that the EpiOcular™ system is lacking. Both the EpiDerm™ and EpiOcular™ tissues are cultured on specially prepared cell culture inserts.

B. Negative Control

Sterile DPBS and sterile deionized water are used as negative controls for the EpiDerm™ and EpiOcular™ assays, respectfully.

C. Positive Control

Known dermal and eye irritants, 5% SDS solution and Methyl Acetate, were used as positive controls for the EpiDerm™ and EpiOcular™ assays, respectfully.

D. Data Interpretation Procedure

a. EpiDerm™

An irritant is predicted if the mean relative tissue viability of the 3 tissues exposed to the test substance is reduced by 50% of the mean viability of the negative controls and a non-irritant's viability is > 50%.

b. EpiOcular™

An irritant is predicted if the mean relative tissue viability of the 2 tissues exposed to the test substance is reduced by 60% of the mean viability of the negative controls and a non-irritant's viability is > 40%.

IV. Method

A. Tissue Conditioning

Upon MatTek kit arrival at Active Concepts, LLC the tissue inserts are removed from their shipping medium and transferred into fresh media and tissue culture plates and incubated at 37°C at 5% CO_2 and 95% relative humidity for 60 minutes. After those 60 minutes the inserts are transferred into fresh media and tissue culture plates and incubated at 37°C at 5% CO_2 and 95% relative humidity for an additional 18 to 21 hours.

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B. Test Substance Exposure

a. EpiDerm™

30µL (liquid) or 25mg (solid) of the undiluted test substance is applied to 3 tissue inserts and allowed to incubate for 60 minutes in a humidified incubator (37°C, 5% CO_2, 95% RH).

b. EpiOcular™

Each tissue is dosed with 20µL DPBS prior to test substance dosing. 50µL (liquid) or 50mg (solid) of the undiluted test substance is applied to 2 tissue inserts and allowed to incubate for 90 minutes in a humidified incubator (37°C, 5% CO_2, 95% RH).

C. Tissue Washing and Post Incubation

a. EpiDerm™

All tissue inserts are washed with DPBS, dried with cotton tipped swab, and transferred to fresh media and culture plates. After 24 hours the inserts are again transferred into fresh media and culture plates for an additional 18 to 20 hours.

b. EpiOcular™

Tissue inserts are washed with DPBS and immediately transferred into 5mL of assay medium for 12 to 14 minutes. After this soak the inserts are transferred into fresh media and tissue culture plates for 120 minutes for liquid substances and 18 hours for solid substances.

D. MTT Assay

Tissue inserts are transferred into 300µL MTT media in pre-filled plates and incubated for 3 hours at 37°C, 5% CO_2, and 95% RH. Inserts are then removed from the MTT medium and placed in 2mL of the extraction solution. The plate is sealed and incubated at room temperature in the dark for 24 hours. After extraction is complete the tissue inserts are pierced with forceps and 2 x 200µL aliquots of the blue formazan solution is transferred into a 96 well plate for Optical Density reading. The spectrophotometer reads the 96-well plate using a wavelength of 570 nm.

V. Acceptance Criterion

A. Negative Control

The results of this assay are acceptable if the mean negative control Optical Density (OD_{570}) is ≥ 1.0 and ≤ 2.5 (EpiDerm™) or ≥ 1.0 and ≤ 2.3 (EpiOcular™).

B. Positive Control

a. EpiDerm™

The assay meets the acceptance criterion if the mean viability of positive control tissues expressed as a % of the negative control is ≤ 20%.

b. EpiOcular™

The assay meets the acceptance criterion if the mean viability of positive control tissues is < 60% of control viability.

C. Standard Deviation

Since each irritancy potential is predicted from the mean viability of 3 tissues for EpiDerm™ and 2 tissues for EpiOcular™, the variability of the replicates should be < 18% for EpiDerm™ and < 20% EpiOcular™.

VI. Results

A. Tissue Characteristics

The tissue inserts included in the MatTek EpiDerm™ and EpiOcular™ assay kits were in good condition, intact, and viable.

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B. Tissue Viability Assay

The results are summarized in Figures 1 and 2. In no case was the tissue viability ≤ 50% for EpiDerm™ or ≤ 60% for EpiOcular™ in the presence of the test substance. The negative control mean exhibited acceptable relative tissue viability while the positive control exhibited substantial loss of tissue viability and cell death.

C. Test Validity

The data obtained from this study met criteria for a valid assay.

VII. Conclusion

Under the conditions of this assay, the test article substance was considered to be **non-irritating**. The negative and positive controls performed as anticipated.

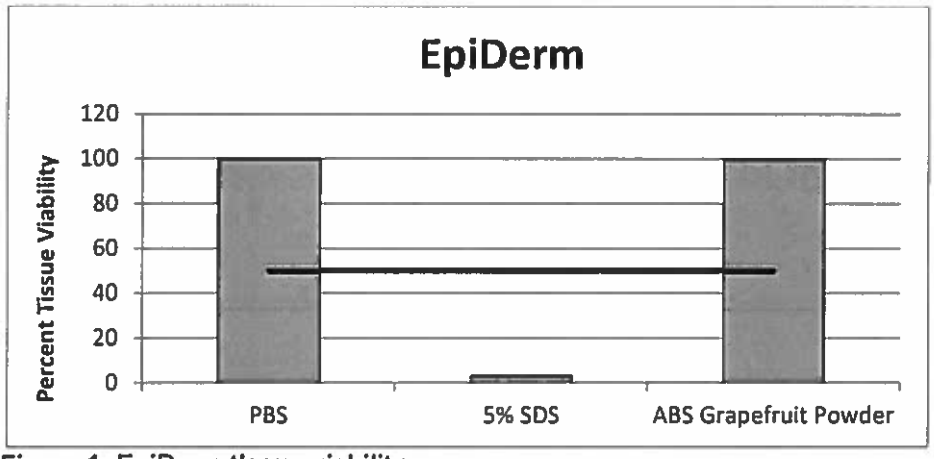

Figure 1: EpiDerm tissue viability

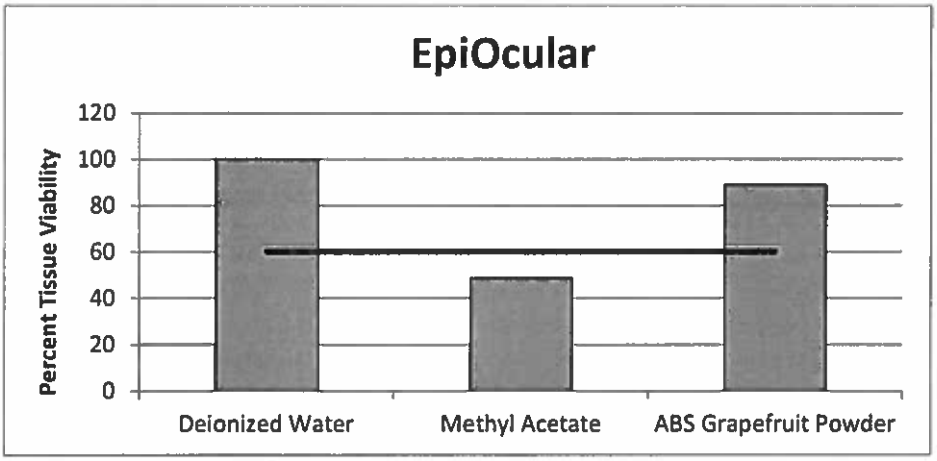

Figure 2: EpiOcular tissue viability

Safety Data Sheet

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SECTION 1. IDENTIFICATION

Product Name/Identifier	ABS Grapefruit Powder
Product Code	10252
Recommended Use	Topical Cosmetic Use
Restrictions on Use	None
Supplier/Manufacturing Site	Active Concepts, LLC
Address	107 Technology Drive Lincolnton, NC 28092, USA
Telephone No. (24hrs)	1-704-276-7100
Fax No.	1-704-276-7101
Emergency Telephone #	1-704-276-7100 (Mon-Fri: 8:00AM – 5:00PM EST)

SECTION 2. HAZARD(S) IDENTIFICATION

Classification:

GHS / CLP
Basis for Classification: Based on present data no classification and labeling is required according to GHS, taking into account the national implementation (United Nations version 2011)

USA
OSHA Regulatory Status: This material is non-hazardous as defined by the American OSHA Hazard Communication Standard (29 CFR 1910.1200).

Europe
Basis for Classification:
-According to present data no classification and labeling is required according to Directives 67/548/EEC or 1999/45/EC.
-This product is not classified as hazardous to health or environment according to the CLP regulation.

Labeling Elements:

Pictograph: No hazard symbol expected

Hazard statements/Signal Word: Not applicable

Precautionary statements:
P233: Keep container tightly closed
P281: Use personal protective equipment as required
P402: Store in a dry place
P404: Store in a closed container
P410: Protect from sunlight
P411: Store at temperatures not exceeding 25°C

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Other hazards which do not result in classification:

No particular fire or explosion hazard.
By mechanical effect: No particular hazards.
By hydroscopic effect: No particular hazards.

US NFPA 704 (National Fire Protection Association) Hazard Rating System:

Health hazard: Rating 0, Normal Material
Flammability: Rating 0, Will Not Burn
Reactivity: Rating 0, Stable
Other Hazard Information: None

Results of PBT and vPvB assessment:

-PBT: Not applicable
-vPvB: Not applicable

SECTION 3. COMPOSITION / INFORMATION ON INGREDIENTS

Common Chemical Name: Citrus Grandis (Grapefruit) Fruit Extract

Generic name:

Chemical Family: Plant Material

Description: Mixture: consisting of the following components. This section describes all components of the mixture

Substance	CAS Numbers	EC Numbers	Percentage
Citrus Grandis (Grapefruit) Fruit Extract	90045-43-5	289-904-6	100.00%

Formula: Not applicable

SECTION 4. FIRST-AID MEASURES

General: In all cases of doubt, or when symptoms persist, seek medical attention.

Inhalation: Move to fresh air from exposure area. Get medical attention for any breathing difficulty.

Skin contact: Rinse with soap and water. Get medical advice if irritation develops.

Eye contact: Immediately rinse with plenty of water for at least 15 minutes, while keeping the eyes wide open. Consult with a physician.

Ingestion: Consult with a physician.

Protection of first-aiders: No special protection required.

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SECTION 5. FIRE-FIGHTING MEASURES

Fire and explosion hazards:	Not considered to be a fire and explosion hazard
Extinguishing media:	
Suitable:	Water, dry chemicals, foam and carbon dioxide
Not suitable:	None known
Fire fighting:	Move container from fire area if it can be done without risk. Avoid inhalation of material or combustion by-products. Stay upwind and keep out of low area
Protection for fire-fighters:	Boots, gloves, goggles.

SECTION 6. ACCIDENTAL RELEASE MEASURES

Personal precautions:	Avoid contact with eyes. Personal Protective Equipment: -Protective goggles
Environmental precautions:	Prevent entry into sewers and waterways. Do not allow material to contaminate ground water system
Methods for cleaning up:	
Recovery:	Pick up free liquid for recycling or disposal. Residual liquid can be absorbed on an inert material.
Cleaning/Decontamination:	Wash non-recoverable remainder with water.
Disposal:	For disposal of residues refer to sections 8 & 13.

SECTION 7. HANDLING AND STORAGE

Handling

Technical measures:	Labeling: Keep out of the reach of children.
Measures:	For industrial use, only as directed.
Safe handling advice:	Wash hands after use. Avoid storage near feed or food stuff.

Storage

Technical measures:	Keep container closed.
Recommended Storage Conditions:	Store in a cool, dry place. This material must be stored at room temperature (23 - 25°C). It should not be exposed to excessive heat or cold. Do not freeze.

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Incompatible products:	Avoid contact with strong oxidizers. Refer to the detailed list of incompatible materials (Section 10 Stability/Reactivity)
Packaging:	Product may be packaged in normal commercial packaging.
Packaging materials:	Recommended - Polypropylene & High Density Polyethylene

SECTION 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Precautionary statements: Ensure adequate ventilation

Control parameters

Occupational exposure Limits:

France:	Not Determined
ACGIH:	Not Determined
Korea:	Not Determined
UK:	Not Determined
Surveillance procedures:	Not Determined
Engineering measures:	Not Determined

Personal Protective Equipment:

Respiratory protection:	Local exhaust
Hand protection:	Protective gloves made of rubber or neoprene.
Eye protection:	Safety glasses.
Collective emergency equipment:	Eye fountain.
Skin and Body Protection:	Suitable protective clothing
Hygiene measures:	Handle in accordance with good industrial hygiene and safety practice.
Measures related to the Environment:	No particular measures.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance:	Off-white to pale yellow powder
Odor:	Characteristic
pH (1% In Water):	2.0 – 5.0
Loss on Drying (1g-1hr-105°C):	10.0% Maximum
Heavy Metals:	< 20 ppm
Arsenic:	< 2 ppm
Microbial Content:	< 100 CFU/g No pathogens

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Specific Gravity:	Not determined
Vapor density:	Not applicable
Boiling Point:	Not applicable
Freezing Point:	Not applicable
Melting point:	Not determined
Flash point:	Not applicable
Oxidizing properties:	Non oxidizing material according to EC criteria.
Solubility:	
In water:	Dispersible
In organic solvents:	Not determined
Log P:	Not determined

SECTION 10. STABILITY AND REACTIVITY

Stability: Stable under ordinary conditions of use and storage up to one year then re-test to full product specifications to extend shelf life

Hazardous reactions: None known

Conditions to avoid: No dangerous reactions known under use of normal conditions. Avoid extreme heat.

Materials to avoid: No dangerous reaction known with common products.

Hazardous decomposition products: None known

SECTION 11. TOXICOLOGICAL INFORMATION

Ingestion:	Not Determined
Dermal:	Non-Irritant (Dermal Irritection Model)
Ocular:	Non-Irritant (Ocular Irritection Model)
Inhalation:	Not Determined
Acute toxicity data:	Not Determined
Sensitization:	Non-Primary Sensitizers
Repeated dose toxicity:	No known effects
Subacute to chronic toxicity:	Not Determined

Additional Toxicological Information: This product is not subject to classification according to the calculation method of the General EU Classification Guidelines for Preparations as issued in the latest version.

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Specific effects:

Carcinogenicity:	No known effects
Mutagenicity:	No known effects
Reproductive toxicity:	No known effects
Neuro-toxicity:	No known effects
For more information:	Does not present any particular risk on handling under normal conditions of good occupational hygiene practice.

This product has not been tested for the following:
-Primary cutaneous and corrosive irritation
-Acute oral toxicity
-Mutagenicity/genotoxicity

SECTION 12. ECOLOGICAL INFORMATION

Ecotoxicity
Effects on the aquatic environment: Not Determined

Biodegradability:
Persistence: Not Determined

Bioaccumulation:
Octanol / water partition coefficient: Not Determined

Mobility:
Precipitation:
Expected behavior of the product: Ultimate destination of the product: Soil & sediment.

Other Adverse Effects: None known

SECTION 13. DISPOSAL CONSIDERATIONS

Residues from product

Prohibition:	Do not allow the product to be released into the Environment.
Destruction/Disposal:	Dispose of in accordance with relevant local regulations

Contaminated packaging

Decontamination/cleaning:	Cleaning is not required prior to disposal.
Destruction/Disposal:	

Note: Take all necessary precautions when disposing of this product according to local regulations.

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SECTION 14. TRANSPORT INFORMATION

UN Number:	None
UN Shipping Name:	None
Transport Hazard Class:	Not classified as dangerous for transport
Land (rail/road):	Material is not restrictive for land transport and is not regulated by ADR/RID
Sea:	Material is not restrictive for sea transport and is not regulated by IMO/IMDG
Air:	Material is not restrictive for land transport and is not regulated by ICA/IATA
Marine Pollutant:	No
Transport/Additional Information:	Not regulated for US DOT Transport in non-bulk containers This material is not dangerous or hazardous
Special Precautions for User:	None known

The above regulatory prescriptions are those valid on the date of publication of this sheet. However, given the possible evolution of transport regulations for hazardous materials and in the event of the MSDS in your possession dating back more than 12 months, it is advisable to check their validity with your sales office.

SECTION 15. REGULATORY INFORMATION

Labeling:

EC regulations:	This product does not need to be labeled in accordance with EC Directives or respective national laws

Further regulations

United Kingdom:	Handle in accordance with relevant British regulation: control of substance Hazardous to Health Regulations Environmental Hygiene Guidance: EH40 Workplace Exposure Limits (revised annually)
Korea regulations:	Industrial safety and hygiene regulation: No Hazardous material control regulation: No Fire prevention regulation: No

Other regulations:

EINECS inventory status:	Citrus Grandis Fruit Extract:	289-904-6
TSCA inventory status:	Exempt	
AICS inventory status:	90045-43-5	
Canadian (CEPA DSL) inventory status:	Listed as Grapefruit, ext. (DSL)	
Japan (MITI list):	Citrus Grandis (Grapefruit) Fruit Extract	
Korea:	Citrus Grandis (Grapefruit) Fruit Extract	

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Other regulations (Continued):

China inventory status:	Citrus Grandis (Grapefruit) Fruit Extract
Philippines inventory status:	Listed as Grapefruit, ext.

*Listed on 2010 INCI Standard Chinese Name Directory

Note: The regulatory information given above only indicates the principal regulations specifically applicable to the products described in this sheet. The user's attention is drawn to the possible existence of additional provision which complete these regulations. Please refer to all applicable international, national and local regulations and provisions

SECTION 16. OTHER INFORMATION

Prohibited uses:	For specific uses, food industry, ask the manufacturer for more information.
Last Revision Date:	08/11/2014
Preparation Date:	03/30/2015
MSDS summary of changes	- Updated Transport Information – Section 14 (Transport Information)

The information given is based on our knowledge of this product, at the time of publication in good faith. The attention of the user is drawn to the possible risks incurred by using the product for any other purpose other than which it was intended. This is not in any way excuse the user from knowing and applying all the regulations governing their activity. It is sole responsibility of the user to take all precautions required in handling the product. The purpose of mandatory regulation mentioned is to help the user to fulfill his obligations regarding the use of products. This information is not exhaustive, this is not exonerate the user from ensuring that legal obligations other than those mentioned, relating to the use and storage.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 22, 2015

SUBJECT: HRIPT Product Containing Citrus Limon (Lemon) Fruit Water

Consumer Product Testing Co. 2005. Repeated insult patch test of a skin cleansing product containing 1% Citrus Limon (Lemon) Fruit Water

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

Consumer Product Testing Co.

EST. 1975

FINAL REPORT

CLIENT:

ATTENTION:

TEST: Repeated Insult Patch Test
Protocol No.: 1.01

TEST MATERIAL: 2005.251.001

Skin cleansing product containing 1% Citrus Limon (Lemon) Fruit Water

EXPERIMENT REFERENCE NUMBER: C05-0648.02

Richard R. Eisenberg, M.D.
Board Certified Dermatologist

Joy Frank, R.N.
Executive Vice President, Clinical Evaluations

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

Consumer Product Testing Co.
ESTABLISHED 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: C05-0648.02

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of clinical laboratory studies. These studies have been performed with adherence to the applicable ICH Guideline E6 for Good Clinical Practice and requirements provided for in 21 CFR parts 50 and 56 and in accordance to standard operating procedures and applicable protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study. All data pertinent to this study will be stored in the Consumer Product Testing Company archive, unless specified otherwise, in writing by the Sponsor.

Quality Assurance personnel involved:

Gaynel Stutzbach 10/4/05

Quality Assurance Date

The representative signature of the Quality Assurance Unit signifies that this study has been performed in accordance with standard operating procedures and study protocol as well as government regulations regarding such procedures and protocols.

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234
Clinical • Toxicology • Analytical Chemistry • Microbiology

Objective: To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.

Participants: One hundred fifteen (115) qualified subjects, male and female, ranging in age from 16 to 79 years, were selected for this evaluation. One hundred two (102) subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

a. Male and female subjects, age 16[a] and over.
b. Absence of any visible skin disease which might be confused with a skin reaction from the test material.
c. Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.
d. Completion of a Medical History form and the understanding and signing of an Informed Consent form.
e. Considered reliable and capable of following directions.

Exclusion Criteria:

a. Ill health.
b. Under a doctor's care or taking medication(s) which could influence the outcome of the study.
c. Females who are pregnant or nursing.
d. A history of adverse reactions to cosmetics or other personal care products.

Test Material: 2005.251.001

Study Schedule:

Panel #	Initiation Date	Completion Date
20050391	August 10, 2005	September 23, 2005
20050393	August 10, 2005	September 23, 2005

[a]With parental or guardian consent

Methodology:

Prior to the initiation of this study, the test material was prepared as a 1% dilution, using distilled water.

The upper back between the scapulae served as the treatment area. Approximately 0.2 ml of the test material, or an amount sufficient to cover the contact surface, was applied to the 3/4" x 3/4" absorbent pad portion of an adhesive dressing*. This was then applied to the appropriate treatment site to form an occlusive patch.

Induction Phase:

Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period. It was noted that due to a holiday weekend, which occurred during the Induction Phase, subjects who required a makeup day experienced a delay between applications.

With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications are discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted.

Rest periods consisted of twenty-four hours following each Tuesday and Thursday removal, and forty-eight hours following each Saturday removal.

Challenge Phase:

Approximately two (2) weeks after the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic twenty-four and seventy-two hours post-application.

*Manufactured by TruMed Technologies, Inc., Burnsville, MN

Evaluation Key:

0 = No visible skin reaction
+ = Barely perceptible or spotty erythema
1 = Mild erythema covering most of the test site
2 = Moderate erythema, possible presence of mild edema
3 = Marked erythema, possible edema
4 = Severe erythema, possible edema, vesiculation, bullae and/or ulceration

Results:

The results of each participant are appended (Table 1).

Observations remained within normal limits throughout the test interval.

Summary:

Under the conditions of this study, test material, 2005.251.001, did not indicate a clinically significant potential for dermal irritation or allergic contact sensitization.

Table 1
Panel #20050391

Individual Results

2005.251.001

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	----------DID NOT COMPLETE STUDY----------											
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	+	+[D]	+	+	1	2[A]	2[X]	-	0	0
17	0	0	0	0	0	0	0	+	+	+	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	---DNC---	
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	----------DID NOT COMPLETE STUDY----------										
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
DNC = Did not complete study
A = Changed to adjacent site
D = Dryness
X = Patching discontinued

Table 1
(continued)
Panel #20050391

Individual Results

2005.251.001

Subject Number	Induction Phase									Virgin Challenge Site	
	24*hr	1	2	3	4	5	6	7	8	9	24*hr	72 hr
30	0	0	0	DID NOT COMPLETE STUDY								
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	DID NOT COMPLETE STUDY											
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	DID NOT COMPLETE STUDY											
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	DID NOT COMPLETE STUDY									
42	0	0	0	0	0	0	0	+	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	DID NOT COMPLETE STUDY										
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	DID NOT COMPLETE STUDY											
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	DID NOT COMPLETE STUDY											
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	DID NOT COMPLETE STUDY						
59	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch

Table 1
(continued)
Panel #20050393

Individual Results

2005.251.001

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	DID NOT COMPLETE STUDY							
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	1	1	1	1	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch

Table 1
(continued)
Panel #20050393

Individual Results

2005.251.001

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	DID NOT COMPLETE STUDY									
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	+	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch

Table 2
Panel #20050391

Subject Data

Subject Number	Initials	Age	Sex
1	RC	27	F
2	JE	48	F
3	EP	38	M
4	KP	39	F
5	LG	58	F
6	DH	42	F
7	GL	58	F
8	AD	55	M
9	PM	57	F
10	JS	65	M
11	RM	67	M
12	JE	55	M
13	ER	61	M
14	MB	75	F
15	MB	73	F
16	LB	57	F
17	GB	53	M
18	SB	68	F
19	WB	71	M
20	MT	34	F
21	SL	64	M
22	DD	69	F
23	WH	39	M
24	JP	61	F
25	JA	33	F
26	RM	55	F
27	AK	75	M
28	HP	75	F
29	RV	61	M

Table 2
(continued)
Panel #20050391

Subject Data

Subject Number	Initials	Age	Sex
30	RT	18	M
31	MD	77	F
32	RL	48	F
33	AM	36	F
34	JT	70	M
35	JT	57	F
36	GM	59	F
37	CP	46	F
38	ED	79	F
39	TD	74	M
40	MB	58	F
41	RB	57	M
42	JV	66	F
43	AK	55	M
44	SB	39	F
45	DH	35	M
46	RC	53	F
47	BM	32	F
48	HG	31	F
49	JF	66	M
50	BF	34	F
51	LS	28	F
52	DW	43	F
53	RD	67	F
54	RL	65	M
55	LB	41	F
56	RS	21	F
57	AS	67	F
58	MS	53	F
59	FR	44	M

Table 2
(continued)
Panel #20050393

Subject Data

Subject Number	Initials	Age	Sex
1	LG	64	M
2	AK	45	F
3	RM	43	F
4	VT	39	F
5	KL	40	F
6	ND	36	M
7	BA	39	F
8	SF	53	F
9	MM	58	M
10	EG	55	F
11	AG	22	M
12	VV	16	M
13	HG	72	M
14	MA	16	F
15	VA	51	M
16	GD	49	F
17	CD	25	F
18	JG	54	F
19	MV	42	F
20	JM	24	F
21	CN	63	F
22	AB	62	M
23	JM	68	F
24	IV	72	F
25	AD	55	M
26	RD	70	M
27	LZ	43	F
28	FS	21	M
29	AD	53	F

Table 2
(continued)
Panel #20050393

Subject Data

Subject Number	Initials	Age	Sex
30	GS	76	F
31	JD	21	M
32	VD	73	F
33	AD	69	M
34	RW	49	M
35	AL	77	F
36	JM	44	M
37	RC	20	M
38	MG	66	F
39	LS	40	F
40	JD	59	F
41	LV	72	F
42	GN	36	F
43	EM	29	F
44	AM	60	F
45	RF	35	F
46	HP	75	F
47	JF	70	F
48	TM	52	F
49	DC	64	F
50	MC	30	F
51	DC	18	F
52	MC	39	F
53	AC	57	F
54	EF	76	F
55	EV	65	F
56	CW	75	F

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 28, 2015

SUBJECT: HRIPTs: Product containing Citrus Grandis (Grapefruit) Fruit Extract; Product Containing Citrus Aurantium Dulcis (Orange) Fruit Water

Product Investigations, Inc. 2006. Determination of the irritating and sensitizing propensities of a toner containing 0.16% Citrus Grandis (Grapefruit) Extract.

TKL Research. 2010. Repeated insult patch test of an eye gel containing 38% Citrus Aurantium Dulcis (Orange) Fruit Water.

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

PRODUCT INVESTIGATIONS, INC.

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

REPORT: PII N!! 20905

DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF

Citrus Grandis (grapefruit) fruit extract 0.16% toner on Human Skin

PREPARED FOR

[redacted]

11 July 2006

PRODUCT INVESTIGATIONS, INC.

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

HUMAN REPEAT INSULT PATCH TEST
SUMMARY

Citrus Grandis (grapefruit) fruit extract 0.16% toner

Study N° (Centre) 06137 [redacted]

Report N° 20905

Study Objective: The main objective of this study is to confirm that the application of the product under the test conditions does not induce delayed contact allergy.
Secondarily the potential irritant effect of the product may be evaluated during the induction phase of the protocol.

Method: Study under dermatological supervision.
Induction: Patches applied on the back, 3 times each week for 3 weeks (total of nine patches). Patches applied for 24 hours.
Rest phase: 14 Days.
Challenge: one 24-hour patch on a virgin site.
Skin Grading: Induction: Immediately after first patch removal and just before each subsequent patch application, and 48 hours after patch #9 removal.
Challenge: Immediately, 48 and 72 hours after patch removal and further if necessary.

Investigator: Morris V. Shelanski, MDCM

Number of subjects: 220 enrolled, 206 completed

Panel description: Male and female subjects ages 18 to 70 years.

Conclusion

Non-sensitizing ☑
Sensitizing ☐

Non-irritating ☑
Irritation acceptable (normal) for product type ☐
Irritation higher than normal for product type ☐

Additional data needed ☐

2 August 2006
Date

Morris Shelanski, MD.CM.
Investigator

TABLE OF CONTENTS

ABSTRACT

A sample identified as Citrus Grandis (graprefruit) fruit extract 0.16% toner was received by Product Investigations on 19 May, 2006. The product was submitted by [redacted] for a patch test to determine whether it possesses any skin-irritating and/or sensitizing potential.

To accomplish this, Product Investigations initiated a repeated insult patch test study on two-hundred and twenty adult volunteers.

The regimen called for nine twenty-four hour applications of the product, i.e. on Mondays, Wednesdays and Fridays during the first three weeks and a single twenty-four hour challenge application on a naive site on Monday of the sixth week. The routine was altered during week 2 due to the Memorial Day Holiday (c.f. Protocol Deviations).

During the induction phase, the skin was examined and graded when the patch was removed on Tuesday of week 1, again just prior to each subsequent application, and on Monday of Week 4. During the challenge phase, the skin was first examined shortly after the patch was removed on Tuesday. Follow-up examinations were conducted Wednesday, Thursday, and Friday.

Data were acquired on two-hundred and fourteen subjects during the Induction Phase of the regimen. No significant adverse effects were detected on any of the subjects.

Data were acquired on two-hundred and six subjects during the Challenge or Diagnostic Phase of the regimen. No significant adverse effects were detected on any of the subjects.

On the basis of the above-cited observations, Citrus Grandis (graprefruit) fruit extract 0.16% toner was found to possess neither clinically significant skin-irritating nor skin-sensitizing propensities.

The investigator concluded that the data do not contraindicate exposure of the skin to Citrus Grandis (graprefruit) fruit extract 0.16% toner for usages entailing repeated applications commensurate with those that prevailed during the course of this study.

COMPLIANCE WITH GOOD QUALITY ASSURANCE STANDARDS

In my review of the data I have found no discrepancies between the information presented in this report and the records that were kept during the conduct of this study.

Date 7/11/06

Samuel J. Charles III
Director, Quality Assurance

DETERMINATION OF THE IRRITATING AND SENSITIZING PROPENSITIES OF

Citrus Grandis (grapefruit) fruit extract 0.16% toner on Human Skin

1.00 OBJECTIVES:

.01 To determine whether Citrus Grandis (graprefruit) fruit extract 0.16% toner is capable of causing visible skin damage under the conditions of the regimen used in this patch test procedure.

.02 To adjudge whether the skin-damaging capability such as the test material manifests can be attributed to an Irritant or sensitizing activity.

.03 To adjudge whether the data acquired in the study population provide an adequate level of confidence in the safety of the appropriate use of the test material by any consumer population.

2.00 SPONSOR: [redacted]

Project Director: [redacted]

Authorization: Dispatch Note dated 17 May, 2006 from [redacted]

3.00 FEATURES OF THE METRO D:

.01 A modified version of the Repeated Insult Patch Test regimen was conducted under double blind conditions on a panel consisting of more than two-hundred subjects at the outset.

.02 The induction regimen called for applications of twenty-four hour durations on Mondays, Wednesdays and Fridays during Weeks Nos. 1, 2, and 3.

.03 The induction regimen called for examinations to be conducted within moments after removal of the first set of applied patching devices on Tuesday and just prior to subsequent applications of the product throughout the remainder of the Initial/Induction Phase. During this phase, the responses that were in evidence just prior to a scheduled application mandated whether applications were to be continued on the same site, switched to a new site, or terminated.

.04 The challenge regimen called for a single application of twenty-four hours duration on a naive site on Monday ofWeek 6. Post-application examinations were conducted within moments after removal of the patching devices on Tuesday and, subsequently, on Wednesday, Thursday, Friday, and the following Monday.

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

4.00 STUDY PRODUCT:

Product Information:	Facial Toner
SampleN:	Citrus Grandis (graprefruit) fruit extract 0.16% toner
[redacted]	[redacted]
Date ofReceipt:	19 May, 2006
Form used in study:	neat
PIN:	20905

5.00 SITE OF STUDY:

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

STAFF:

Medical Director:	Morris V. Shelanski, MDCM
Dermatologist:	Clinton E. Prescott Jr. MD
Dir. Derm. Studies:	Joseph E. Nicholson III
Chief Technician:	Lisa Cortez
Quality Assurance:	Samuel J. Charles III

6.00 DATES OF STUDY: Start: 22 May, 2006 Finish: 30 June, 2006

7.00 SELECTION OF SUBJECTS:

.01 RECRUITING:

Individuals interested in participating were recruited from local areas by telephone, flyers, and direct contact.

.02 INFORMED CONSENT:

Individuals who expressed interest in participating were given an informed consent document to read and, after they professed to have a thorough understanding of its contents and were still intent on participating, to sign. This document presented the following information:

a. The number of people that were to be enrolled in the study;
b. the intended use of the product;
c. why the product was being tested;
d. how the test was to be performed;
e. that the regimen was not intended to benefit a subject's health, well being, or quality of life.
f. The different ways that participation may be detrimental to a subject's health, well being, or quality of life.
g. that not all detrimental effects could be foreseen and made known at the time the informed consent was presented for the prospective subject's signature.
h. the commitments which a subject would have to make to ensure that meaningful data would be generated;
i. the responsibilities which a subject would assume in care of the product.
j. the rights endowed on a subject for her/his protection;
k. the avenues of recourse available to a subject who believes that she/he has been misused; and
l. the considerations a subject was entitled to receive and the conditions for receiving them.

.03 DETERMINATION OF ELIGIBILITY:

An individual's eligibility was determined by checking her/his medical history and the answers given in response to specific questions in the informed consent document against the criteria listed below.

a. Inclusion Criteria: Satisfaction of all the following items was obligatory for enrolment:
   1) The candidate was between eighteen (18) and seventy (70) years of age inclusive, and
   2) agreed to comply fully with the scheduled study regimen, and
   3) expressed awareness that a participant would incur risks that would affect her/his well-being, and
   4) denied that the stipend had induced her/him to volunteer against her/his better judgement, and
   5) had assured the interviewer that she/he had read the informed consent form and had no questions about the informed consent's contents that had not been answered to her/his satisfaction, and
   6) had signed the consent form willingly and without reservation.
   7) was not participating in any other clinical trials.

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

.04 PANEL No.06137:

a. Dedication: The subjects in Panel No. 06137 were engaged exclusively in the studies of products submitted by [redacted]

8.00 SITE INFORMATION:

.01 LOCATION:

Citrus Grandis (graprefruit) fruit extract 0.16% toner was assigned Band #2 on the right side of the back of each subject.

.02 IDENTIFICATION OF A CONTACT SITE:

The skin around the contact site in current use was marked at each visit. These markings enabled the technicians to locate the site for examinations and for positioning subsequently-applied devices as precisely as was feasible on the previously contacted skin in the absence of the device or other means of identification.

9.00 PATCHING DEVICES:

.01 TYPE OF DEVICE:

Occlusive patching devices were used to convey the product to the skin and to maintain it on its assigned site on each subject. These devices consisted of a 2cm x 2cm absorbent pad centered on the adhesive-coated surface of a 4cm x 4cm water-impermeable plastic film.

.02 PREPARATION OF A PATCHING DEVICE:

a. Approximately 0.15 ml of the product was spread uniformly over the surface of the pad of a patching device.

.03 POSITIONING AND REMOVING A PATCHING DEVICE:

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

10.00 DATA ACQUISITION:

.01 GRADING PROCEDURE:

a. As each subject came in on a scheduled examination day, the technician examined the skin of the contact site.

   i. If no adverse effect was detected, a "0" was recorded in the subject's examination record.
   ii. If an adverse effect was detected, the technician entered a grade indicating her assessment of the response's intensity.

b. The subject was then sent into the patching room where the site was examined again by a second technician to ascertain independently whether or not the site should be used again. If she disagreed with the first technician's assessment, the application was held in abeyance until the issue could be resolved with the help of the supervisor and/or the investigator.
c. The supervisor or the investigator was called when a disagreement had to be resolved and when responses had to be validated, e.g. responses assigned grades ::-2 or responses showing a decrease ::-2 from the previous value.

.02 CRITERIA FOR GRADING RESPONSE INTENSITY:

Grades were assigned in accordance with the following criteria to designate the intensity of the effects elicited on the skin by the test material.

Morphology	Visible Change	Grade
Preclinical Stage	None	0
Inflammation		
Vascular Dilation:	Faint redness with poorly defmed margins	1
	Redness with well-defined margins	2
Infiltration:	Redness plus well-defmed edema	3
	Redness plus papules, vesicles or ulceration	4
	Extension beyond the contact area	5

.04 SITE CHANGES:

a. Switch to a Naive Site:
   i. A grade 2 response appearing for the first time on a subject mandated switching the next application to a naive contact site immediately.

b. Discontinuation of Applications:
   i. A grade 2 response appearing for the second time on a subject mandated immediate termination of applications for the remainder of the induction phase on the affected subject.
   ii. A grade 3 response appearing on a subject mandated immediate termination of applications for the remainder of the induction phase on the affected subject.

11.00 REGIMEN FLOW CHART·

	Monday	Tuesday	WP Jn Jov	Thursday	Friday	Saturday	Sunday
Week#!	Applied	Removed/Graded	Graded/Applied	Removed in clinic	Graded/Applied	Removed at home	–
Week#2	Holiday	Graded/Applied	Rem/Grade/Apply	Removed in clinic	Graded/Applied	Removed at home	–
Week#3	Graded/Applied	Removed in clinic	Graded/Applied	Removed in clinic	Graded/Applied	Removed at home	–
Week#4	Graded	–	–	–	–	–	–
Week #6	Applied naive site	Removed/graded	Graded	Graded	Graded-	–	–
~~Week#7~~	–	–	–	–	–	–	–

12.00 INSTRUCTIONS BEFORE INTERRUPTIONS IN THE REGIMEN

.01 WEEKENDS:

Before being dismissed for the weekends during Weeks 1, 2, and 3, subjects were given instructions to remove their patch at home on Saturday at a specified time, record the time of removal on the provided form, and notify the investigator without delay if the skin showed any of the following changes:

a. a substantial increase in the intensity of an already-elicited response,
b. the spread of a response beyond the area of contact, or
c. the outbreak of a rash on a hitherto unaffected site.

.02 INTERMEDIATE PHASE:

Before being dismissed for the hiatus between the phases the subjects were instructed to notify the investigator without delay if the skin showed any of the changes listed above.

13.00 REGIMEN:

.01 INITIAL/INDUCTION PHASE:

Week#1:

MONDAY:

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

TUESDAY:

i. As each subject returned, the site-identifying marks were reinforced.
ii. The device was removed by a technician.
iii. The contact site was examined; skin status was graded; the grade was recorded.
tv. The subject was instructed to return on Wednesday.

WEDNESDAY:

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

THURSDAY:

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

FRIDAY:

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

Week #2 and Week #3:

MONDAY(Week2): Memorial Day Holiday
TUESDAY (Week2) and MONDAY (Week3):

i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. The time at which the device was removed on Saturday was recorded.
iii. A freshly-prepared device was applied.
iva. The site-identifying marks were reinforced and the subject was instructed to return on Wednesday (Wk .2).
ivb. The site-identifying marks were reinforced and the subject was instructed to return on Tuesday (Wk. 3).

TUESDAY (Week3):

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

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

THURSDAY:
i. As each subject returned, the site-identifying marks were reinforced.
ii. The device was removed by a technician and the subject was dismissed with instructions to return on Friday.

FRIDAY:
i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. A freshly-prepared device was applied.
iii. The site-identifying marks were reinforced.
iv. The subject was dismissed with the standard instructions and told to return on the following Tuesday.

Week#4:

MONDAY:
i. As each subject returned, the skin of the contact site was graded. The grade was recorded.
ii. The time at which the patch was removed on Saturday was recorded.
iii. a) If the subject had undergone all nine induction applications, she/he received instructions to:
i) report back to the clinic on the following Monday to receive the challenge applications, and
ii) notify the investigator without delay should any significant changes occur in the skin of the contact site.
b) If the subject had not received nine induction applications and was deficient without a valid reason, applications were continued.

.02 HIATUS/MAKE UP PHASE-

Week #4 and Week #5:

After the examination on Monday, no procedures were scheduled for the remainder of this week except make-up applications and examinations.

.03 CHALLENGE PHASE-

Week#6:

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

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

WEDNESDAY:
i. As each subject returned, the skin of the contact site was graded; the grade was recorded.
ii. The subject was instructed to return on Thursday.

THURSDAY:
i. As each subject returned, the skin of the contact site was graded; the grade was recorded.
ii. The subject was instructed to return on Friday.

FRIDAY:
i. As each subject returned, the skin of the contact site was graded; the grade was recorded.
ii. The subject was dismissed unless follow-up treatment or examination was indicated, in which case, he/she was instructed to return on the following Monday.

.04 FOLLOW-UP PHASE:

Week #7 and Week #8:

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

14.00 TABULATION OF CYCLES COMPLETED:

Table Ia

INITIAL/INDUCTION PHASE - (Weeks I, 2, 3 and 4)					
NUMBER OF AECs REQUIRED	NO DATA ACQUIRED		DATA ACQUIRED		
	DROPOUTS	EXCUSED	EXCUSED	NON-COMPLIANT	COMPLIANT
9	6 subjects	0 subjects	0 subjects	8 subjects	206 subjects

Table Ib.

CHALLENGE/DIAGNOSTIC PHASE - (WEEK 6)					
NUMBER OF AECS REQUIRED	NO DATA ACQUIRED		DATA ACQUIRED		
	DROPOUTS	EXCUSED	EXCUSED	NON-COMPLIANT	COMPLIANT
I	14 subjects	0 subjects	0 subjects	0 subjects	206 subjects

15.00 SUMMARY OF RESULTS:

Table II: Maximum Assigned Grades per Individual Participant (MAGPIPs)

GRADE	TYPE OF RESPONSE	INDUCTION	CHALLENGE
0	NO VISIBLE CHANGE	214 SUBJECTS	206 SUBJECTS
1	FAINT REDNESS, UNDEFINED BORDER	0 "	0 "
2	MODERATE REDNESS, DEFINED BORDER	0 "	0 "
3	REDNESS + EDEMA	0 "	0 "
4	REDNESS + DEFINITE EDEMA and/or PAPULES	0 "	0 "
	NUMBER OF RESPONDERS	0 SUBJECTS	0 SUBJECTS
	NUMBER OF SUBJECTS PATCHED	220 "	206 "
	NUMBER OF SUBJECTS PROVIDING DATA	214 "	206 "
	NUMBER PROVIDING NO DATA	6 "	14 "

Table III: WEEKLY INCIDENCE OF RESPONSES•

WeekN£	I			2			3			4			6			7
GRADE	M	T	W-F	T	W	F	M	W	F	M	W	F	M	T	W-F	M
I	B	0	0	0	0					0						
2	B	0	0	0	0	0	0	0	0	0	0		B	0	0	
3	B	0	0	0	0	0	0	0	0	0	0		B	0	0	
4		0	0	0	0	0	0	0	0	0	0			0	0	–
TOTAL		0	0	0	0	0	0	0	0	0	0			0	0	–

16.00 PROTOCOL DEVIATIONS:

Monday of week 2 was the Memorial Day Holiday. The patch scheduled for that day was applied on Tuesday and removed and the effect graded on Wednesday. A fresh patch was applied immediately without the usual24 hour hiatus.

17.00 SIGNIFICANCE OF THE RESPONSES:

.01 INITIAL/Induction PHASE:

No responses were noted on any of the 214 subjects who participated in this phase of the study. The absence of responses characterize the product as one that is devoid of clinically significant skin irritating propensities.

.02 CHALLENGE PHASE:

No responses were noted on any of the 206 subjects who participated in this phase of the study. The absence of responses characterize the product as one that is devoid of clinically significant skin sensitizing propensities.

.03 FOLLOW-UP PHASE:

The investigator received no communications from any of the subjects during this period that provided a basis for altering his opinion concerning the safety of the test material.

18.00 CLINICAL RELEVANCE:

.01 Inasmuch as the test product proved to be incapable of eliciting persistent skin damage of any substantial degree, a projection can be made with a 95% level of confidence that the incidence of clinically significant skin damage that will be occasioned by the appropriate use of this product will be very low.

.02 This projection is based on these postulates:

a. The regimen which the test product has undergone has proven itself to be one that affords products ample time and opportunity to exercise any latent propensities for eliciting gross skin changes.
b. The regimen imposed a substantially greater degree of stress on the skin than the appropriate daily use of the test product would call for.

19.00 CONCLUSIONS:

.01 Sample Citrus Grandis (graprefruit) fruit extract 0.16% toner was found to be neither a significant skin irritant nor a skin sensitizer.

.02 The data do not contraindicate exposure of the skin to the product represented by the sample identified as Citrus Grandis (graprefruit) fruit extract 0.16% toner for usages entailing repeated applications commensurate with those that prevailed during the course of this study.

PRODUCT INVESTIGATIONS, INC.

Morris V. Shelanski, MD.CM.
Investigator

Date

TKL RESEARCH

REPEATED INSULT PATCH TEST

TKL STUDY NO. DS101410/102210-3

[redacted]

Eye gel containing 38%
Citrus Aurantium Dulcis (orange)
Fruit Water

CONDUCTED FOR:

[redacted]

DATE OF ISSUE:

April29, 2010

III TKL Clinical Trials Division II TKL Clinical Site Division III TKL Recruitment Management Division
Corporate Office: 365 W. Passaic Street, Rochelle Park, NJ 07662 Phone: 201•587•0500 www.tklresearch.com

TABLE OF CONTENTS

APPENDICES

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

Jonathan S. Dosik, MD
Dermatologist
Principal Investigator

Date 4/29/10

Kathleen Georgeiall
Director, Dermatologic Safety Testing

Date 4/28/10

Michelle Medina
Clinical Research Coordinator

Date

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

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[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on ▌May 1996.

TITLE OF STUDY

Repeated Insult Patch Test

SPONSOR

[redacted]

STUDY MATERIAL

Citrus Aurantium Dulcis (orange) fruit water 38% Eye Gel

DATE STUDY INITIATED

February 22, 2010

DATE STUDY COMPLETED

April 8, 2010

DATE OF ISSUE

April 29, 2010

INVESTIGATIVE PERSONNEL

Jonathan S. Dosik, MD - Dermatologist
Principal Investigator

Kathleen Georgeian
Director, Dermatologic Safety Testing

Michelle Medina
Clinical Research Coordinator

CLINICAL SITES

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4 Forest Avenue
Paramus, NJ 07652

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Bloomfield NJ 07003

SUMMARY

One (1) study material, Citrus Aurantium Dulcis (orange) fruit water 38% Eye Gel, was evaluated neat to determine its ability to sensitize the skin of volunteer subjects with normal skin using an occlusive repeated insult patch study. Two hundred fourteen (214) subjects completed the study.

One subject on DS102210 showed definite erythema, no edema and damage to epidermis (+D) at the 5th Induction reading to the product. The subject was patched with the product at a new site following the reaction. The subject showed no reaction (-) at the new site for the rest of the Induction phase and also showed no reaction (-) at Challenge.

Under the conditions employed in this study, there was no evidence of sensitization to Citrus Aurantium Dulcis (orange) fruit water 38% Eye Gel.

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 200 completed subjects. In the absence of any sensitization reactions in this sample size (200 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. were males or females, 18 to 70 years of age, in general good health;
2. were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;
3. were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. had completed a medical screening procedure; and
5. had read, understood, and signed an informed consent agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. had psoriasis and/or active atopic dermatitis/eczema;
4. were females who were pregnant, planning to become pregnant during the study, or breast-feeding;
5. had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated; and/or
6. were participating in another study or had been recruited to participate in another study concurrently.

3.1.3 Informed Consent

A properly executed informed consent document was obtained from each subject prior to entering the study. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2] Following the ninth evaluation, the subjects were dismissed for a rest period of approximately 10-15 days.

Subjects who were absent once during the induction phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during induction, and a single application and 2 readings during challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1*	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK 2

DAY	ACTIVITIES
1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK 3

DAY	ACTIVITIES
1-6	Same as Week 2

WEEK 4

DAY	ACTIVITIES
1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU patches
3	Staff graded MU induction sites at MU visit
2-7	Rest period

WEEK 5

DAY	ACTIVITIES
1-7	Rest period

* Study flow starting with Week 1, Day 1, was altered when enrollment occurred on Wednesday or Friday. Study flow could be altered if a holiday occurred during the study.

WEEK 6

DAY	ACTIVITIES
1	Staff applied patches
2	Subject removed patches
3	Staff graded sites
4	Staff graded sites

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

SYMBOL		REACTION
-	=	No reaction
?	=	Minimal or doubtful response, slightly different from surrounding normal skin
+	=	Definite erythema, no edema
++	=	Definite erythema, definite edema
+++	=	Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E	=	Marked/severe erythema
S	=	Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p	=	Papular response > 50%
pv	=	Papulovesicular response > 50%
D	=	Damage to epidermis: oozing, crusting and/or superficial erosions
I	=	Itching
X	=	Subject absent
PD	=	Patch dislodged
NA	=	Not applied
NP	=	Not patched (due to reaction achieved)
N9G	=	No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification: Citrus Aurantium Dulcis (orange) fruit water 38% Eye Gel
Amount: 0.2 g
Special Instructions : Volatilized for 30 minutes prior to patch application.

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material was kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the sponsor. Material was applied in an amount proportionate to the patch type or as requested by the sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patches are secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad. The pads are affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the challenge phase of a Repeated Insult Patch Test (RIPT) than that seen during induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch

site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the challenge phase is generally similar to that seen during induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred rechallenge procedure involves the application of the product to naïve sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, adverse events, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the sponsor's review on the premises of TKL.

7.0 RESULTS AND DISCUSSION

Two hundred thirty-four (234) subjects between the ages of 18 and 70 were enrolled and 214 subjects completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II).

The following table summarizes subject enrollment and disposition.

Number enrolled:		234
Number discontinued:		20
Lost to follow-up:	5	
Voluntary withdrawal:	14	
Protocol violation: (Psoriasis)	1	
Number completed:		214

Source: Table 1, Appendix I

There were no adverse events reported on either study.

One subject (No. 082) on DS102210 showed definite erythema, no edema and damage to epidermis (+D) at the 5th Induction reading. The subject was patched with the product at a new site following the reaction. The subject showed no reaction (-) at the new site for the rest of the Induction phase and also showed no reaction (-) at Challenge.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3 and residual readings in Data Listing 3A, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to Citrus Aurantium Dulcis (orange) fruit water 38% Eye Gel.

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

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Zhai H, Maibach HI. Dermatotoxicology. 6th ed. New York:Hemisphere, 1996.

Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980: 41-53.

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Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

[redacted]

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 12, 2015

SUBJECT: Comments on the Draft Report Prepared for the March 16-17, 2015 CIR Expert Panel Meeting: Safety Assessment of Citrus Fruit-Derived Ingredients as Used in Cosmetics

Key Issues

Chemistry - It is not clear why the published literature was not searched for composition information. Certainly information on the composition of the juice of major citrus species used as beverages can be found and included in this report. For example, the following reference (attached) may be helpful.

Selli S, Cabaroghu T, Canbas A. 2004. Volatile flavour components of orange juice obtained from the cv. Kozan of Turkey. J of Food Composition and Analysis 17: 789-796.

As all of the oils included in this report are volatile oils, it is not clear why fixed oils are mentioned in the Chemistry section. It would be helpful if the Chemistry section would mention all of the types of preparations included in this report.

Somewhere in the report, it would be helpful to state which of the species included in this report are not used as food.

The report needs to acknowledge that there are alternative genus species names that can be used for the same species. One example is orange, the Dictionary uses both *Citrus aurantium dulcis* and *Citrus sinensis* for orange.

Additional Comments

The following ingredient have not yet been included in a concentration of use survey:

Citrus Grandis (Grapefruit) Fruit/Peel Water
Citrus Iyo Fruit Water
Citrus Tamurana Fruit Extract

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

Defatted Citrus Unshiu Fruit
Hydrolyzed Citrus Aurantium Dulcis Fruit Extract

Cosmetic Use - Please state the specific product category in which 0.0038% Citrus Japonica Fruit Extract was reported to be used.

Summary - Please correct "nigh skin care products"

Table 3 - Please indicate the ingredients in which the constituents listed in this table may be found.

Table 5 - Why is the format of the first two pages of Table 5 different than the format of the last two pages of this table?

Table 7, Reference 17 - Please revise "after48h after irradiation"

Table 8, Reference 18 - It is not clear what happened "for at least 15 min in duration"

Reference 24 - Please correct "rah on right thigh"

Reference 26 - Please revise (occurs in two places): "patient presented 5 days after squeezing lime juice with large blisters" (it would be clearer if it stated "5 days after squeezing limes, the patient presented with large blisters..."). Please correct "equivalent to ba burn"