Safety Assessment of Citrus-Derived Peel Oils as Used in Cosmetics

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The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Christina Burnett, Senior Scientific Analyst/Writer and Monice Fiume, Senior Scientific Analyst/Writer.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: May 16, 2014
Subject: Draft Report on Citrus Peel Oil-Derived Ingredients

At the March 2014 meeting, the Panel tabled further discussion of 198 citrus-derived ingredients to allow CIR staff to reorganize the report and to obtain clarification from the Research Institute for Fragrance Materials (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 will focus on all citrus-derived peel oils.

Citrus limon (lemon) peel oil has the most reported uses in cosmetics and personal care products, with a total of 490; more than half of the uses are in leave-on skin care preparations. The range of highest maximum use concentrations for citrus limon (lemon) peel oil is 0.0001% to 0.5%, with 0.5% reported in "other" skin care preparations. Citrus aurantium dulcis (orange) peel oil (reported as citrus sinensis (sweet orange) peel oil to the VCRP) has the second greatest number of overall uses reported, with a total of 289; about half of those uses are in leave-on skin care preparations. Citrus aurantium dulcis (orange) peel oil had a highest maximum use concentration range of 0.00002% to 29%, with 29% reported in non-coloring hair conditioners.

Since the March meeting, we have yet to receive clarification from RIFM on the fragrance use of these ingredients. Of the 16 ingredients in this report, 5 ingredients are reported in the Dictionary as solely functioning as fragrances. Additionally, no other data have been received. Comments that were relevant to the reorganized report received from the Council prior to the March meeting have been considered. The comments are available for your review in this report package.

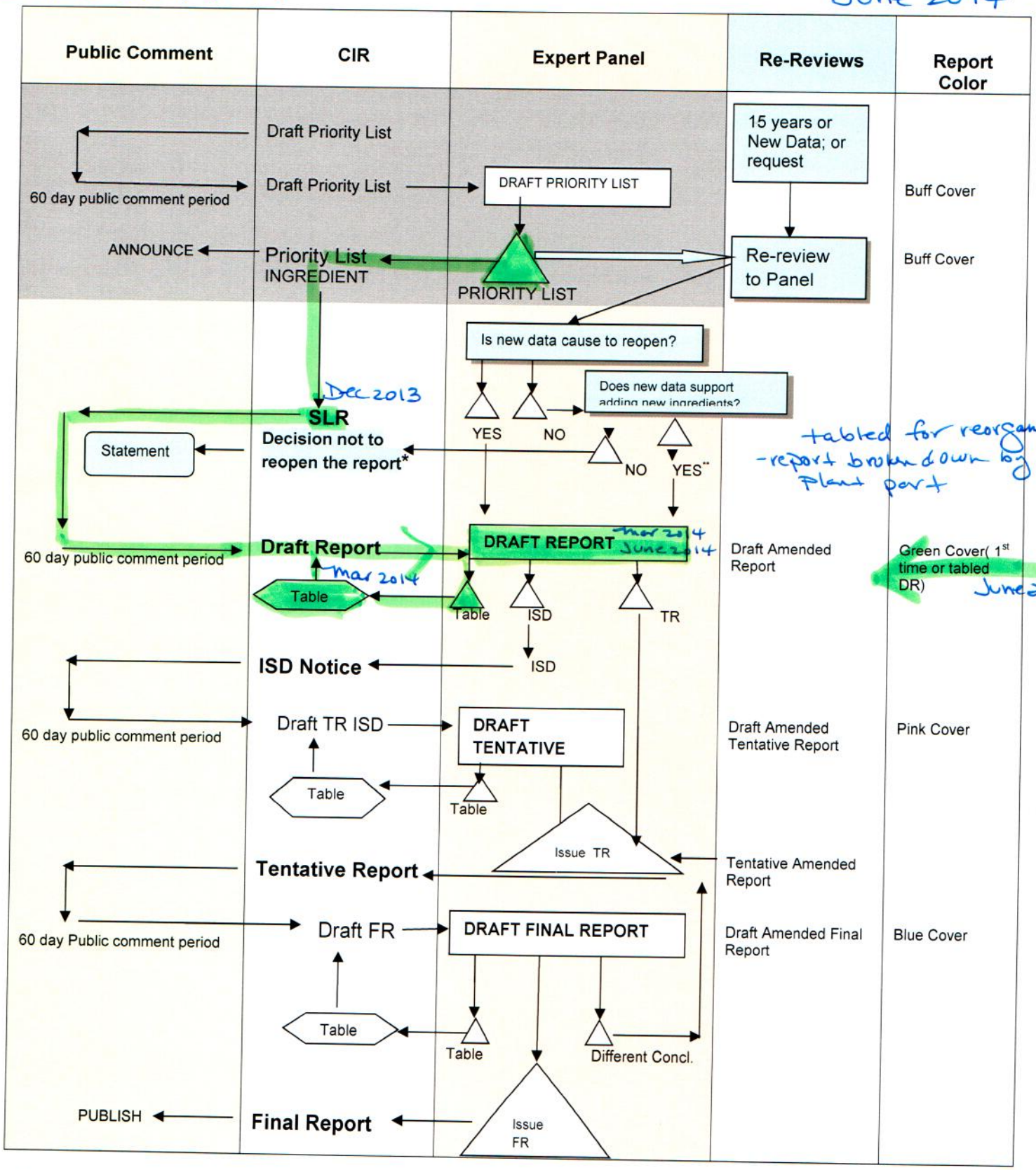
If no further data are needed, the Panel should issue a Tentative Report.

1620 L Street NW, Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

SAFETY ASSESSMENT FLOW CHART

Citrus Peel Oils

June 2014



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

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Citrus 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 will focus on all citrus-derived peel oils.

Citrus-Derived Ingredients Data Profile – June 2014 – Writers, Christina Burnett and Monice Fiume											
	In-Use	**Physical/Chemical Properties**	**Method of Manufacturing**	**Composition**	**Acute Toxicity**	**Carcinogenicity**	**Irritation/Sensitization - Animal**	**Irritation/Sensitization - Clinical**	**Ocular/Mucosal**	**Phototoxicity**	**Case Studies**
Citrus Limon (Lemon) Seed Oil	X										
Citrus Paradisi (Grapefruit) Seed Oil	X										
Citrus Aurantium Amara (Bitter Orange) Peel Oil	X										
Citrus Aurantium Dulcis (Orange) Peel Oil	X										
Citrus Grandis (Grapefruit) Peel Oil	X										
Citrus Junos Peel Oil	X										
Citrus Limon (Lemon) Peel Oil	X										
Citrus Nobilis (Mandarin Orange) Peel Oil	X										
Citrus Paradisi (Grapefruit) Peel Oil	X										
Citrus Reticulata (Tangerine) Peel Oil		X									
Citrus Sinensis (Sweet Orange) Peel Oil	X										
Citrus Tangerina (Tangerine) Peel Oil	X										
bergamot oil (generic)		X	X					X		X	X
bitter orange oil (generic)		X	X					X		X	
biter orange peel oil (generic)										X	
grapefruit oil (generic)		X	X			X				X	
lemon oil (generic)		X	X	X		X	X	X		X	
lime oil (generic)		X	X	X		X				X	X
mandarin oil			X	X	X			X		X	
mandarin peel oil (generic)							X	X			
sweet orange oil (generic)		X	X			X		X		X	
tangerine oil (generic)		X	X	X						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.
Shaded cells indicate ingredients that have been previously reviewed by CIR.

Search Strategy for Citrus-Derived Peel Oil Ingredients

- 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 April, 2014 using "citrus peel" – no new relevant references found.

Online Info

- 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)
  - Lemon Oil
  - Lime Oil
  - Bitter Orange Extract (mixture)
  - Orange Flower Water???
- 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
  - Bitter orange peel oil
  - Grapefruit oil
  - Lemon oil cold pressed
  - Bergamot oil expressed
  - Lime oil expressed
  - 7-methoxycoumarin
  - Standard for citrus oils and other furocoumarins containing essential oils. Ingredients include:

Citrus Aurantifolia (Lime) Oil
Citrus Aurantifolia (Lime) Peel Oil
Citrus Aurantium Amara (Bitter Orange) Peel Oil
Citrus Aurantium Bergamia (Bergamot) Fruit Oil
Citrus Aurantium Bergamia (Bergamot) Peel Oil
Citrus Aurantium Currassuviensis Peel Oil
Citrus Aurantium Dulcis (Orange) Oil
Citrus Aurantium Dulcis (Orange) Peel Oil
Citrus Clementina Peel Oil
Citrus Grandis (Grapefruit) Peel Oil
Citrus Iyo Peel Oil
Citrus Junos Peel Oil
Citrus Limon (Lemon) Fruit Oil
Citrus Limon (Lemon) Peel Oil
Citrus Medica Vulgaris Peel Oil
Citrus Nobilis (Mandarin Orange) Oil
Citrus Nobilis (Mandarin Orange) Peel Oil
Citrus Paradisi (Grapefruit) Peel Oil
Citrus Tachibana/Reticulata Peel Oil
Citrus Tangerina (Tangerine) Peel Oil
Citrus Unshiu Fruit Oil

Citrus Peel Oils, formerly known as Citrus-Derived Ingredients – March 17-18, 2014

Belsito's Team

DR. BELSITO: Now citrus. Hydrolyzed wheat we did, okay. So citrus, yes. Let me just save these. Now citrus.

So first and foremost, this makes to me absolutely no sense lumping all of these together. And in terms of dermatologic toxicity, the citrus with the problems is lime. So we need to get rid of lime completely and separate that citrus out because it's going to be an issue with the furocoumarins, which are distinct with lime in terms of phototoxicity. And we need to clarify with IFRA and RIFM and get rid of any ingredients that are fragrance only, and I'm not sure if that has yet been done.

MS. BURNETT: We are supposed to receive something hopefully by the end of the month from IFRA.

DR. EISENMANN: Would you also do bitter orange in there, too?

DR. BELSITO: Yeah.

DR. BRESLAWEC: Industry is very concerned about grouping justifications. This is one example. There are other examples, and I can speak on those later. From our perspective, you have to have a rationale for grouping ingredients together. A rationale is used to support read- across data. You cannot simply take every ingredient in the dictionary that has citrus in it and group them. That is not adequate justification for grouping for the purpose of read-across. This category includes many different types of ingredients. It includes oils. It includes fruit extracts. It includes seeds, whatever. They can't just be lumped together. We believe that the Panel credibility is enhanced when there is robust justification for grouping. And for a situation like this, the Panel I think opens itself up to risk of not conducting the kind of robust evaluation of the safety of ingredients that you traditionally do.

DR. BELSITO: Well, I mean I agree. I think what we're hearing is in this effort to -- I think this is yin and yang. We have been always asking did we miss anything. We're going to go ahead with this group. Is there something sitting out there that we missed? And then the yang to that was well, okay, so we don't get that question from the Panel. Let's just look at all citrus. But I think the problem here is that the writers have invested all this time and then we're going to tear it apart, and that's going to be particularly true for the sulfates because that entire report is going to go away as far as I'm concerned. So I totally agree with you, and my comment was first of all, lime has to be moved totally out. And then the next question is, how do we group? And I agree with you, we group by PO. We group by fruit. We group by oil. We group by wax. We look at that grouping, not at orange or bitter orange. We group by the chemicals that are extracted from the citrus fruits, but I don't think lime can be included in any of those groups because I'm going to be concerned about furocoumarin contamination in anything that's extracted from lime; that's my point. I mean we could put it in and then pull it out.

DR. LIEBLER: Do you think there will be a separate lime report?

DR. BELSITO: I don't know how to handle lime. I mean I think the first thing to do is probably to put lime into the citrus waxes and see what lime wax looks like and see what kind of contamination there is with furocoumarin. But peel is going to be a problem with lime because that's where the furocoumarins are.

DR. BRESLAWEC: There are a lot of different, obviously, legitimate ways to group ingredients. You can base them on major chemical components. You can base them on structural similarities. Do essential oils. Do waxes. Do butter extracts. Do whatever. What is difficult, and I think you mentioned one of these issues, is the staff puts in a lot of time pulling together information on a huge category of ingredients. That translates from our perspective of having to go out and ask the industry for a lot of information on a huge range of types of ingredients. And we can't do that effectively for a large number of ingredients that aren't related.

DR. BELSITO: No, but my point is that before we get to this step where we see a document on sulfates or we see a document on citrus, what I would like to see is proposed -- particularly in a case of botanicals -- the proposal and just whatever we can get from Dr. Duke's Phytobiology on what is actually in those products and just present that. I mean just like before when we were looking at grouping, it seemed to me we were just getting the names and chemical structures and we were just looking and saying yep, no, yep, no. This time with the sulfates and the citrus, we seem to have gotten everything without ever making a decision on the part of the Panel, at least if we did I don't remember doing it, that yes, that's the way we wanted to go. Certainly I don't remember the sulfates because I mean the sulfate is not the driver, it's the metal that's the driver.

DR. BRESLAWEC: I agree.

DR. HELDRETH: For the citrus, the way we would like to group them is based on component. What are the components in these botanical ingredients? Well, we don't know what those components are, and even with something like Dr. Duke's is another failure at telling us what these industry-specific ingredients have in them. So to be able to group them based on those chemical similarities, we need to know what they are and they're only available from the industry. They're not published in the literature. Our writers have searched trying to find that component data and it's not available.

So I can understand the idea of not wanting to group these just based on the name "citrus," but I think it's also not right to separate them just based on the name "lemon" or just based on the name "lime." I understand the idea that lime has a known component that's a red flag and we want to review it separately, but what if other citrus ingredients have those same furocoumarins? What if there's other components that we may want to group together? We don't know what they are.

So we brought you a large retrospective of what citrus was, leaving you the option to cut it into separate reports as you saw fit once we had data that we could base those separations on. So we could have a lime report if the furocoumarins seemed to be the dominating force within it or likewise with any other groupings. Maybe lemon and grapefruit end up being very similar. I don't know. We don't have the component data on those. Even if we look in Dr. Duke's and say these subcomponents are within grapefruit, we don't know what's in the extract or the PO extract or the leaf extract because we don't have that data. We don't even have the extraction data, whether it's cold pressed or whether it's used with a solvent or all these other methodologies.

DR. BELSITO: But if that's the case, then we don't have sufficient data. My gut feeling, obviously, was get rid of lime and then to look at waxes' oils. So why don't we -- instead of looking at everything citrus, why don't we just -- and not to waste Panel time -- why don't we make a decision that we want to look at citrus oils.

DR. EISENMANN: When you say oils, you mean essential oils.

DR. BELSITO: Essential oils, assuming that they have other than fragrance uses. And if the citrus essential oils do not have uses other than fragrances, then why don't we say we want to look at citrus waxes and just see where we get with that. I mean what's a high volume of use in citrus products?

DR. EISENMANN: It could be essential oils use, just means fruit and peel.

DR. BELSITO: Right. But let's take a high volume nonessential oil just in case all the essential oils are just fragrances.

DR. BRESLAWEC: Citrus lemon fruit extract.

DR. EISENMANN: You've more or less I think done the seed oils already.

DR. BELSITO: Okay, so let's look at citrus fruit extract? That's a high volume.

DR. BRESLAWEC: Well, I mean you could look at what drove this into the priority list in the first place.

MS. BURNETT: Peel oil had the most uses.

DR. EISENMANN: Lemon, right?

MS. BURNETT: Lemon peel oil, yes, with 510. And then lemon fruit extract was the second greatest with 448.

DR. BELSITO: So let's say we want to look at the citrus peel oils, assuming that they have other than a fragrance use, and see what we get. Because if we're not getting a lot of data there and we issue an insufficient data announcement for something with a high volume of use like that, it's going to happen down the road. And then we can just say okay industry, you've got problems if you want to continue to use these because we're going to keep going and we're going to keep telling you they're insufficient.

DR. BRESLAWEC: And I guess the other point that's worth noting is the bulk of these ingredients are not used.

DR. BELSITO: Right.

MS. FIUME: That is a point, but whenever we've done groupings, we have been. Just because they're not used, they are in the dictionary, so we've not been excluding based on that fact.

DR. BELSITO: I understand. If we have sufficient data to read-across and say that the component in bitter orange is the same as the component in regular orange or in grapefruit or in tangerine. Now if we don't have chemical composition for that other citrus fruit, it's going to be insufficient. And then it gets out of the dictionary, right, after two years?

DR. BRESLAWEC: No, it does not get out of there.

DR. BELSITO: It doesn't get out of the dictionary, it just --

DR. BRESLAWEC: It's not approved. It's not considered to be substantiated for safe use.

DR. BELSITO: I see. Okay, so I guess at this point is tabling the right word since we're not even going to proceed with this report as it is? We're going to split it, and we're going to look at either the essential oils if they have other than fragrance -- or the peel oils if they have other than fragrance use and if they do not, then we're going to look at the fruit extracts as the first cut for these groupings. Does that make sense?

DR. SNYDER: I like the peel and fruit approach because that captures the majority of the uses. It's 448 uses up to 1.2 percent for the peel extract, and then the next biggest is for the fruit extract.

DR. BELSITO: So we're going to --

DR. SNYDER: The lemon peel.

DR. BELSITO: The first cut is we're going to look at citrus peel oils.

DR. BRESLAWEC: What's the main driver here, Christina?

DR. BELSITO: Lemon peel if not all fragrance.

DR. SNYDER: Lemon peel extract.

DR. BELSITO: If they end up being all fragrances, if all peel oils have fragrance use only, then we're going to look at fruit extract as the next one, right? But we're only going to do one. We're not going to proceed with more than one until we see how it works.

DR. LIEBLER: One, you mean like lemon?

DR. BELSITO: No, we're going to do --

DR. LIEBLER: One category?

DR. BELSITO: We're going to do the first group. So we're going to do citrus peel oils. We're not going to do citrus fruit extract if it turns out the peel oils have other than fragrance use. If it turns out that all peel oils only are used as fragrances, then it's not our purview. The next hit would be the fruit extracts.

DR. LIEBLER: Okay, okay.

MS. FIUME: Dr. Belsito, can I ask a few questions because if you table it tomorrow when we go into the meeting, then discussion will have to stop. So, hopefully, some of that can be worked out in the public meeting before it's tabled so we have rationale.

But one of my first questions is we've done botanicals before. We've grouped more than just the fruit extract, and we've grouped the seeds and everything together. So either as we look forward or for the purpose of citrus, what will drive that grouping rationale and is it unique to citrus?

DR. BELSITO: Well, I think when we've grouped seed oils and waxes, it's been for one specific botanical. It's not been for a group of botanicals. The difference here is you're giving us a whole bunch of different fruits, not one fruit from which we derive everything or one plant like rosmarinus where we're looking at seeds and oils and stuff like that. You're giving us citrus fruit, some of which contain very different chemical compositions, i.e., lime, and others that may have different chemical compositions. We don't know. And you're giving us all types of chemicals within or ingredient types, constituents, within those. It's too unwieldy to try and handle that.

So if you want to try and group by citrus that may be reasonable for everything other than lime. It may be reasonable for lime for everything other than peel oils.

DR. SNYDER: But it may be confounded by the fact that there may be a majority of fragrance uses, which then are not in our group.

DR. BELSITO: Right. Well, that's what we need to do. I mean I think if you're getting any slowdown -- well, first of all, Anne Marie has already commented that grouping this way was illogical. I spoke to her just last week in Brussels. I thought she had already sent you the list.

MS. FIUME: Oh, no, she had told us not until at least the end of March.

DR. BELSITO: Okay, so I will bother her and let her know that she needs to get that to you. I think she was probably overwhelmed getting ready for this QRA meeting in Brussels, but she'll get it to you.

MS. FIUME: Then the other point was that if we go with the lemon peel oils based on the frequency of use of the citrus fruit extract, if we were looking at prioritization, that number would put it back on our prioritization list probably for next year. So even if we're taking it one at a time, it should fit back into our prioritization list.

DR. BELSITO: Yeah, but I think that we need to see what's going to happen before we waste a huge amount of writers' time trying to do -- even if both of them were on the priority list, I would say since we've already looked at

some of the data and we're having issues with it, let's deal with one first and see how it goes and see how much data we can get from industry, how much data -- we heard from Bart that trying to get composition on these things was difficult. If we can't get good composition information on the stuff that's out there that's really being used, how far down are we going to be able to drill into this? Not very far. Then we're going to know, fine, we'll review them. But hey guys, we're going to find them all insufficient.

MS. FIUME: And so that will even within the table will go out to industry that we need composition data?

DR. BRESLAWEC: We are completely prepared to say we are not able to defend this list of ingredients, completely prepared to say that. What we want to try to avoid is going out for a million ingredients where some of them have 500 uses and the majority of them don't even have composition information. We'd like to be able to provide you real information that you can use in an assessment.

DR. HELDRETH: So if we're going to go for the peel oils and temporarily hold up on the rest of the ingredients in here, wouldn't that just be the next cycle where you'll see the peel oils come back as a report, and we'll hold up on the other ones as a separate report once we see how the peel oils turn out instead of tabling it?

DR. SNYDER: Again, the peel oils as long as they're not -- there's 448 uses and 447 of them are fragrance because then all of a sudden it's different. We just need to know that.

DR. BELSITO: Yeah, I mean we need to know which ones we eliminate and if we're eliminating most of them, then I would move to fruit extracts as a group, okay? That was my point.

DR. EISENMANN: See, rather than continuing this report, it'd be nice to see an SLR done on the peel oils and a 60-day comment period on the SLR before you see it rather than moving it on and having a report at the next meeting.

DR. BELSITO: So what do we say? That this report is closed? It's off the table and we've decided to issue a new SLR? Is that how -- I mean I don't know the rules.

MS. BURNETT: Well, I will let you know that the lemon peel oil is not in the list of potentially only fragrance that I came up with.

DR. BELSITO: Right.

MS. BURNETT: So, there's a potential that there are other uses for that one that's not in my --

DR. LIEBLER: Skin conditioner. You can always count on skin conditioning.

DR. SNYDER: I was actually waiting for Dan for his comment. He really wants the line to go into the coconut report.

DR. LIEBLER: But that wouldn't have been my comment.

DR. BRESLAWEC: At least all of the peel oils are used as fragrance, but not just fragrance.

MS. BURNETT: It took me nine months. We've searched the data. So we can issue another SLR, but there won't be much added from the published literature.

DR. BELSITO: That's fine and then we go insufficient.

MS. FIUME: And it would ultimately be -- rather than go back to the SLR stage and backtrack that far, if we provided a list of what will be in that report, would that --

DR. BELSITO: I don't think -- I don't know -- I've never concentrated on the rules and regulations. I'm not the chair. I'm not the head of CIR. Whatever we need to do to get rid of this report as a group and start a new report that we've now decided the way to group citrus is by oils, waxes, peels. And the first one we want to do are the peel oils, assuming they have other than fragrance use. And it appears that the high volume of the lemon peel oil does, so that will be the driver. We want to see what happens when we look at citrus peel oils, what kind of data we've got. And if we're not getting sufficient data on those, then I suspect as we go down the entire citrus category, it will be one insufficient after the other. But that's fine.

DR. LIEBLER: So perhaps the easiest way to do it is just to delete everything from the report except for the peel oils.

DR. BELSITO: That's fine.

DR. LIEBLER: That way you don't have to go back -- you get to use the work you've already done. We can talk, but we're not tabling it. And we leave all the rest of that stuff to work on in subsequent reports.

DR. BELSITO: Sounds good.

DR. BRESLAWEC: Thought I knew what you were going to say, which is delete everything but the peel oils and put them in one report and then take the fruit extracts and put them in another report.

DR. BELSITO: Yeah, that makes sense, too.

MS. FIUME: This isn't being thrown away. I just meant rather than go back out for an SLR and start the whole process all over again --

DR. LIEBLER: Right, because you've done that. It's not going to get any better, right.

DR. BELSITO: So we're just going to break up this report into separate reports based on peel oils, fruit extracts, waxes, you get the general drift. So there will be five or six new things coming out of this.

DR. SNYDER: Essential oils.

DR. BELSITO: And the next report we want to see is the peel oils.

DR. HELDRETH: And we'll let the conclusion and how that goes determine which one you see next after that.

DR. BELSITO: Yeah, I mean -- well, I think the next highest volume of use is fruit extracts. That would be the next one we'd want to see. But if we can't come to some type of safety conclusion with the data from peel oils, the chances of us coming to a safety conclusion on anything below that is going to be minimal because even though they may have nonfragrance uses, I suspect we're going to get a lot of data from RIFM on these. And if the data we get from RIFM can't support their safe use other than as fragrances, then we really have issues for everything else.

DR. SNYDER: And it still addresses why we put it on the priority list because we're still capturing the uses.

DR. BELSITO: Okay, have we killed this? Everyone happy with our decision? Any comments?

Marks' Team

DR. MARKS: Okay. Next. Citrus. So, that's easy. We can just table that. So, this is the first review. There are just slightly under 200 ingredients. Some are fragrances and will be deleted in the future. In 2010, the CIR Expert Panel issued a report that lime, orange, and grapefruit oils are safe. I'd ask Tom and Rons are the ingredients okay, but I might prior to that ask the Council. So, Jay, if you want to speak to recommending separate reports for each species. Start with citrus lemons since it has the highest use. And, actually I had Halyna please comment, but it's going to be Jay.

MR. ANSELL: Yes. I suspect Halyna would is commenting on the other side. I think there's some confusion between a report and a family. It's quite possible to have a report which addresses multiple families, but each of the members of the family, each of the data points on a member of the family should form the safety conclusion of all members of those families.

And, what we see in these reports, like the sulfate report this morning and like the citrus report is that it's a mix and match of a whole series of different materials. Some of the data points informs some members but -- are informative of some members of the family but not all members of the family, and that we think specific to the citrus report here that we really need to figure out what the appropriate grouping is so that each of the data points under that grouping can be used for all the members of that grouping. And, the report as currently organized simply doesn't allow that.

I also would like to point out that this, as I did this morning -- this is really, really very important to us. The ability to use computational approaches to assess these materials that not every question can be answered or should be answered by an animal study, so we feel that getting these reports right, defining the families correctly, is really critical to the underpinning of the credibility of the whole process.

And so we really would like the staff to go back and to take a look at the groupings and to provide some positive statement as to why they've been formed in the way they have, not a negative statement that they -- I don't have the negative statement written down, but just because. So, we would like to see a much more robust discussion of why the families were formed, even if they are addressed within a single report.

DR. MARKS: Rons? Tom?

DR. SHANK: I felt that the report should be split in two individual species. For many reasons, there are all kinds of differences between the citrus species, and even within one species you have complexity. We say orange, but do you mean a Valencia orange, a navel orange, a Mandarin orange, a blood orange, et cetera? Same thing for limes. Same thing for all of them. So, it got more complicated, I thought, than could be handled as a single report. If we keep it in a single report, then I have a suggestion for splitting the report, within one report three different groups.

MR. ANSELL: We're thinking fragrances and flavors, maybe waxes, essential oils grouped together. How are we going to address the non-edible versus the edible citruses?

DR. SHANK: Well, if we keep it one report, then I would separate it into GRAS ingredients and non-GRAS ingredients, and then within the non-GRAS, rinse-offs and leave-ons. That would make it a little easier to handle, but I like just orange by itself, lying by itself, et cetera.

Certainly with the discussion we just had on tea products and on rosemary, it seems like if we start including multiple species then it really becomes more complex and the report becomes, I think, much more difficult. Come to specific conclusions that aren't a conclusion which has lots of mixed results, so to speak.

MR. ANSELL: It may or may not, but there's certainly nothing in this report which would allow us to support that conclusion, you know. It's quite possible a thoughtful analysis will show that all the lemonenes are consistent enough, but they all contribute to the assessment. But, it just isn't here.

DR. MARKS: So, how should we -- Tom and Ron Hill, do you like going into the species and do it that way? The results of all those -- she's not here to comment. Anne Marie Api, from RIFM, also commented on feeling that using species is the way to approach this. Go ahead, Jay.

MR. ANSELL: Well, I actually think the staff had a good suggestion in their own, although they thought it was industry's responsibility, but, to provide the panel with a comprehensive report, CIR suggests that a complete component and property profiles, in addition to relevant tox data, be provided by the cosmetics industry for these ingredients in accordance with the guidelines presented by the cosmetic industry for assessing botanical ingredients. So, I think the structures (inaudible) we just think that that, at this stage, should have been a staff responsibility.

DR. HILL: Because, I'm thinking along different lines, which is not necessarily separate by species but separate all the peel extracts, all the leaf oils, so that we're getting comparable preparations. And, then if we have some idea about constituents, then read-across from me becomes much more reasonable, because ultimately we're looking at constituents of concern, which there may not be any in any of these, but if we had, it may be that they're quite similar between lime and orange and lemon and grapefruit for peel extract. And, it might be that they're quite similar between lime and orange and varies species of oranges in leaf oil.

I think if we get, you know -- I feel like I'm the separation person, but I was perfectly comfortable with 400 and some vegetable oils, because what we had in that was constituent breakdown and we could do read-across, and we knew when we had toxicology studies this, this, and this, that we could include all the rest, and we knew exactly what the tox data was being generated on with ranges and a coherent body of data. So, I don't know what that would look like, but ultimately chemicals and mixtures of chemicals is what we're trying to -- and what are the concentrations and how did they get into the body, right?

DR. MARKS: Actually, my concern wasn't how they get in but what their phototoxic effect would be, and there was only two really, oil of bergamot and lime, which I was most concerned about.

DR. SLAGA: Yeah, but they didn't show (inaudible).

DR. MARKS: Oh, yeah. There's concern.

SPEAKER: Low concentrations (inaudible).

DR. SLAGA: There's a table that shows it.

DR. MARKS: But, anyway, let's get -- Tom, you were going to comment about how to approach this large group of ingredients, this 198 ingredients. So, we have one approach with species. Another approach essentially looking at the plant (inaudible) perhaps, everything that's derived from the peel or whatever. Tom, what's your sense? Which way would you want to go?

DR. HILL: Well, the reason I was thinking along the lines of -- is that the kinds of processes that you use to prepare an oil from a leaf for example are going to collect a certain kind of molecule, whereas another type of extraction process used on pulp is going to get a whole different group of molecules than in terms of, like I say, any read-acrossed. To me, it makes sense to have like versus like from a chemical constituent point of view, but if you're just looking at maybe only three things out of all of this, pull out the constituents of concern, keep them all in there, figure out how all of those relate to that.

MR. BOYER: And, if I could add a little bit of information to that. RIFM actually separates these by species, by plant part, and also by extraction process, and there's a lot of information out there in the literature, but it doesn't necessarily apply to what is in the cosmetic ingredients. I think that's one of our biggest problems in getting a hold of that information. It's our position at this point that this is information that we can obtain only from industry reliably.

DR. MARKS: So, Ivan, how would you approach it then as a toxicologist? Would you have a big lump, all 198, or do you like the idea of taking smaller bites out of this group of citrus --

MR. BOYER: Well, I think, again, RIFM's approach is a pretty good one. They have a tiered approach. You start with the whole ingredient, and if you have the information, the patch testing results and so forth and they chose nothing, you've got genotoxicity studies that have been performed on the whole ingredient, and there's no concern there, then you're in the clear. Once you find that there's a flag or if you don't have sufficient information in one way or another, the next tier would be to look at specific components. And, there, of course, we're going to need the information, the data about just what are the constituents present in specific extracts from a specific plant part of a specific species. So, that's the point where you'd want to break it up.

DR. MARKS: So, Tom?

DR. SLAGA: I mean, the really big concern here is usually with -- and as Ron brought up, with the peel, some of the oils -- the peel is -- actually it is. Some people eat it. They make marmalade and things out of it, so, but --

DR. HILL: I eat it quite a bit, but I also trust my liver to do it's thing in my digestive tract before whatever gets in my body. My liver should bake glucuronides very efficiently and then my skin doesn't do that.

DR. SLAGA: On the one hand, if you look -- these are all related and a lot of variations here are man-made. You know, a tangerine is not natural. It was made, right, from an orange, wasn't it? Californians should know that.

DR. SHANK: A tangelo is a hybrid. A tangerine, I think, is an honest species.

DR. SLAGA: Honest, wild. Yeah.

DR. MARKS: So, let's get -- I think we need to get back to do we want to continue the approach at looking all 198 or take these in smaller bites and the smaller bites being by species. So, we'd look at, as was suggested in the PCPC letter, start with citrus lemon since that is the most used.

DR. SLAGA: What if we find later that there is a lot similarity? Do we bring them back together?

MS. BURNETT: I'm not throwing anything away, so I can cut it, dice it, but things are going to be saved and stored. So, just be kind and not do it too many different times. (Laughter)

DR. MARKS: So, panel members, a suggestion was made to table it by Council and then to go back and look at it in smaller groups based on species.

MR. ANSELL: I think the more precisely is we would like to table it and come back with a much more robust discussion as to how it's been organized. I wouldn't at this point, pre-judge. Pre-judge it -- I think it would be very difficult. There's a lot of data in here. I mean, it's quite extensive, but then to go through and have all this breakdown of ingredients across all the different species and the way it's been sliced and diced and then just dump it in and say all data points are relevant to every one of the ingredients is, we think, insufficient.

And, a lot of this stuff has been thought about. I mean, we had a very good discussion of a number of different ways of doing it. I'd like to have seen a discussion as to why one of those was better. I mean, even in the sulfates this

morning, you know, Ron, you had done that thinking already and had already divided it into soluble and insolubles. I mean, even that discussion would have helped it form the formation of an appropriate family more than it currently appears in the reports.

DR. MARKS: Well, actually, Ron Shank had already done that thaw process. You have, what, GRAS not GRAS, and then what was your third group.

DR. SHANK: GRAS, non-GRAS, minimum (inaudible) non-GRAS was good between rinse-off and leave-on.

MS. FIUME: Just as the CIR staff and the writers -- the one thing, regardless of what the outcome is tomorrow, what we do request, and, Jay, you had touched on it on your memo about the constituent data, is, I think we know the cosmetics are different than maybe what we do find in nature. So, as part of this as we go forward, as the writers, we do believe we really need the constituent information, either a certificate of analysis from a supplier or something on the specific cosmetic ingredient based on extraction in order to be able to complete this document, no matter how it's sliced, diced, or not. So, just as we got forward, that's one thing that we see as needed.

MR. ANSELL: There's nothing in our suggestion which shortcuts any of these elements. It's just really focusing on that very first step and our discomfort over the last year or so in how these families are being formed. It doesn't suggest that things won't go insufficient, you know, that we will be able to answer all the questions. We just feel very concerned that it's totally opaque as to how these families are formed and that we'd like to see a much more robust discussion as to why these are being reviewed in the way they are, so that we feel much more comfortable that all the data within a family supports all of the members.

DR. MARKS: So, Ron, Ron, and Tom, do you want to -- perhaps we'll be seconding a motion tomorrow that we table this to review individual species versus GRAS/not- GRAS, go back in how do we approach this group of citrus- derived ingredients, because we need to have some sort of direction here in terms of what do we as a team want to recommend.

I must say, when I looked over and I was concerned about the phototoxic effects, there were mixed results of that as you went through, and lemon and orange oil -- we had results, the ones I was concerned about, with oil of bergamot and lime, I didn't see any. I may have overlooked it, but I didn't see any data on the phototoxicity, and they're the ones I'm concerned about clinically. So, I couldn't set limits. That would be an insufficient, so I would be going through sort of mix/match, and it would be a lot easier on citrus lemon to say, okay, that species and all the components are okay. I kind of like the species approach, actually.

Now, you aren't going to throw your data away. We hear Christina.

MS. BURNETT: I'm sorry?

DR. MARKS: You aren't going to throw -- you're going to have that saved as citrus-derived and be able to pull it out. Yeah, you may get frustrated in 5 or 8 years as we approach the last one of these, saying let's re-group it all together. (Laughter) Okay. So, I'm going to move forward with this table of review, individual species versus GRAS/not GRAS. We'll see what the discussion leads to tomorrow. One of the conclusions I had, just again, sort of a preview of possible conclusion could be formulate to be not phototoxic.

DR. BERGFELD: That would be new. (Laughter) That's new.

DR. MARKS: Well, we went from non-irritating to non-sensitizing. Now, I think we could move on to phototoxic.

DR. SHANK: Just don't --

DR. MARKS: That would solve all the issues in my mind of -- it would put the onus on the manufacturer to have tested their product, before it went out, to be non- phototoxic.

DR. SHANK: Just don't let this lead to eventually when formulated to have no toxicological concerns.

(Laughter)

DR. MARKS: Ron Shank, I was hoping you would -- this is sort of the slippery slope, huh? (Laughter) Okay. This was really, I thought, a good discussion. I know we didn't come to a definitive conclusion, but we'll see what we come to tomorrow. We have some options, and it also gives us overnight to think a bit more about it, all of what you were talking about, Jay.

MS. BURNETT: And, just a note, I don't know if you said it clearly in any transmission since the report went out, but RIFM is supposed to provide us with the list of fragrance-only ingredients, hopefully, by the end of March, so that we will know for sure what ingredients are not under our purview.

DR. MARKS: This I found -- I'm not sure -- was it put on over lunchtime? I didn't look at it. Is there anything in here that we should be addressing? Nice, very good images. I love the images.

MS. BURNETT: It came from RIFM. It was with the letter that Dr Api sent. I just didn't include it in the package originally, and, if anything, it does clarify what the unknown bigarade petitgrain oil was. We had no idea what that was, and that kind of answers our question.

DR. MARKS: Okay. Any other comments about the citrus-derived ingredients?

Full Panel Meeting

DR. BERGFELD: Then moving on to another big group, Dr. Belsito on citrus.

DR. BELSITO: Yeah. So none of us could wrap our hands around this and it just creates great dilemmas. And so we felt that we cannot do citrus as a family. And in fact, in particular, we may need to kick lime out of the family. But we went around as to what is the logical breakup for these?

So we saw that citrus peel oils were the most frequently used of all the various citrus parts, and if the RIFM assures us that they're just fragrance ingredients and we don't need to review them, then the next most frequently used part would be fruit extracts.

So our recommendation would be let's take one baby step to try and wrap our hands and feet around this citrus group and look at citrus peel oils, assuming they're not only fragrance ingredients first, see how that works for this entire citrus family in terms of ability to get compositions, et cetera, and that will give us some sense since these are the high users-- that's where the data should be, hopefully-- how to proceed with the rest of the group.

So we want to split up these reports into multiple reports. The first one, either citrus peel oil if there are other than fragrance uses. If there are only fragrance uses for the peel oils then it would be the fruit extracts we would look at first.

DR. BERGFELD: Dr. Marks, do you want to comment?

DR. MARKS: We also had difficulty on how to divide this group up. We agree it was too large. And so we felt we needed to table the discussion of these ingredients. We were actually waiting to see how you were going to divide it up so we could react to that. We wondered whether or not, as was suggested in the Council letter, to do individual species, or if we didn't do that, Dr. Shank had an interesting approach of doing one group of grass, or divide them up in a report like grass/not grass, and then split the rinse-off and the leave-ons for the not grass ingredients. So that was an interesting approach to this.

I like the idea of taking, as you said, Don, the baby steps, and we certain can move forward with looking at, as far as a portion of the fruit and see where that takes us and we may come back to a different way of grouping these ingredients. But at least that's a start.

And Christina assures us she's going to keep all her data so she can pull it out instantly when we rearrange the "deck of cards," so to speak.

DR. BERGFELD: So I just consulted with Lillian. So we would have to table this to allow it to be divided.

DR. MARKS: Unless it's in a motion. I could move -- yeah.

DR. BERGFELD: There is no motion, I don't believe.

Did you have a motion?

DR. BELSITO: No.

DR. BERGFELD: You were just discussing it?

DR. BELSITO: No, I was just saying I don't know the proper CIR procedures to do this, but this report is, in my view, going to disappear and be broken up into a number of smaller reports. The exact way they're broken up, our suggestion, again, was to go with a highest volume of use, which was a peel oil. If there are other than fragrance uses, which we believe there are, and see how that goes because a lot of these are not used, and when we start drilling down into them we may start finding as we move down the volume of use -- well, first of all, do the highest volume of use and then see where the rest of them prioritize out.

DR. BERGFELD: Ron Shank, do you want to comment?

DR. SHANK: No, that's fine with me. And Dr. Hill had recommended the same approach by the pieces of the fruit rather than splitting it by species or splitting it by grass versus nongrass. So I'm happy with your proposal.

DR. BERGFELD: So I'll entertain a motion to table.

Dr. SNYDER: Second.

MS. BURNETT: I just want to go on record before discussion stops.

DR. BERGFELD: Yes.

MS. BURNETT: We just want to make sure for our marching orders because we want to make sure it's clear. We are going to go ahead and divide this into peel oils. If peel oils come back mainly as fragrances, we will not be reviewing peel oils. We'll go ahead and move to extracts.

DR. BELSITO: Fruit extracts.

MS. BURNETT: Fruit extracts. And then after that we'll see how that goes and then move on. Just, we want to make sure we have this.

DR. BELSITO: One step at a time until we see how it's going.

MS. BURNETT: We don't want to be -- staff doesn't want to be in limbo trying to figure out how to work.

DR. HILL: But I heard you say mainly just fragrances. We're talking only as fragrances.

MS. BURNETT: I meant --

DR. HILL: Okay. I was just making sure.

MS. BURNETT: -- if the majority of the peel oils turn out to be only used as fragrances.

DR. BERGFELD: Did I hear a motion to table? I sort of heard it from Marks, but I had a second over here with Don.

Okay. Call the vote then to table. Unanimous. Ron Hill?

DR. HILL: Yes.

DR. BERGFELD: Okay. Unanimous.

(Motion passed)

Safety Assessment of Citrus-Derived Peel Oils as Used in Cosmetics

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The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Christina Burnett, Senior Scientific Analyst/Writer and Monice Fiume, Senior Scientific Analyst/Writer.

INTRODUCTION

Citrus-derived peel oils are widely used as cosmetic ingredients, and function primarily as skin conditioning agents-miscellaneous and fragrance. This report assesses the safety of 16 citrus-derived peel oils. The full list of ingredients in this report is found in Table 1.

The CIR Expert Panel (Panel) has previously reviewed citrus aurantifolia (lime) seed oil, citrus aurantifolia (lime) seed oil unsaponifiables, citrus aurantium dulcis (orange) seed oil, citrus aurantium dulcis (orange) seed oil unsaponifiables, citrus grandis (grapefruit) seed oil, citrus grandis (grapefruit) seed oil unsaponifiables, citrus limon (lemon) seed oil, and citrus paradisi (grapefruit) seed oil and concluded that these ingredients were "safe in the present practices of use and concentration" as described in the safety assessment of plant-derived fatty acid oils.[1]

Usually, the CIR does not review ingredients that only function as fragrance ingredients because, as fragrances, the safety of these ingredients is evaluated by the Research Institute for Fragrance Materials (RIFM). Five of the citrus-derived peel oils in this report function only as fragrance ingredients, according to the International Cosmetic Ingredient Dictionary and Handbook (see Table 2).[2] The CIR is in the process of confirming with RIFM that these ingredients are fragrance ingredients; if confirmed, these ingredients will be deleted from this safety assessment.

Botanicals such as citrus are comprised of hundreds of constituents, some of which have the potential to cause toxic effects; for example, bergapten (aka 5-methoxysporalen or 5-MOP) is a naturally occurring furanocoumarin (psoralen) in bergamot oil that causes phototoxicity. Presently, CIR is reviewing the information available on the potential toxicity of each citrus-derived peel oil as a whole, complex substance; CIR is not reviewing the potential toxicity information on the individual constituents of which the citrus-derived ingredients are comprised. CIR requested information on the concentrations (including ranges, means, upper 95 percent confidence limits, detection limits, etc…) of individual constituents in the citrus-derived peel oils used in cosmetics, to facilitate the safety assessment of these ingredients as used in cosmetics. Such information on constituents that have been identified as constituents of concern by the Panel in previous safety assessments, or by other recognized scientific expert review bodies, is especially important.

Some toxicological data on lemon oil and sweet orange oil (synonyms: lemon, ext. and orange, sweet, ext.) in this safety assessment were obtained from robust summaries of data submitted to the European Chemical Agency (ECHA) by companies as part of the REACH chemical registration process. These data are available on the ECHAwebsite.[3,4]

Note: In many of the published studies, the information provided is not sufficient to determine how well the substance being tested represents the cosmetic-grade ingredient. In this safety assessment report, if a substance tested in a study is not clearly a cosmetic-grade ingredient, the test substance will be referred to by a common name (e.g. lime oil). If the substance is clearly a cosmetic-grade ingredient, the International Nomenclature of Cosmetic Ingredients (INCI) name will be used to refer to the test substance (e.g. "citrus aurantifolia (lime) peel oil"). In some instances, it is not known from which part of the plant the oil has been expressed, but according to method of manufacturing, it can be expressed from the peels of the citrus fruit.

CHEMISTRY

The definitions and functions of the citrus-derived peel oils 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 structures can vary rather widely. Fixed oils, on the other hand are hydrophobic, nonvolatile, fatty compounds from plants. These are primarily comprised 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.

Physical and Chemical Properties

Physical and chemical properties of the citrus-derived peel oils are provided in Table 3.

Method of Manufacturing

Bergamot Oil

Bergamot oil (cold-pressed) is obtained by pressing, without the use of heat, the fresh peel of the fruit of *Citrus bergamia* [5].

Bitter Orange Oil

Bitter orange oil (cold-pressed) is obtained by expression, without the use of heat, from the fresh peel of the fruit of *Citrus aurantium*.[5]

Lemon Oil

Lemon oil, expressed, is produced by pressing the outer rind of the ripe fruit by hand or by machine.[6] More economical processes involve an integrated juice-oil procedure. Lemon oil can also be produced by distillation of expressed oils or direct distillation of fruit. Distilling (rectifying) removes terpenes. Steam distillation removes non-volatile furocoumarins.

Lime Oil

Lime oil is produced using the same methods previously described for lemon oil.[6]

Grapefruit Oil

Grapefruit oil (cold-pressed) is obtained by expression from the fresh peel of the grapefruit *Citrus paradisi*.[5]

Mandarin Oil – Expressed

Mandarin peel oil expressed (identified as *Citrus reticulata*) is prepared by the expression of the peels of the ripe fruit of the mandarin orange.[7]

Orange Oil

Orange oil (cold-pressed) is obtained by the expression, without the use of heat, from the fresh peel of the ripe fruit of *Citrus sinensis*.[5] Distilled orange oil is obtained from the fresh peel or juice of the fruit of *Citrus sinensis*, with or without the previous separation of the juice, pulp, or peel.

Tangerine Oil

Tangerine oil (cold-pressed) is obtained from the peels of the ripe fruit of the Dancy tangerine, *Citrus nobilis* or *Citrus reticulata*, and from some other closely related varieties.[5]

Constituents/Composition

The citrus-derived peel oils are complex botanicals made up of numerous constituents. Table 4 lists major constituents by citrus plant species. Table 5 gives the typical levels of 5-MOP that are found in some of the oils and Table 6 provides the levels of major coumarins and furocoumarins in lemon and lime oil. Table 7 lists citrus constituents that are established contact allergens, according the European Commission's Scientific Committee on Consumer Safety (SCCS).

USE

Cosmetic

Table 8 presents the current product-formulation use data for citrus-derived peel oils. These ingredients function primarily as skin conditioning agents-miscellaneous and fragrance.[2]

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), citrus limon (lemon) peel oil has the most reported uses in cosmetic and personal care products, with a total of 490; more than half of the uses are in leave-on skin care preparations.[8] Citrus aurantium dulcis (orange) peel oil (reported as citrus sinensis (sweet orange) peel oil to the VCRP) has the second greatest number of overall uses reported, with a total of 289; about half of those uses are in leave-on skin care preparations.

In the Personal Care Products Council's use concentration survey, citrus limon (lemon) peel oil had a highest maximum use concentration range of 0.0001% to 0.5% with 0.5% reported in "other" skin care preparations.[9] Citrus aurantium dulcis (orange) peel oil had a highest maximum use concentration range of 0.00002% to 29%, with 29% reported in non-coloring hair conditioners.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided. For example, citrus junos peel oil is reported to be used in 6 formulations, but no use concentration data were available. In other cases, no reported uses were received from the VCRP, but a maximum use concentration was provided in the industry survey. For example, citrus grandis (grapefruit) peel oil was not reported in the VCRP database to be in use, but the industry survey indicated that it is used at concentrations up to 0.05%. It should be presumed that citrus grandis (grapefruit) peel oil is used in at least one cosmetic formulation.

Table 9 lists all citrus-derived peel oils not indicated to be in use based on the VCRP data or the results of the Council concentration of use survey.

Citrus paradisi (grapefruit) peel oil was reported to be used in hair spray and could possibly be inhaled. This ingredient was reported to be used in a pump hair spray at 0.00068%. 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.[10-13] 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.[11,12]

Under the rules governing cosmetic products in the European Union, citrus-derived ingredients must have furocoumarin content below 1 mg/kg in sun-protection products and in bronzing products.[14] The International Fragrance Association (IFRA) has issued standards for citrus oils and other furocoumarin-containing essential oils.[15] Thus, 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 0.0075% or 75 ppm in a fragrance compound 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. Restrictions for furocoumarin-containing essential oils have been recommended for bergamot oil expressed, bitter orange oil expressed, grapefruit oil expressed, lemon oil cold pressed, and lime oil expressed.

An IFRA standard also has been issued for 7-methoxycoumarin, which is prohibited for use in fragrance compounds.[16] Based on established maximum levels of this substance from commercially-available natural sources (like essential oils, extracts and absolutes), exposure to 7-methoxycoumarin from the use of these oils and extracts is regarded to be acceptable if the level of 7-methoxycoumarin in the finished product does not exceed 100 ppm. An example maximum concentration based on this standard is 0.1% for lime cold pressed oil.

The IFRA has also set limits on the amounts of some citrus-derived oils in finished products. For leave-on products applied to skin areas exposed to direct sunlight, these limits include: 1.25% bitter orange peel expressed;[17] 0.4% bergamot oil expressed;[18] 4% grapefruit oil expressed;[19] 2% lemon oil cold-pressed;[20] 0.7% lime oil expressed.[21] There are no restrictions for any of these oils in rinse-off products and products that are not applied to the skin. IFRA specified that if combinations of phototoxic fragrance ingredients are used, the use levels must be reduced accordingly, so that the sum of the concentrations of all phototoxic fragrance ingredients, expressed as a percentage of their respective recommended maximum levels, shall not exceed 100% in the consumer product. Additionally, the general standard described above for 'Citrus oils and other furocoumarins-containing essential oils' must be considered.

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.[22]

Bergamot oil is used in aromatherapy and is an analgesic, antidepressant, antimicrobial, digestive aid, sedative, fever reducer, and has anticholesterol effects.[23]

TOXICOLOGICAL STUDIES

Acute Toxicity

The citrus ingredients in this assessment are found in foods, and the daily exposure from food use would result in a much larger systemic dose than that resulting from use in cosmetic products. Also, as noted earlier, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from 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, bergamots, grapefruits, bitter oranges, oranges, and tangerines are described as flavoring agents in the USP Food Chemicals Codex.[5] Consequently, the systemic toxicity potential via oral exposure is not addressed further in this report. The safety focus of use of these citrus ingredients as cosmetic ingredients is on the potential for irritation and sensitization from dermal exposure.

Dermal – Non-Human

Lemon Oil

The dermal LD_{50} of lemon oil was greater than 10 g/kg in rabbits.[3] An occlusive patch of undiluted oil was applied to the skin of six animals for 24 h. One animal died during the observation period.

Mandarin Oil – Expressed (*Citrus reticulata*)

The dermal LD_{50} of mandarin peel oil (Citrus reticulata) was greater than 5 g/kg in rabbits.[7] An occlusive patch of undiluted oil was applied to the skin of seven animals for 24 h.

Orange Oil

The dermal LD_{50} of sweet orange oil was greater than 5 g/kg in female New Zealand White rabbits.[4] An occlusive patch of undiluted oil was applied to the skin of 10 animals for 24 h. Skin irritation indicated by moderate redness in 10/10 animals, slight edema in 3/10 animals, and moderate edema in 5/10 animals was observed.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No published reproductive and developmental studies on citrus-derived peel oils were identified in a literature search for these ingredients and no unpublished data were submitted.

GENOTOXICITY

Genotoxicity studies for in vitro assays are summarized in Table 10. No genotoxic effects were observed in lemon oil or sweet orange oil in bacterial reverse mutation assays, mouse lymphoma cell mutation assays, or Chinese hamster chromosome aberration assays.[3,4]

CARCINOGENICITY

Orange Oil, Lemon Oil, Grapefruit Oil and Lime Oil

Tumor-promoting activity was observed in mouse skin exposed to essential oils of orange (sweet), lemon, grapefruit, or lime.[24] Chemical constituents of these oils were not fully analyzed in this study other than to separate terpene and non-terpene fractions. In the study, groups of 10 male and 10 female strain 101 mice received a single application of 9,10-dimethyl-1,2-benzanthracene (DMBA) in acetone (300 µg in 0.2 ml in 4 groups, 225 µg in 0.15 ml in a fifth group). Group 1 was a control group that received no further treatments. Groups 2-5 received weekly applications of 0.25 ml of the test substances 3 weeks after the application of DMBA.

By the fifth week, papillomas were observed in Group 3 (lemon oil), Group 4 (grapefruit oil), and Group 5 (lime oil). Papillomas were observed in Group 2 (orange oil) by the 12th week. After 33 weeks, 10/20 mice in the lemon oil and lime oil treatment groups and 13/20 mice in the grapefruit oil and orange oil groups had papillomas. Only 1 mouse in the control group had papillomas after 33 weeks, and the affected site was not on the treated skin. Additionally, 1 female mouse of the lemon oil group developed a sebaceous-gland tumor of the nipple. No malignant skin tumors were observed in the orange oil group: treatment was stopped after 42 weeks. Squamous cell carcinomas of the skin were observed in 2 mice from the lemon oil group and 2 mice of the grapefruit oil group between weeks 36 and 55. One malignant skin tumor was observed in the lime oil group at week 34; however, the mouse was found dead and a proper histological examination was not possible. No malignant skin tumors were observed in the control group. Non-dermal tumors during the treatment period were observed in 1 mouse of the orange oil group (a hemangioma of the subcutaneous tissue starting at week 7) and in 1 mouse of the grapefruit oil group (a spindle cell sarcoma of the subcutaneous tissues). No tumors of the internal organs were observed. The survival of all the mice in this experiment was poor due to a very high incidence of renal disease.[24]

Orange Oil

Tumor-promoting activity was observed in mouse skin exposed to orange (sweet) oil.[24] In the study, groups of 10 male and 10 female strain 101 mice received a single application of DMBA in acetone (300 µg in 0.15 ml). One group (15 mice of each sex) was a control group that received no further treatments. Two groups received weekly applications of 0.25 ml of 40% orange oil in acetone or 80% orange oil in acetone 3 weeks after the initial application of DMBA. The applications continued for 37 weeks.

Papillomas were observed in both groups treated with orange oil starting on the 12th week. After 33 weeks, 5/10 mice treated with 40% orange oil and 10/10 mice treated with 80% orange oil has papillomas, and at study end, only 1 tumor of each group was found outside of the treated area. Four mice in the control group had papillomas by week 33, but these tumors were outside of the treated area of the skin. Malignant tumors were observed in one mouse of each treatment group, arising from the pre-existing papilloma. Both tumors were squamous-cell carcinomas infiltrating the panniculus muscle. Additionally, tumors of the urethral orifice were observed in 4 female mice of the 40% orange oil group. The survival of all the mice in this experiment was poor due to a very high incidence of renal disease.

In the same study, tumor-promoting activity was observed in mice exposed to undiluted orange oil after pretreating the mice with either dermal or intraperitoneal injections of urethane. The effect was weak compared to the effects observed after DMBA induction.

A similar experiment performed in the same study tested the carcinogenic effects of orange oil without pretreatment with DMBA or urethane. This study found no evidence of direct tumorigenic effects on the treated mouse skin. Urethral orifice tumors were observed in one female mouse of the 40% orange oil group and in one female mouse of the 80% orange oil group. A papilloma was observed on the head of a mouse (outside of the treatment site) that was treated with 80% orange oil.[24]

IRRITATION AND SENSITIZATION

Dermal Irritation

Dermal irritation studies are summarized in Table 11. Irritation was observed in animals treated with unreported concentrations of mandarin peel oil. In human subjects, no irritation was observed after topical exposure to bergamot oil (up to 15%), lemon oil (up to 20%), or mandarin peel oil (8%).[3,4,7,25]

Ocular Irritation

Lemon Oil

Lemon oil tested at 5% was not irritating to the eyes of 3 albino rabbits.[3] Each rabbits had 0.1 ml of the test material instilled into the right eye with no further treatment. The left eye served as the control. Eyes were examined every 24 h for 4 days and then again on the 7th day. No corneal opacity or iris congestion was observed. An intense conjunctival irritation occurred involving chemosis and discharge. Treated eyes were normal on the 7th day.

Orange Oil

Orange oil tested undiluted did not induce significant or irreversible damage to the eyes of 3 male New Zealand White rabbits.[4] The test was performed in accordance to OECD guideline 405. The test material (0.1 ml) was instilled into one eye of each rabbit. The mean scores calculated for the three animals across 3 scoring times were 0.0 for corneal opacity and iris lesions and 1.0 for reddening of the conjunctivae.

Sensitization

Sensitization studies are presented in Table 12. Mandarin peel oil was not sensitizing in human maximization tests. In studies of 250 dermatitic patients, less than 2.5% had positive reactions to bergamot oil, bitter orange oil, lemon oil, or sweet orange oil tested at 2% in paraffin.[3,4,7,26]

Phototoxicity and Photosensitization

Phototoxicity and photosensitization studies are presented in Table 13. Mixed results were observed in non-human and human phototoxicity and photosensitization studies of diluted and undiluted bergamot oil, lime oil, lemon oil, grapefruit oil, mandarin oil, tangerine oil, bitter orange oil, and bitter orange peel oil. Many of the citrus-derived peel oils contain constituents that are photoactive agents, although those noted to be furocoumarin-free tended not to induce photosensitization.[17,27-31]

Case Reports

Case reports describing reactions to citrus-derived peel oils are summarized in Table 14. Phototoxicity and photosensitization were noted in several patients exposed to bergamot oil.[32,33]

Occupational Exposure

In a retrospective study (2001-2010) of professional food handlers in Denmark, 8.5% (16/188) of the patients had positive skin prick test reactions to orange peel and 7.9% (15/191) of the patients had positive skin prick test reactions to lemon peel.[34]

SUMMARY

The 16 citrus-derived peel oils described in this report function primarily as skin conditioning agents-miscellaneous and fragrance. Botanicals such as citrus are comprised of hundreds of constituents, some of which have the potential to cause toxic effects; for example, bergapten (aka 5-methoxysporalen or 5-MOP) is a naturally occurring furanocoumarin (psoralen) in bergamot oil that causes phototoxicity. Presently, CIR is reviewing the information available on the potential toxicity of each citrus peel oil-derived ingredient as a whole, complex substance; CIR is not reviewing the potential toxicity information on the individual constituents of which the citrus-derived ingredients are comprised. CIR requested information on the concentrations (including ranges, means, upper 95 percent confidence limits, detection limits, etc.) of individual constituents in the citrus peel oil-derived ingredients used in cosmetics, to facilitate the safety assessment of these ingredients as used in cosmetics. Such information on constituents that have been identified as constituents of concern by the CIR Expert Panel in previous safety assessments, or by other recognized scientific expert review bodies, is especially important.

Citrus limon (lemon) peel oil has the most reported uses in cosmetics and personal care products, with a total of 490; more than half of the uses are in leave-on skin care preparations. The range of highest maximum use concentrations for citrus limon (lemon) peel oil is 0.0001% to 0.5%, with 0.5% reported in “other” skin care preparations. Citrus aurantium dulcis (orange) peel oil (reported as citrus sinensis (sweet orange) peel oil to the VCRP) has the second greatest number of overall uses reported, with a total of 289; about half of those uses are in leave-on skin care preparations. Citrus aurantium dulcis (orange) peel oil had a highest maximum use concentration range of 0.00002% to 29%, with 29% reported in non-coloring hair conditioners.

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. Restrictions for furocoumarin-containing essential oils and limits on the amounts of citrus-derived oils in finished products have been recommended for bergamot oil expressed, bitter orange oil expressed, grapefruit oil expressed, lemon oil cold pressed, and lime oil expressed.

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

The dermal LD_{50} of undiluted mandarin peel oil (*Citrus reticulata*) and undiluted sweet orange oil was greater than 5 g/kg in rabbits. In undiluted lemon oil, the dermal LD_{50} was greater than 10 g/kg in rabbits.

No genotoxic effects were observed in lemon oil or sweet orange oil in bacterial reverse mutation assays, mouse lymphoma cell mutation assays, or Chinese hamster chromosome aberration assays.

Tumor-promoting activity was observed in mouse skin exposed to undiluted essential oils of orange (sweet), lemon, grapefruit, or lime after pretreatment with DMBA. Related studies of 40%, 80%, or 100% orange oil following pretreatment with DMBA or urethane also reported tumor-promoting activity, although the effect was weaker in the mice induced with urethane. No tumorigenic effects were observed in mice tested with orange oil without pretreatment with DMBA or urethane. Survival rates of the mice in these experiments were poor because of a very high incidence of renal disease

Irritation was observed in animals treated with unreported concentrations of mandarin peel oil. In human subjects, no irritation was observed after topical exposure to bergamot oil (up to 15%), lemon oil (up to 20%), or mandarin peel oil (8%).

In rabbits, lemon oil tested at 5% was not irritating and orange oil tested undiluted did not induce significant or irreversible damage to the eyes.

Mandarin peel oil was not sensitizing in human maximization tests. In studies of 250 dermatitic patients, less than 2.5% had positive reactions to bergamot oil, bitter orange oil, lemon oil, or sweet orange oil tested at 2% in paraffin.

Mixed results were observed in non-human and human phototoxicity and photosensitization studies of diluted and undiluted bergamot oil, lime oil, lemon oil, grapefruit oil, mandarin oil, tangerine oil, bitter orange oil, and bitter orange peel oil. Many of the citrus-derived peel oils contain constituents that are photoactive agents, although those noted to be furocoumarin-free tended not to induce photosensitization.

Phototoxicity and photosensitization were noted in several patients exposed to bergamot oil. A retrospective occupational study of food handlers noted positive reactions to orange and lemon peels.

No published studies on reproductive and development toxicity of citrus-derived peel oils were discovered and no unpublished data were submitted to address these topics.

TABLES

Table 1. Definitions and functions of Citrus-derived ingredients. [2]

Ingredient	Definition	Function
Citrus Aurantifolia (Lime) Peel Oil	Citrus Aurantifolia (Lime) Peel Oil is the volatile oil obtained from the peel of *Citrus aurantifolia.*	Fragrance Ingredients
Citrus Aurantium Amara (Bitter Orange) Peel Oil CAS No. 68916-04-1	Citrus Aurantium Amara (Bitter Orange) Peel Oil is the volatile oil obtained from the peel of *Citrus aurantium amara*.	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Bergamia (Bergamot) Peel Oil CAS No. 89957-91-5	Citrus Aurantium Bergamia (Bergamot) Peel Oil is the volatile oil obtained from the peel of *Citrus aurantium bergamia.*	Fragrance Ingredients
Citrus Aurantium Currassuviensis Peel Oil	Citrus Aurantium Currassuviensis Peel Oil is the volatile oil derived from the peel of the laraha orange, *Citrus aurantium currassuviensis.*	Fragrance Ingredients
Citrus Aurantium Dulcis (Orange) Peel Oil CAS No. 8008-57-9	Citrus Aurantium Dulcis (Orange) Peel Oil is the volatile oil obtained by expression from the peel of *Citrus sinensis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Clementina Peel Oil	Citrus Clementina Peel Oil is the volatile oil obtained from the peel of *Citrus clementina*.	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Peel Oil CAS No. 8016-20-4	Citrus Grandis (Grapefruit) Peel Oil is the volatile oil obtained from the peel of the grapefruit, *Citrus grandis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Iyo Peel Oil	Citrus Iyo Peel Oil is the volatile oil obtained from the peel of *Citrus iyo*.	Skin-Conditioning Agents - Emollient
Citrus Junos Peel Oil	Citrus Junos Peel Oil is the volatile oil obtained from the peel of *Citrus junos.*	Cosmetic Astringents
Citrus Limon (Lemon) Peel Oil CAS No. 8008-56-8; 8020-19-7; 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Peel Oil is the volatile oil obtained from the peel of *Citrus limon.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Medica Vulgaris Peel Oil	Citrus Medica Vulgaris Peel Oil is the volatile oil obtained from the peel of *Citrus medica vulgaris.*	Fragrance Ingredients
Citrus Nobilis (Mandarin Orange) Peel Oil CAS No. 8008-31-9; 84696-35-5	Citrus Nobilis (Mandarin Orange) Peel Oil is the oil obtained from the peel of the mandarin orange, *Citrus nobilis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Paradisi (Grapefruit) Peel Oil CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Peel Oil is the volatile oil obtained from the peel of *Citrus paradisi.*	Fragrance Ingredients
Citrus Reticulata (Tangerine) Peel Oil CAS No. 8008-31-9	Citrus Reticulata (Tangerine) Peel Oil is the volatile oil obtained from the peel of *Citrus reticulata*.	Deodorant Agents; Flavoring Agents; Fragrance Ingredients
Citrus Tachibana/Reticulata Peel Oil	Citrus Tachibana/Reticulata Peel Oil is the volatile oil obtained from the peel of the hybrid of *Citrus tachibana* and *Citrus reticulata.*	Skin-Conditioning Agents - Emollient
Citrus Tangerina (Tangerine) Peel Oil	Citrus Tangerina (Tangerine) Peel Oil is the volatile oil obtained from the peel of *Citrus tangerina*.	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous

*Previously reviewed by CIR.[1]

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

Citrus Aurantifolia (Lime) Peel Oil
Citrus Aurantium Bergamia (Bergamot) Peel Oil
Citrus Aurantium Currassuviensis Peel Oil
Citrus Medica Vulgaris Peel Oil
Citrus Paradisi (Grapefruit) Peel Oil

Table 3. Physical and chemical properties of Citrus-derived peel oils.

Property	Description	Reference
	Bergamot Oil (Cold-Pressed)	
Color	green to yellow-green or yellow-brown	5
Odor	fragrant, sweet-fruity	5
optical rotation/angular rotation	+12º to +30º	5
Solubility	miscible with alcohol and glacial acetic acid; soluble in most fixed oils; insoluble in glycerin and propylene glycol	5
solubility in alcohol	1 ml of sample dissolves in 2 ml of 90% alcohol	5
Esters	no less than 36.0% of esters, calculated as linalyl acetate	5
refractive index	1.465-1.468 at 20º C	5
residue of evaporation	no more than 6.0%	5
specific gravity	0.871-0.879	5
UV absorbance	max. at 315 nm; no less than 0.32	5
	Bitter Orange Oil (Cold-Pressed)	
Color	pale yellow or yellow-brown	5
Odor	characteristic aromatic odor of the Seville orange	5
optical rotation/angular rotation	+88º to +98º	5
Solubility	miscible with absolute alcohol and with an equal volume of glacial acetic acid; soluble in fixed oils and mineral oil; slightly soluble in propylene glycol; relatively insoluble in glycerin	5
Aldehydes	no less than 0.5% and no more than 1.0% of aldehydes, calculated as decyl aldehyde	5
refractive index	1.472-1.476 at 20º C	5
residue of evaporation	2.0-5.0%	5
specific gravity	0.845-0.851	5
	Grapefruit Oil (Cold-Pressed)	
Color	yellow, sometimes red	5
optical rotation/angular rotation	+91º to +96º	5
Solubility	soluble in most fixed oils and mineral oil with opalescence or cloudiness; slightly soluble in propylene glycol; insoluble in glycerin	5
refractive index	1.475-1.478 at 20º C	5
residue of evaporation	5.0% -10.0%	5
specific gravity	0.848-0.856	5
	Citrus Aurantifolia (Lime) Oil	
Color	colorless to greenish yellow	6
Odor	fresh citrus, intense	6
optical rotation	+34º to +47º	6
Solubility	insoluble in water, soluble in ethanol and propylene glycol	6
refractive index	1.4477-1.4745	6
specific gravity	0.855-0.863	6
	Lime Oil (Distilled)	
Color	colorless to greenish yellow	5
Odor	mild citrus, floral	5
optical rotation/angular rotation	+34º to +47º	5
Solubility	soluble in most fixed oils and mineral oil; insoluble in glycerin and propylene glycol	5
solubility in alcohol	1 ml sample dissolves in 5 ml of 90% alcohol	5
Aldehydes	between 0.5% and 2.5% of aldehydes, calculated as citral	5
refractive index	1.474 – 1.477 at 20 ºC	5
specific gravity	0.855-0.863	5
	Lime Oil (Cold-Pressed)	
Color	yellow to brown green to green	5
Odor	fresh lime peel	5
optical rotation/angular rotation	Mexican type: +35º to +41º; Tahitian type: +38º to +53º	5
Solubility	soluble in most fixed oils and mineral oil; insoluble in glycerin and propylene glycol	5
Aldehydes	Mexican type: no less than 4.5% and no more than 8.5% of aldehydes, calculated as citral; Tahitian type: no less than 3.2% and no more than 7.5% of aldehydes, calculated as citral	5
refractive index	Mexican type: 1.482-1.486; Tahitian type: 1.476-1.486	5
residue of evaporation	Mexican type: 10.0% to 14.5%; Tahitian type: 5.0% to 12.0%	5
specific gravity	Mexican type: 0.872-0.881; Tahitian type: 0.858-0.876	5
UV absorbance	max. at 315 nm; Mexican type: no less than 0.45; Tahitian type: no less than 0.24	5
	Citrus Limon (Lemon) Oil	
Color	pale to deep yellow or greenish yellow	6
Odor	fresh citrus, intense	6
optical rotation	+57 to +65.6	6
Solubility	insoluble in water, soluble in ethanol and propylene glycol	6
refractive index	1.474-1.467	6
specific gravity	0.849-0.855	6

Table 3. Physical and chemical properties of Citrus-derived peel oils.

Property	Description	Reference
	Lemon Oil (Distilled)	
Color	colorless to pale yellow	5
Odor	fresh lemon peel	5
optical rotation/angular rotation	+55º to +75º	5
Solubility	soluble in most fixed oil, mineral oil, and alcohol (with haze); insoluble in glycerin and propylene glycol	5
solubility in alcohol	1 ml sample dissolves in 5 ml of 90% alcohol	5
Aldehydes	between 1.0% and 3.5% of aldehydes, calculated as citral	5
refractive index	1.470 – 1.475 at 20 ºC	5
specific gravity	0.842-0.856	5
UV absorbance	max. at 315 nm, no less than 0.01	5
	Lemon Oil (Cold-Pressed)	
Color	pale to deep yellow or green-yellow	5
Odor	fresh lemon peel	5
optical rotation/angular rotation	California and Italian types: +57º to +65.6º; Desert type: +67º to +78º	5
Solubility	miscible with dehydrated alcohol and glacial acetic acid	5
solubility in alcohol	1 ml of sample dissolves in 3 ml of 95% alcohol, slight haze possible	5
Aldehydes	Desert type: no less than 1.7% of aldehydes, calculated as citral; California type: no less than 2.2% and no more than 3.8% of aldehydes, calculated as citral; Italian type: no less than 3.0% and no more than 5.5% of aldehydes, calculated as citral	5
refractive index	1.473-1.476 at 20 ºC	5
residue of evaporation	between 5.0% to 14.5%	5
specific gravity	Desert type: 0.846-0.851; California and Italian types: 0.849-0.855	5
UV absorbance	max. at 315 nm; Desert and California types: no less than 0.2; Italian type: no less than 0.49	5
	Orange Oil (Distilled)	
Color	colorless to pale yellow	5
Odor	mild citrus floral	5
optical rotation/angular rotation	+94º to +99º	5
Solubility	soluble in most fixed oil, mineral oil, and alcohol (with haze); insoluble in glycerin and propylene glycol	5
solubility in alcohol	1 ml sample dissolves in 5 ml of 90% alcohol	5
refractive index	1.471 – 1.474 at 20 ºC	5
specific gravity	0.840-0.844	5
UV absorbance	max. at 330 nm, no less than 0.01	5
	Orange Oil (Cold-Pressed)	
Color	intensely yellow, orange, or deep orange	5
Odor	characteristic of fresh, sweet orange peel	5
optical rotation/angular rotation	+94º to +99º	5
Solubility	miscible with dehydrated alcohol and carbon disulfide; soluble in glacial acetic acid	5
Aldehydes	no less than 1.2% and no more than 2.5% of aldehydes, calculated as decyl aldehyde	5
refractive index	1.472-1.474 at 20 ºC	5
specific gravity	0.842-0.846	5
UV absorbance	max. at 330 nm; California type: no less than 0.130; Florida type: no less than 0.240	5
	Citrus Reticulata Peel Oil	
physical state and appearance	clear, mobile, dark-orange to reddish-orange or brownish-orange liquid	7
Odor	orange-like	7
optical rotation	+63° to +78°	7
refractive index	1.4730-1.4770 (20°C)	7
specific gravity	0.847-0.853 (25/25°C)	7
	Tangerine Oil (Cold-Pressed)	
Color	red-orange to brown-orange	5
Odor	pleasant, orange	5
optical rotation/angular rotation	+88º to +96º	5
Solubility	soluble in most fixed oils and mineral oil; slightly soluble in propylene glycol; relatively insoluble in glycerin	5
Aldehydes	0.8% to 1.9% of aldehydes, calculated as decyl aldehyde	5
refractive index	1.473-1.476 at 20 ºC	5
residue of evaporation	2.3% - 5.8%	5
specific gravity	0.844-0.854	5

Table 4. Major constituents of some of the Citrus species

Citrus species	Constituents
Citrus aurantiifolia (lime)[35] pericarp, i.e., fruit, including skin and pulp	- contains an essential oil (7%), whose main components are citral, limonene, β-pinene, and fenchone (up to 15%); - lime oil contains oxypeucedanin. - contains terpineol, bisabolene and other terpenoids - fresh juice of acid limes averages approximately 7.7% citric acid and 0.3% invert sugar - the peel contains a volatile oil, including limonene and citral
Citrus aurantiifolia (lime) plant part not specified[36,37]	- contains coumarins (e.g., isopimpinellin, and limettin), furocoumarins (e.g., psoralens, such as bergapten and xanthotoxin), pyranocoumarins, citral, (+)-limonene, pinenes, alkanes, alkanols, alkanals, citrus acid, and flavonoids
Citrus aurantium (bitter orange)	- contains synephrine alkaloids and para-octopamine[38] - contains the furocoumarins bergapten and oxypeucedanin[38] - the peel, flowers, and leaves contain the flavonoids limonene, hesperidin, neohesperidin, naringin, and tangaretin; the flavonoid content is higher in the flowers than the leaves[38] - the main constituents of the peel are the volatile oil and the glucoside aurantiamarin; other constituents include hesperidin, isohesperidin, hesperic acid, and aurantiamaric acid[22] - in the peel of the immature fruit, the main constituents are naringin and hesperidin[22] - in the flesh of the immature fruit, the main constituent is umbelliferone[22] -volatile oil contains limonene, nerol, geraniol, linalool, linalyl acetate, neryl acetate, geranyl acetate, citronellyl acetate, and methyl anthranilate[37]
Citrus limon (lemon) peel[39]	- 0.2% to 0.6% essential oil, with (+)-limonene, citral, and other monoterpenes as major components -flavonoids such as neohesperidosides and rutinosides of hesperetin and naringenin -flavone glycosides -carotenoids -citric acid and other plant acids -coumarin derivatives -pectins
Citrus limon (lemon) Plant part not specified[40]	-(+)-limonene, citral, n-nonanal, n-decanal, n-dodecanal, linalyl acetate, geranyl acetate, citronellyl acetate, methyl anthranilate, sinensetin, furocoumarins, naringin, nehesperidin dyhydro chalcones, hesperidin, rutin
Citrus paradisi (grapefruit)[41]	- the juice contains vitamin C, furanocoumarins (bergamottin, 6',7'-epoxybergamottin, 6',7'-dihydroxybergamot-tin), flavonoids (naringenin, naringin) and sesquiterpen (nootkatone), bergapten, polyamines (e.g. putrescine), and limonoids; naringin is the most abundant flavonoid in grapefruit juice, present in concentrations of up to 1mM/L - the dried peels contain high amounts of ascorbic acid, polyphenols, and carotenoids
Citrus reticulata (tangerine)[42]	- contains carotenoids, such as beta-cryptoxanthin - the juice concentrate contains beta-cryptoxanthin xanthophyll esters (zeaxanthin and lutein) - the peel contains fat, protein, ash, magnesium, carotenoids, dietary fiber, and polyphenols
Citrus reticulata oil (from the mandarin orange)[7]	- limonene, p-cymene, γ-terpinene, α-thujene, α-pinene, camphene, sabinene, β-pinenemyrcene, methyl heptenone, octanol, octanol, terpinolene, linalool, nonanal, citronellal, terpinen-4-ol, α-terpineol, decanal, nerol, citronellol, neral, geranial, thymol, *N*-methyl anthranilate, caryophyllene, α-humulene, longifolene
Citrus sinensis (sweet orange)[37]	-(+)-limonene, citral, citronellal, nootkatone, sinesal, n-nonanal, n-necanal, n-dodecanal, linalyl acetate, geranyl acetate, citronellyl acetate, methyl anthranilate, furocoumarins, and flavonoids

Table 5. Typical levels of 5-methoxypsoralen (5-MOP)

Ingredient	5-MOP level[15]
Petitgrain Mandarin oil	50 ppm
Tangerine oil cold pressed	50 ppm
Mandarin oil cold pressed	250 ppm

Table 6. Levels of major coumarins and furocoumarins in lemon oil and lime oil

Compound	% in Lemon Oil[6]	% in Lime Oil[6]	Photosensitizing Activity[6]
5-geranoxypsoralen	0.0387	2.2-2.5	0
5-geranoxy-7-methoxycoumrin	0.0603	2.2-5.2	0
5-geranoxy-8-methoxypsoralen	not analyzed	0.945	0
5,7-dimethoxycoumarin	0.0295	0.464	0
5,8-dimethoxypsoralen	not analyzed	0.508	0
Oxypeucedanin	0.005-0.073	0.0025	+
5-methoxypsoralen	0.0001-0.0087	0.17-0.33	++++

Table 7. 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) [43]
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 8. Frequency (2014) and concentration of use (2013) according to duration and type of exposure for Citrus-derived ingredients. [8,9]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Citrus Aurantium Amara (Bitter Orange) Peel Oil		**Citrus Aurantium Dulcis (Orange) Peel Oil****		**Citrus Bergamia (Bergamot) Peel Oil**[7]		**Citrus Grandis (Grapefruit) Peel Oil**	
Totals[1]	**127**	**0.05-2**	**289**	**0.00002-29**	**188**	**NR**	**NR**	**0.00004-0.05**
Duration of Use								
Leave-On	74	0.2-2	156	0.00038-0.54	106	NR	NR	0.0004-0.0008
Rinse-Off	45	0.05-0.25	110	0.00002-29	65	NR	NR	0.00004-0.05
Diluted for (Bath) Use	8	NR	23	0.33	17	NR	NR	0.0014
Exposure Type								
Eye Area	2	NR	3	0.1	1	NR	NR	NR
Incidental Ingestion	1	0.75	4	NR	2	NR	NR	NR
Incidental Inhalation-Spray?[2,6]	55	NR	124	0.00038	83	NR	NR	NR
Reported Spray[3]	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder?[4,6]	47	NR	99	NR	51	NR	NR	NR
Reported Powder[3]	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	115	0.05-2	218	0.001-0.4	160	NR	NR	0.00004-0.05
Deodorant (underarm)-Spray?[2]	NR	NR	1	NR	1	NR	NR	NR
Reported Spray[3]	NR	NR	NR	NR	NR	NR	NR	NR
Reported as Not Spray[3]	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	11	NR	65	0.00002-29	26	NR	NR	0.005
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	2	0.5-0.54	NR	NR	NR	NR
Mucous Membrane	21	0.25-0.75	56	0.1-0.33	47	NR	NR	0.0014
Baby Products	6	NR	8	NR	NR	NR	NR	NR

	Citrus Junos Peel Oil		**Citrus Limon (Lemon) Peel Oil**		**Citrus Nobilis (Mandarin Orange) Peel Oil**		**Citrus Paradisi (Grapefruit) Peel Oil**	
Totals[1]	**6**	**NR**	**490**	**0.0001-0.5**	**152**	**0.00005-0.1**	**206**	**0.00068-0.5**
Duration of Use								
Leave-On	4	NR	297	0.0001-0.5	86	0.00005-0.1	123	0.00068-0.5
Rinse-Off	2	NR	165	0.0006-0.001	58	0.00005-0.03	73	NR
Diluted for (Bath) Use	NR	NR	28	0.012	8	NR	10	NR
Exposure Type								
Eye Area	NR	NR	9	NR	NR	NR	1	NR
Incidental Ingestion	NR	NR	8	NR	1	0.0099	2	NR
Incidental Inhalation-Spray?[2,6]	2	NR	201	0.06	74	NR	94	NR
Reported Spray[3]	NR	NR	NR	NR	NR	NR	NR	0.00068[a]
Incidental Inhalation-Powder?[4,6]	1	NR	163	0.06	66	NR	76	NR
Reported Powder[3]	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	6	NR	411	0.0001-0.5	136	0.00005-0.1	177	0.5
Deodorant (underarm)-Spray?[2]	NR	NR	NR	NR	NR	NR	NR	NR
Reported Spray[3]	NR	NR	NR	NR	NR	NR	NR	NR
Reported as Not Spray[3]	NR	NR	NR	0.002	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	67	NR	15	0.00005-0.03	27	0.00068
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	3	0.0001-0.14	NR	0.012	NR	NR
Mucous Membrane	1	NR	96	0.001-0.012	40	0.0099	44	NR
Baby Products	NR	NR	8	NR	NR	NR	3	NR

Table 8. Frequency (2014) and concentration of use (2013) according to duration and type of exposure for Citrus-derived ingredients. [8,9]

	# 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 Reticulata (Mandarin Orange) Peel Oil[7]		**Citrus Sinensis Sanguinello (Blood Orange) Peel Oil[7]**		**Citrus Tangerina (Tangerine) Peel Oil**			
Totals[1]	**2**	**NR**	**8**	**NR**	**34**	**0.0000013**		
Duration of Use								
Leave-On	1	NR	4	NR	18	0.0000013		
Rinse-Off	1	NR	4	NR	15	0.0000013		
Diluted for (Bath) Use	NR	NR	NR	NR	1	NR		
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	NR	1	NR		
Incidental Inhalation-Spray?[2,6]	1	NR	4	NR	14	0.0000013		
Reported Spray[3]	NR	NR	NR	NR	NR	NR		
Incidental Inhalation-Powder?[4,6]	1	NR	3	NR	13	NR		
Reported Powder[3]	NR	NR	NR	NR	NR	NR		
Dermal Contact	2	NR	8	NR	26	NR		
Deodorant (underarm)-Spray?[2]	NR	NR	NR	NR	NR	NR		
Reported Spray[3]	NR	NR	NR	NR	NR	NR		
Reported as Not Spray[3]	NR	NR	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	NR	NR	7	0.0000013		
Hair-Coloring	NR	NR	NR	NR	NR	NR		
Nail	NR	NR	NR	NR	NR	NR		
Mucous Membrane	NR	NR	4	NR	7	NR		
Baby Products	NR	NR	NR	NR	NR	NR		

NR = Not reported.

1. 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.
2. It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
3. Use in a spray product has been reported in response to a survey conducted by the Council.
4. It is possible these products may be powders, but it is not specified whether the reported uses are powders.
5. Use in a powder product has been reported in response to a survey conducted by the Council.
6. Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
7. Not listed as an INCI name; included because of similarity

** Recently changed name from Citrus Sinensis (Sweet Orange) Peel Oil to Citrus Aurantium Dulcis (Orange) Peel Oil. VCRP database still reflects old nomenclature.

a. 0.00068% in a pump hair spray.

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

Citrus Aurantifolia (Lime) Peel Oil
Citrus Aurantium Bergamia (Bergamot) Peel Oil
Citrus Aurantium Currassuviensis Peel Oil
Citrus Clementina Peel Oil
Citrus Iyo Peel Oil
Citrus Medica Vulgaris Peel Oil
Citrus Reticulata (Tangerine) Peel Oil
Citrus Tachibana/Reticulata Peel Oil

Table10 . Genotoxicity

Test Article	Concentration/Dose	Procedure	Results	Reference
		IN VITRO		
lemon oil in ethanol	10-5000 µg/plate	Reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA, with and without S9 metabolic activation.	Toxicity was observed in all test strains except WP2uvrA with and without S9; no significant dose-related increases in the number of revertant colonies in any test strain at any dose level, with or without metabolic activation; controls yielded expected results; lemon oil was not mutagenic in this assay.	[3]
lemon oil in ethanol	40-100 µg/ml	Cell mutation assay in mouse lymphoma L5178Y TK+/-cells in accordance with OECD guideline 476 in 2 independent experiments; with and without S9 metabolic activation	No significant increases in the mutation frequency were observed in either experiment, with or without S9 activation; controls yielded the expected results; lemon oil did not induce gene mutations in mouse lymphoma cells	[3]
lemon oil in ethanol	up to 0.125 mg/ml	Chromosome aberration study using Chinese hamster lung fibroblasts (CHL) in accordance with OECD guideline 473, without metabolic activation, 100 metaphases examined	The incidence of polyploidy cells at 24 h post-treatment was 1.0%, and the incidence of cells with structural chromosome aberrations at 24 h after treatment was 2.0%; the test material did not significantly induce chromosomal aberrations in CHL cells; lemon oil was not considered clastogenic.	[3]
sweet orange oil in ethanol	1-5000 µg/plate	Reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA, with and without S9 metabolic activation.	Cytotoxicity was observed in all test strains except WP2uvrA with and without S9; no significant dose-related increases in the number of revertant colonies in any test strain at any dose level, with or without metabolic activation; controls yielded expected results; sweet orange oil was not mutagenic in this assay.	[4]
sweet orange oil in ethanol	40-100 µg/ml	Cell mutation assay in mouse lymphoma L5178Y TK+/-cells in accordance with OECD guideline 476 in 2 independent experiments; with and without S9 metabolic activation	The test material did not induce a significant increase in the mutation frequency in both experiments, with or without metabolic activation; sweet orange oil did not induce gene mutations in mouse lymphoma cells	[4]
sweet orange oil in ethanol	up to 0.125 mg/ml	Chromosome aberration study using Chinese hamster lung fibroblasts (CHL) in accordance with OECD guideline 473, without metabolic activation, 100 metaphases examined	The incidence of polyploidy cells at 48 h post-treatment was 1.0%, and the incidence of cells with structural chromosome aberrations at 48 h after treatment was 1.0%; the test material did not significantly induce chromosomal aberrations in CHL cells; sweet orange oil was not considered clastogenic.	[4]

Table 11. Dermal irritation studies for Citrus-derived ingredients

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
NON-HUMAN					
lemon oil	5 ml/kg1	6 New Zealand White rabbits	acute dermal toxicity limit test scored under the Draize method; 24-h occlusive patches on intact and abraded skin	irritating	[3]
orange oil, cold pressed	0.5 ml of undiluted material	3 male albino rabbits	skin irritation study conducted according to OECD guideline 404; semioccluded patch for 4 h	mean erythema/eschar scores were 2.0, 1.7, and 2.0; mean edema scores were 2.0, 1.3, and 1.3; irritating to skin	[4]
mandarin peel oil, expressed (described as *Citrus reticulata*)	5 mg/kg	7 rabbits	24-h occlusive, single dose study	slight erythema and edema	[7]
mandarin peel oil, expressed (described as *Citrus reticulata*)	not reported	hairless mice and miniature swine; details not provided	open patch tests; details not provided	2 of 3 samples were irritating	[7]
HUMAN					
bergamot oil	0.3%, 2% or 15%; multiple vehicles	304 subjects at 0.3%, 30 subjects at 2%, and 29 subjects at 15%	24-72 h occlusive patch tests	no irritation at 2% or 15%, 3 $\pm$, and 9 + reactions at 0.3%	[25]
lemon oil	0.3%, 2% or 20%; multiple vehicles	34 subjects at 0.3%, 30 subjects at 2%, and 35 subjects at 20%	24-72 h occlusive patch tests	no irritation at 0.3% and 20%, 1 $\pm$ reaction at 2%	[25]
mandarin peel oil, expressed (described as *Citrus reticulata*)	8% in petrolatum	5 subjects	48 h closed patch test; details not provided	no irritation	[7]

Table 12. Sensitization studies for Citrus-derived ingredients

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
HUMAN					
bergamot oil	2% in paraffin	200 patients with dermatitis tested with 35 essential oils plus an additional 50 patients with balsam sensitivity	sensitization patch study, details not provided	4 positive reactions, details not provided	[26]
bitter orange oil	2% in paraffin	200 patients with dermatitis tested with 35 essential oils plus an additional 50 patients with balsam sensitivity	sensitization patch study, details not provided	6 positive reactions	[26]
lemon oil	2% in paraffin	200 patients with dermatitis tested with 35 essential oils plus an additional 50 patients with balsam sensitivity	sensitization patch study, details not provided	4 positive reactions, details not provided	[26]
lemon oil	not reported	100 subjects	Marzulli-Maibach sensitization technique; open patches	2% of the subjects had a positive skin reaction at the first reading after challenge, no reactions were noted at the 48 and 72 h readings, study concluded the test material was not sensitizing	[3]
mandarin oil, expressed (described as *Citrus reticulate*)	8% in petrolatum	25 subjects	maximization study, details not provided	not sensitizing	[7]
sweet orange oil	2% in paraffin	200 patients with dermatitis tested with 35 essential oils plus an additional 50 patients with balsam sensitivity	sensitization patch study, details not provided	3 positive reactions, details not provided	[26]
sweet orange oil	not reported	100 subjects	Marzulli-Maibach sensitization technique; open patches	4% of the subjects had positive skin reaction at the first reading after challenge, no reactions were noted at the 48 and 72 h readings, study concluded the test material was not sensitizing	[4]

Table 13. Photosensitization and phototoxicity studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			ALTERNATIVE STUDIES		
bergamot oil	concentrations not reported; tested in phosphate buffered saline (PBS), ethanol, or dimethyl sulfoxide (DMSO) with samples from 4 suppliers	3T3 Balb/c fibroblasts	-3T3 neutral red uptake phototoxicity test -light source was a doped mercury-metal halide lamp, filtered with 50% transmission at 335 nm to diminish UVB	borderline phototoxic, positive phototoxic results observed more frequently with the vehicles PBS and ethanol with certain supplied samples	[27]
orange oil, including deterpenated kind	concentrations not reported; tested in PBS, ethanol, or DMSO with samples from 3 suppliers	same as above	same as above	borderline phototoxic, positive phototoxic results observed more frequently with the vehicles PBS and ethanol with certain supplied samples	[28]
lemon oil, including deterpenated kind	same as above	same as above	same as above	borderline phototoxic, positive phototoxic results observed in all 3 vehicles, but were more prominent in the deterpenated sample	[28]
bergamot oil	up to 3.16% in water; up to 10.0% in sesame oil with samples from 4 suppliers	reconstructed human skin	-EpiDerm skin phototoxicity test -irradiated with 6 J/cm^2 in the UVA range -light source was a doped mercury-metal halide lamp, filtered with 50% transmission at 335 nm to diminish UVB	phototoxic, although no precise prediction of safe, non-phototoxic concentrations	[27]
orange oil, including deterpenated kind	up to 3.16% in water with samples from 3 suppliers	same as above	same as above	potential for phototoxicity observed	[28]
lemon oil, including deterpenated kind	same as above	same as above	same as above	cytotoxicity observed with deterpenated lemon oil; potential for phototoxicity observed	[28]
			NON-HUMAN		
bergamot oil	undiluted	male albino Hartley guinea pigs, 4/wavelength tested	-test material (30 µl) was applied for 1 h to 4 sites on clipped, depilated back skin of animals -another 4 sites were treated with solvent or untreated and served as controls -after pretreatment, the skin was exposed to monochromatic light at 4 different intensities -light source was a monochromator composed of a 5kW Xenon lamp with continuously variable wavelengths 200-700 nm, with an irradiance plane at exit 0.74 mW/cm^2 ·sec at 280 nm and 1.35 mW/cm^2 ·sec at 335 nm -skin specimens excised at 24 h post irradiation and reviewed microscopically for number of sunburn cells	-exposure to UVB radiation at 280, 295, or 310 nm induced dose-dependent increases in sunburn cells, with or without pretreatment with bergamot oil; no significant differences in regression coefficients were observed between the bergamot-oil treated and control sites -exposure to UVA radiation at 325, 335, 345, 350, or 365 nm induced many sunburn cells in bergamot oil treated sites, but not in untreated sites; regression coefficients indicated that the action spectrum for bergamot-oil induced sunburn cell formation was in the range of 325-365 nm, with a peak at 335-345 nm	[29]

Table 13. Photosensitization and phototoxicity studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
bergamot oil, expressed	undiluted and diluted; 20 µl	hairless mice, 6/grp	- a single dose was applied to a 2 cm^2 area on the back; animals were exposed to irradiation 30 min after dosing - one group was exposed to a compact-arc xenon lamp for 2 min (wavelengths <295 nm or 320-280 nm excluded) - one group was exposed to a long-arc xenon lamp for 40 min at a distance of 1 m; the weighted energy was 0.1667 W/m^2 - one group was exposed to 4 fluorescent black light lamps (UVB eliminated) for 1 h at an integrated UVA intensity of 3 W/m^2 -positive controls were treated with 0.01% 8-methoxypsoralen in methanol; negative controls with an appropriate vehicle - test sites were examined 4, 24, 48, 72, and 96 h after exposure	- a phototoxic response was observed with all three light sources - the lowest phototoxic concentration was 10%	30
bergamot oil, expressed	undiluted and diluted; 20 µl	miniature swine, 2/grp	as above	- a phototoxic response was observed with all three light sources - the lowest phototoxic concentration was 20%	30
bergamot oil, twice rectified (bergapten-free)	undiluted; 20 µl	hairless mice, 6/grp	as above	- a phototoxic response was not observed with any of the light sources	30
bergamot oil, twice rectified (bergapten-free)	undiluted; 20 µl	miniature swine, 2/grp	as above	- a phototoxic response was not observed with any of the light sources	30
lime oil, distilled (psoralen-free)	undiluted; 20 µl	hairless mice, 6/grp	as above	- a phototoxic response was not observed with any of the light sources	30
lime oil, distilled (psoralen-free)	undiluted; 20 µl	miniature swine, 2/grp	as above	- a phototoxic response was not observed with any of the light sources	30
lime oil, expressed	undiluted and diluted; 20 µl	hairless mice, 6/grp	as above	- a phototoxic response was observed with all three light sources - the lowest phototoxic concentration was 15%	30
lime oil, expressed	undiluted and diluted; 20 µl	miniature swine, 2/grp	as above	- a phototoxic response was observed with all three light sources - the lowest phototoxic concentration was 30%	30
bergamot oil, twice rectified (free of furocoumarin)	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- a single dose was applied to a 2 cm^2 area on the back - 30 min after dosing, the animals were exposed to UVA irradiation by a long-arc xenon lamp for 40 min at a distance of 1 m (weighted erythemal energy was 0.1667 W/m2) or 4 fluorescent blacklight lamps for 1 h (integrated UVA intensity of 3 W/m^2)	not photosensitizing	30
grapefruit oil	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	30
bergamot oil (free of furocoumarin)	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	30

Table 13. Photosensitization and phototoxicity studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
lime oil distilled (psoralen-free)	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
lime oil; expressed and rectified	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
lime oil Persian Florida; expressed and rectified	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
mandarin oil	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
mandarin oil, Italian	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
oil of lemon, California	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
oil of lemon, distilled	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
oil lemon petitgrain	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
oil mandarin, Italian	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
oil of tangerine	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
orange oil; cold pressed	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	not photosensitizing	[30]
bergamot oil, expressed (4samples)	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	[30]
California lemon oil	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	[30]
Italian lemon oil	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	[30]
oil lemon, Greek; cold pressed	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	[30]
oil lemon, Italian	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	[30]
oil lemon, IC	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	[30]
lime oil expressed	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	[30]
oil limes Persian	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	[30]

Table 13. Photosensitization and phototoxicity studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
oil limes, expressed and rectified	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	30
lime oil, expressed and rectified	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	30
bitter orange oil	undiluted; 20 µl	6 hairless mice and 2 miniature swine	- as above	- a phototoxic response was observed	30
lemon oil from multiple regional sources	20, 50, or 100% in ethanol	albino guinea pigs	- the oil was applied to the shaved back of the animals - the animals were then exposure to UVA radiation (320-400 nm, 13 J/cm^2) - erythema was evaluated 24, 48, and 72 h after irradiation - the samples were then fractionated subsequent phototoxicity testing of the isolated components was performed	-concentrations of 50% and 100% elicited phototoxicity in most of the samples tested - lemon oils from different regions had different phototoxicity potencies -oxypeucedanin and 5-methoxypsoralen (furocoumarins) were identified as phototoxic	31
HUMAN					
bitter orange peel oil	undiluted; 5 µl/cm^2	8 subjects	- an occlusive patch was applied to a 2 cm x 2 cm area - 1 cm site on each subject was exposed to visible light t of 20 J/cm^2 UVA - the test sites were scored after 24 and 48 h	all subjects reacted (details not provided)	17
bergamot oil	up to 10% in sesame oil and up to 1% in water from samples from 4 suppliers	5 female subjects	-2occlusive 10 mm diameter Finn Chambers on both sides of the lower back -exposure time to test material was 1 h -irradiation immediately to 1 site after patch removal at a dose of 5 J/cm^{2}as measured in the UVA range -test sites scored after 24, 48, and 72 h -light source was a doped mercury-metal halide lamp, filtered with 50% transmission at 335 nm to diminish UVB	-all subjects had positive reactions at all 3 time periods to bergamot in water at 0.1% and 0.0316% from 2 suppliers; however, no reactions were observed at 1% in water from 2 other suppliers -no reactions observed to bergamot oil in sesame oil	27
lemon oil, including deterpenated kind	up to 1% in water from samples from 3 suppliers	5 female subjects	-same as above	-phototoxic reactions concurrent with an irritation reactions were observed in lemon oil at 1% in 4/5 subjects up to 72 h after irradiation -phototoxic reactions were observed in deterpenated lemon oil at 0.1% in 2/5 subjects at 48 and 72 h after irradiation -no reactions were observed at concentrations of 0.1% or lower in lemon oil and 0.01% in deterpenated lemon oil	28
orange oil, including deterpenated kind	same as above	same as above	-same as above	-phototoxic reaction were observed in orange oil at 1% in 3/5 subjects at 24 h and 2/5 subjects at 48 and 72 h after irradiation -no reactions were observed at concentrations of 0.1% or lower in orange oil or 0.1% and 0.01% in deterpenated orange oil	28

Table 13. Photosensitization and phototoxicity studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
bergamot oil, expressed	undiluted and diluted; 20 µl	10 Caucasian subjects	- a single dose was applied to a 2 cm^2 area on the back - 30 min after dosing, subjects were exposed to sunlight for 30 min, a compact-arc xenon lamp for 2 min (wavelengths <295 nm or 320-280 nm excluded), or 4 fluorescent black light lamps (UVB eliminated) for 1 h at an integrated UVA intensity of 3 W/m^2 -positive controls were treated with 0.01% 8-methoxypsoralen in methanol; negative controls with an appropriate vehicle - test sites were examined 4, 24, 48, 72, and 96 h after exposure	- a phototoxic response was observed with all three light sources - the lowest phototoxic concentration with the simulated light sources was 20%	[30]
bergamot oil, twice rectified	undiluted	10 Caucasian subjects	- a single dose was applied to a 2 cm^2 area on the back - 30 min after dosing, subjects were exposed to sunlight for 30 min or a compact-arc xenon lamp for 2 min (wavelengths <295 nm or 320-280 nm excluded) -positive controls were treated with 0.01% 8-methoxypsoralen in methanol; negative controls with an appropriate vehicle - test sites were examined 4, 24, 48, 72, and 96 h after exposure	no phototoxic response was observed	[30]
lime oil, distilled	undiluted	10 Caucasian subjects	- a single dose was applied to a 2 cm^2 area on the back - 30 min after dosing, subjects were exposed to sunlight for 30 min or a compact-arc xenon lamp for 2 min (wavelengths <295 nm or 320-280 nm excluded) -positive controls were treated with 0.01% 8-methoxypsoralen in methanol; negative controls with an appropriate vehicle - test sites were examined 4, 24, 48, 72, and 96 h after exposure	no phototoxic response was observed	[30]
lime oil, expressed	undiluted and diluted; 20 µl	10 Caucasian subjects	- a single dose was applied to a 2 cm^2 area on the back - 30 min after dosing, 1 treated site and the control untreated site were exposed to sunlight for 30 min, a compact-arc xenon lamp for 2 min (wavelengths <295 nm or 320-280 nm excluded), or 4 fluorescent black light lamps (UVB eliminated) for 1 h at an integrated UVA intensity of 3 W/m^2 -positive controls were treated with 0.01% 8-methoxypsoralen in methanol; negative controls with an appropriate vehicle - test sites were examined 4, 24, 48, 72, and 96 h after exposure	- a phototoxic response was observed with all three light sources - the lowest phototoxic concentration with the simulated light sources was 30%	[30]

Table 14. Case reports

Mode of Contact	Patient(s)	Indication	Reference
bergamot aromatherapy oil followed by several hours of sun exposure	54-year-old woman with Fitzpatrick skin type III	-painful, red, edematous, sharply demarcated areas with bullae and crusting on the face in a butterfly-like distribution	[32]
bergamot aromatherapy oil (6 drops) in a bath followed by 20-30 minutes UV exposure from a tanning bed	33-year-old woman	-48 h after exposure, developed increasing erythema and blistering of exposed areas -admitted to hospital burn unit with approximately 70% superficial partial thickness burns	[33]
bergamot aromatherapy oil aerosolized in a sauna followed by UVA radiation from a tanning bed	41-year-old woman with Fitzpatrick skin type II	-disseminated, painful, red, edematous, sharply demarcated areas with bullae mainly on the face, neck, arms, palms, and thighs	[32]

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2014 FDA VCRP Raw Data

01A - Baby Shampoos	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	1
01C - Other Baby Products	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	5
02A - Bath Oils, Tablets, and Salts	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	3
02B - Bubble Baths	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	4
02C - Bath Capsules	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	1
03G - Other Eye Makeup Preparations	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	2
05A - Hair Conditioner	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	4
05F - Shampoos (non-coloring)	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	3
07E - Lipstick	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	1
10A - Bath Soaps and Detergents	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	8
10E - Other Personal Cleanliness Products	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	4
11A - Aftershave Lotion	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	1
11D - Preshave Lotions (all types)	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	1
11E - Shaving Cream	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	2
12A - Cleansing	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	20
12C - Face and Neck (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	19
12D - Body and Hand (exc shave)	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	9
12F - Moisturizing	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	13
12G - Night	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	4
12H - Paste Masks (mud packs)	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	2
12I - Skin Fresheners	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	2
12J - Other Skin Care Preps	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	10
13A - Suntan Gels, Creams, and Liquids	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	2
13C - Other Suntan Preparations	CITRUS AURANTIUM (BITTER ORANGE) PEEL OIL	3
02A - Bath Oils, Tablets, and Salts	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	10
02B - Bubble Baths	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	3
02D - Other Bath Preparations	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	4
03D - Eye Lotion	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	1
04A - Cologne and Toilet waters	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	2
04B - Perfumes	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	4
04E - Other Fragrance Preparation	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	16
05A - Hair Conditioner	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	4
05C - Hair Straighteners	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	5
05F - Shampoos (non-coloring)	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	7
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	8
05I - Other Hair Preparations	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	2
07E - Lipstick	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	1
07F - Makeup Bases	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	1
09C - Other Oral Hygiene Products	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	1
10A - Bath Soaps and Detergents	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	23
10B - Deodorants (underarm)	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	1
10E - Other Personal Cleanliness Products	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	5

11E - Shaving Cream	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	1
11G - Other Shaving Preparation Products	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	1
12A - Cleansing	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	16
12C - Face and Neck (exc shave)	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	4
12D - Body and Hand (exc shave)	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	19
12F - Moisturizing	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	22
12G - Night	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	2
12H - Paste Masks (mud packs)	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	2
12I - Skin Fresheners	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	4
12J - Other Skin Care Preps	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	18
13B - Indoor Tanning Preparations	CITRUS BERGAMIA (BERGAMOT ORANGE) PEEL OIL	1
04A - Cologne and Toilet waters	CITRUS JUNOS PEEL OIL	1
07C - Foundations	CITRUS JUNOS PEEL OIL	2
10A - Bath Soaps and Detergents	CITRUS JUNOS PEEL OIL	1
12A - Cleansing	CITRUS JUNOS PEEL OIL	1
12F - Moisturizing	CITRUS JUNOS PEEL OIL	1
01A - Baby Shampoos	CITRUS LIMON (LEMON) PEEL OIL	3
01B - Baby Lotions, Oils, Powders, and Creams	CITRUS LIMON (LEMON) PEEL OIL	1
01C - Other Baby Products	CITRUS LIMON (LEMON) PEEL OIL	4
02A - Bath Oils, Tablets, and Salts	CITRUS LIMON (LEMON) PEEL OIL	16
02B - Bubble Baths	CITRUS LIMON (LEMON) PEEL OIL	9
02D - Other Bath Preparations	CITRUS LIMON (LEMON) PEEL OIL	3
03D - Eye Lotion	CITRUS LIMON (LEMON) PEEL OIL	2
03G - Other Eye Makeup Preparations	CITRUS LIMON (LEMON) PEEL OIL	6
04A - Cologne and Toilet waters	CITRUS LIMON (LEMON) PEEL OIL	2
04B - Perfumes	CITRUS LIMON (LEMON) PEEL OIL	7
04E - Other Fragrance Preparation	CITRUS LIMON (LEMON) PEEL OIL	11
05A - Hair Conditioner	CITRUS LIMON (LEMON) PEEL OIL	17
05B - Hair Spray (aerosol fixatives)	CITRUS LIMON (LEMON) PEEL OIL	1
05F - Shampoos (non-coloring)	CITRUS LIMON (LEMON) PEEL OIL	25
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS LIMON (LEMON) PEEL OIL	17
05I - Other Hair Preparations	CITRUS LIMON (LEMON) PEEL OIL	4
07C - Foundations	CITRUS LIMON (LEMON) PEEL OIL	2
07E - Lipstick	CITRUS LIMON (LEMON) PEEL OIL	8
07F - Makeup Bases	CITRUS LIMON (LEMON) PEEL OIL	1
07I - Other Makeup Preparations	CITRUS LIMON (LEMON) PEEL OIL	4
08C - Nail Creams and Lotions	CITRUS LIMON (LEMON) PEEL OIL	1
08G - Other Manicuring Preparations	CITRUS LIMON (LEMON) PEEL OIL	2
09A - Dentifrices	CITRUS LIMON (LEMON) PEEL OIL	1
10A - Bath Soaps and Detergents	CITRUS LIMON (LEMON) PEEL OIL	42
10E - Other Personal Cleanliness Products	CITRUS LIMON (LEMON) PEEL OIL	17
11A - Aftershave Lotion	CITRUS LIMON (LEMON) PEEL OIL	10
11D - Preshave Lotions (all types)	CITRUS LIMON (LEMON) PEEL OIL	2
11E - Shaving Cream	CITRUS LIMON (LEMON) PEEL OIL	8

11F - Shaving Soap	CITRUS LIMON (LEMON) PEEL OIL	1
11G - Other Shaving Preparation Products	CITRUS LIMON (LEMON) PEEL OIL	2
12A - Cleansing	CITRUS LIMON (LEMON) PEEL OIL	31
12C - Face and Neck (exc shave)	CITRUS LIMON (LEMON) PEEL OIL	44
12D - Body and Hand (exc shave)	CITRUS LIMON (LEMON) PEEL OIL	52
12F - Moisturizing	CITRUS LIMON (LEMON) PEEL OIL	50
12G - Night	CITRUS LIMON (LEMON) PEEL OIL	4
12H - Paste Masks (mud packs)	CITRUS LIMON (LEMON) PEEL OIL	16
12I - Skin Fresheners	CITRUS LIMON (LEMON) PEEL OIL	12
12J - Other Skin Care Preps	CITRUS LIMON (LEMON) PEEL OIL	51
13B - Indoor Tanning Preparations	CITRUS LIMON (LEMON) PEEL OIL	1
02A - Bath Oils, Tablets, and Salts	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	7
02D - Other Bath Preparations	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	1
04E - Other Fragrance Preparation	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	4
05A - Hair Conditioner	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	5
05F - Shampoos (non-coloring)	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	4
07A - Blushers (all types)	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	1
07E - Lipstick	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	1
07F - Makeup Bases	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	1
10A - Bath Soaps and Detergents	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	21
10E - Other Personal Cleanliness Products	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	10
11A - Aftershave Lotion	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	1
12A - Cleansing	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	14
12C - Face and Neck (exc shave)	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	10
12D - Body and Hand (exc shave)	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	16
12F - Moisturizing	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	34
12G - Night	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	4
12H - Paste Masks (mud packs)	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	2
12I - Skin Fresheners	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	2
12J - Other Skin Care Preps	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	7
13B - Indoor Tanning Preparations	CITRUS NOBILIS (MANDARIN ORANGE) PEEL OIL	1
01A - Baby Shampoos	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	1
01C - Other Baby Products	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	2
02A - Bath Oils, Tablets, and Salts	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	6
02B - Bubble Baths	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	2
02D - Other Bath Preparations	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	2
03D - Eye Lotion	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	1
04E - Other Fragrance Preparation	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	14
05A - Hair Conditioner	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	9
05F - Shampoos (non-coloring)	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	12
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	4
05H - Wave Sets	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	1
07E - Lipstick	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	2

07I - Other Makeup Preparations	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	2
10A - Bath Soaps and Detergents	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	21
10E - Other Personal Cleanliness Products	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	11
11E - Shaving Cream	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	1
11G - Other Shaving Preparation Products	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	1
12A - Cleansing	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	14
12C - Face and Neck (exc shave)	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	24
12D - Body and Hand (exc shave)	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	12
12F - Moisturizing	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	29
12G - Night	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	3
12H - Paste Masks (mud packs)	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	2
12I - Skin Fresheners	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	8
12J - Other Skin Care Preps	CITRUS PARADISI (GRAPEFRUIT) PEEL OIL	22
12D - Body and Hand (exc shave)	CITRUS RETICULATA (MANDARIN ORANGE) PEEL OIL	1
12H - Paste Masks (mud packs)	CITRUS RETICULATA (MANDARIN ORANGE) PEEL OIL	1
01A - Baby Shampoos	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	4
01B - Baby Lotions, Oils, Powders, and Creams	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	3
01C - Other Baby Products	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
02A - Bath Oils, Tablets, and Salts	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	10
02B - Bubble Baths	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	6
02D - Other Bath Preparations	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	7
03E - Eye Makeup Remover	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
03G - Other Eye Makeup Preparations	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	2
04E - Other Fragrance Preparation	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	11
05A - Hair Conditioner	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	18
05B - Hair Spray (aerosol fixatives)	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
05F - Shampoos (non-coloring)	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	17
05G - Tonics, Dressings, and Other Hair Grooming Aids	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	14
05H - Wave Sets	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
05I - Other Hair Preparations	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	10
07E - Lipstick	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	2
07I - Other Makeup Preparations	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
08B - Cuticle Softeners	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
08G - Other Manicuring Preparations	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
09A - Dentifrices	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
09B - Mouthwashes and Breath Fresheners	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
10A - Bath Soaps and Detergents	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	27
10B - Deodorants (underarm)	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
10E - Other Personal Cleanliness Products	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	2
11A - Aftershave Lotion	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
11G - Other Shaving Preparation Products	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	2

12A - Cleansing	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	25
12C - Face and Neck (exc shave)	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	29
12D - Body and Hand (exc shave)	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	25
12E - Foot Powders and Sprays	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	1
12F - Moisturizing	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	26
12G - Night	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	8
12H - Paste Masks (mud packs)	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	11
12I - Skin Fresheners	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	7
12J - Other Skin Care Preps	CITRUS SINENSIS (SWEET ORANGE) PEEL OIL	11
04E - Other Fragrance Preparation	CITRUS SINENSIS SANGUINELLO (BLOOD ORANGE) PEEL OIL	1
10A - Bath Soaps and Detergents	CITRUS SINENSIS SANGUINELLO (BLOOD ORANGE) PEEL OIL	4
12C - Face and Neck (exc shave)	CITRUS SINENSIS SANGUINELLO (BLOOD ORANGE) PEEL OIL	2
12F - Moisturizing	CITRUS SINENSIS SANGUINELLO (BLOOD ORANGE) PEEL OIL	1
02B - Bubble Baths	CITRUS TANGERINA (TANGERINE) PEEL OIL	1
04A - Cologne and Toilet waters	CITRUS TANGERINA (TANGERINE) PEEL OIL	1
05A - Hair Conditioner	CITRUS TANGERINA (TANGERINE) PEEL OIL	2
05E - Rinses (non-coloring)	CITRUS TANGERINA (TANGERINE) PEEL OIL	1
05F - Shampoos (non-coloring)	CITRUS TANGERINA (TANGERINE) PEEL OIL	4
07E - Lipstick	CITRUS TANGERINA (TANGERINE) PEEL OIL	1
07I - Other Makeup Preparations	CITRUS TANGERINA (TANGERINE) PEEL OIL	1
10A - Bath Soaps and Detergents	CITRUS TANGERINA (TANGERINE) PEEL OIL	4
10E - Other Personal Cleanliness Products	CITRUS TANGERINA (TANGERINE) PEEL OIL	1
12A - Cleansing	CITRUS TANGERINA (TANGERINE) PEEL OIL	2
12C - Face and Neck (exc shave)	CITRUS TANGERINA (TANGERINE) PEEL OIL	3
12D - Body and Hand (exc shave)	CITRUS TANGERINA (TANGERINE) PEEL OIL	5
12F - Moisturizing	CITRUS TANGERINA (TANGERINE) PEEL OIL	4
12H - Paste Masks (mud packs)	CITRUS TANGERINA (TANGERINE) PEEL OIL	1
12I - Skin Fresheners	CITRUS TANGERINA (TANGERINE) PEEL OIL	1
12J - Other Skin Care Preps	CITRUS TANGERINA (TANGERINE) PEEL OIL	2

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: March 10, 2014

SUBJECT: Comments on the Draft Report Prepared for the March 17-18, 2014 Meeting: Safety Assessment of Citrus-Derived Ingredients as Used in Cosmetics

Key Issues

Information provided to CIR by RIFM (powerpoint file titled bitter orange; file not included with the draft report or in wave 2) indicates that "petitgrain bigarade oil" is made from the leaves of bitter orange. The incorrect association of "petitgrain bigarade oil" with Citrus Reticulata (Tangerine) Leaf Oil in the Dictionary has been deleted from the Dictionary database. Although Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil is included in the Dictionary, bitter orange leaf oil is not in the Dictionary.

There is information on the ECHA website (found by searching Citrus) on:

232-433-8 8028-48-6 Orange, sweet, ext. Full Joint Submission 10,000+ tonnes per annum

284-515-8 84929-31-7 Lemon, ext. Full Joint Submission 100 - 1,000 tonnes per annum

As the submission on Orange includes at least one genotoxicity assay on "Orange Oil Cold Pressed 1-Fold-Orange, ext. (Citrus sinensis, Rutaceae)", the submission to ECHA does not appear to have been considered for inclusion in the CIR report.

Table 12 - Do not state that the Council "confirmed" that some uses are sprays and powders. Footnote 3 is not correct. THE COUNCIL DID NOT "CONFIRM" THAT CERTAIN USES WERE SPRAYS OR POWDERS. The Council just reports the results of the survey. Use of the word "confirmed" is very misleading. It suggests that there was independent confirmation of the form of the product. This did not happen.

This draft report does not include a rationale for including all ingredients derived from "citrus" in one report. What are the characteristics of plants in the genus Citrus? Why is it appropriate to include plants of the Microcitrus genus in this report?

As the composition of waxes, seed oils and unsaponifiables differs from the essential oils, waters and extracts, the waxes, seed oils and unsaponifiable ingredients should be removed from the report. If the seed oils are left in the report, the composition of the oils from the CIR report on plant seed oils should be added to this report.

Additional Comments

Memo, Introduction and Reference Section - Reference 1 in the reference section is a CIR report. This is not the correct reference for information cited to it in the memo and the Introduction.

Table of Contents - Without page numbers, the Table of Contents is not helpful.

Cosmetic Use - It would be helpful if the Cosmetic Use section stated that the VCRP includes a few reports of deodorant uses of these ingredients, while no concentrations of use were reported to the Council survey. The following does not make sense (it does not end with a period, so it is not clear if there is something missing): "Based on this standard, the maximum concentration of lime cold pressed oil is 0.1%, for example"

Occupational Exposure - What type of reactions were observed in food handlers with positive reactions to orange and lemon peels?

Table 12 - For those ingredients found in the VCRP for which the Council did not complete a concentration of use survey, NR should be changed to not surveyed (NS). The VCRP and Council survey information should be combined for different names of the same species, e.g., the Dictionary mostly uses *Citrus aurantium dulcis* for orange, while the VCRP uses *Citrus sinensis* - these are two names for the same plant. In the near future, it is likely that the INCI Committee will change the name of all orange (sweet)-derived ingredients to *Citrus sinensis*.