Safety Assessment of Anthemis Nobilis-Derived Ingredients as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	November15, 2013
Panel Date:	December 9-10, 2013

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, 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 Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: November 15, 2013
Subject: Draft Final Report on the Anthemis Nobilis-Derived Ingredients

At the September 9-10, 2013 CIR Expert Panel meeting, the Panel concluded that anthemis nobilis flower extract, anthemis nobilis flower oil, anthemis nobilis flower powder, and anthemis nobilis flower water are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing. The issuance of a tentative report with this conclusion was approved.

Included in this package for your review is the Draft Final Report, the CIR report history, Literature search strategy, Ingredient Data profile, 2013 FDA VCRP data, Minutes from the September 2013 Expert Panel Meeting, Comments from the Council (pcpc1 pdf file), and use concentration data received from the Council - previously reviewed (data1 pdf file). Comments received from the Council have been addressed. According to one of the comments, the discussion should state that the ingredients considered safe are "safe when formulated to be non-sensitizing," as opposed to simply "safe as used," because:

- The composition, including concentrations of plant constituents that have the potential to be sensitizing (e.g., sesquiterpene lactones), can be quite variable in the ingredients, depending on the growth conditions of the plant and the extraction methods used to produce the ingredient.
- The available sensitization tests evaluated a limited number of ingredient preparations and, thus, the results of these tests do not address the full spectrum of the concentrations of potentially sensitizing constituents that might be present in this ingredient, as used in cosmetic formulations.
- The concentrations of potentially sensitizing constituents may exceed levels of concern in a formulation if the formulation contains extracts from multiple plant species, in that each can contribute such constituents to the overall formulation.

Thus, the report discussion has been revised (statements underlined) accordingly.

After considering the data included in this safety assessment, the Panel needs to determine whether a final report with the conclusion stated in the first paragraph should be issued at this Panel meeting.

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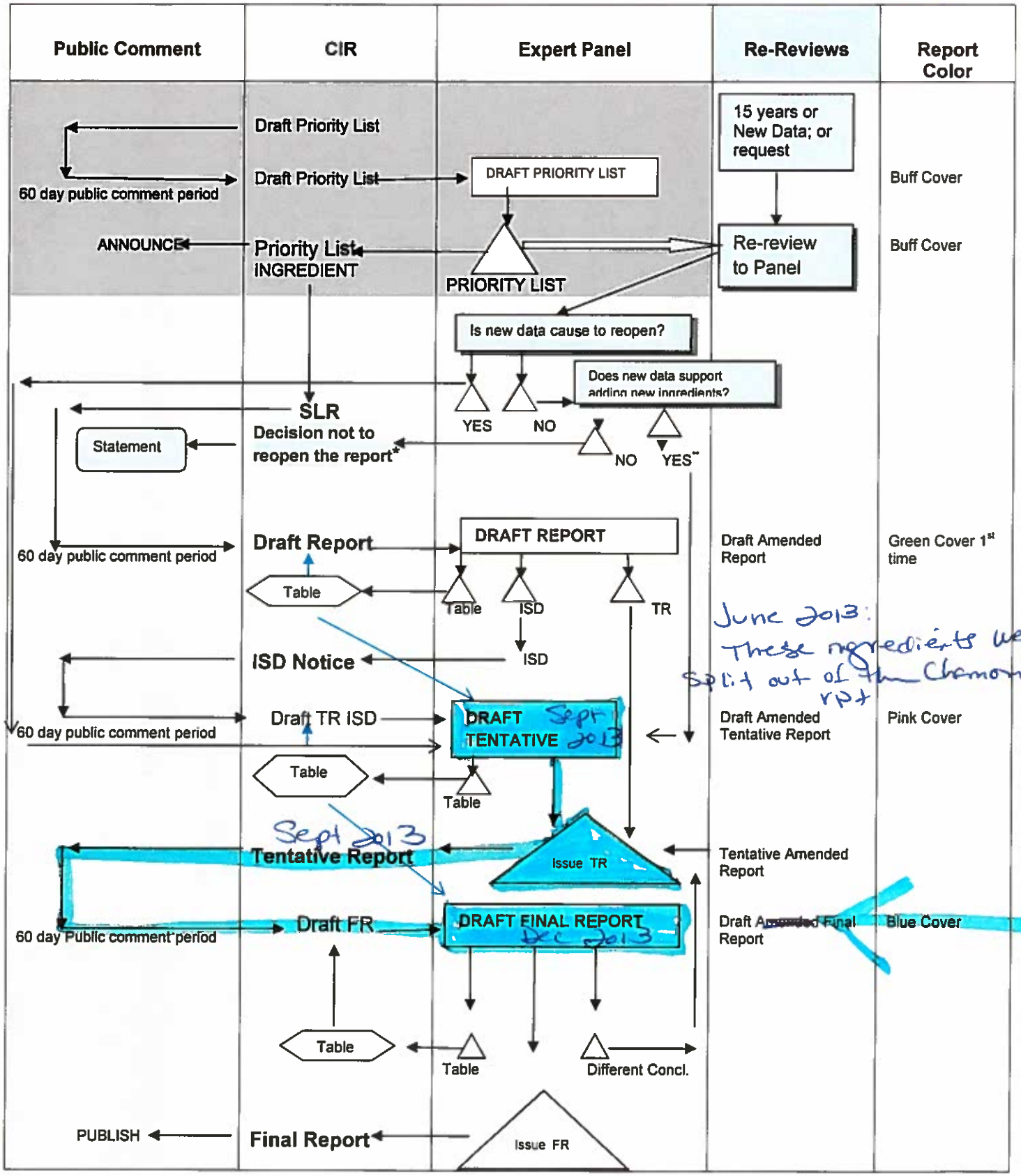
SAFETY ASSESSMENT FLOW CHART

Anthemis Nobilis

Dec 2013



CIR History of:

Chamomile Ingredients

A Scientific Literature Review (SLR) Notice was announced on February 11, 2013, and unpublished data from the Personal Care Products Council (Council) were received during the 60-day comment period.

Draft Report, Belsito and Marks Teams/Panel: June 10-11, 2013

The Draft Report now contains the following unpublished data that were received from the Council:

(1) composition data on anthemis nobilis oil (data1 pdf file),
(2) composition data on trade name mixtures containing chamomile extracts + genotoxicity data on chamomilla recutita (matricaria) flower extract (data2 pdf),
(3) ocular and skin irritation data on a chamomilla rexcutita (matricaria) flower extract trade name mixture (data3 pdf),
(4) ocular and skin irritation data on another chamomilla recutita (matricaria) flower extract trade name mixture (data4 pdf),
(5) ocular and skin irritation data on an anthemis nobilis flower extract trade name mixture (data5 pdf),
(6) ocular and skin irritation data on a third chamomilla recutita (matricaria) flower extract trade name mixture (data6 pdf),
(7) use concentration data on *Chamomilla recutita*- and *Anthemis nobilis*-derived ingredients.

The Panel determined that there are sufficient differences in composition between chamomile ingredients from *Chamomilla recutita* (so-called German Chamomile) and *Anthemis nobilis*, (so-called Roman Chamomile) to split these into two reports. One report will be *Chamomilla recutita*-derived ingredients and the other will be *Anthemis nobilis*-derived ingredients.

The Panel also determined that the available data are insufficient for evaluating the safety of the *Anthemis nobilis*-derived ingredients in cosmetic products and that the the following data are needed: (1) Composition data on all anthemis nobilis ingredients, except anthemis nobilis flower oil, and (2) Skin irritation and sensitization data on all anthemis nobilis ingredients, except anthemis nobilis flower oil, at a use concentration of 10%. The Panel also noted that the pesticides and heavy metals content should be below levels of toxicologic concern.

Draft Tentative Report, Belsito and Marks Teams/Panel: September 9-10, 2013

HRIPT data on a leave-on skin care product containing 3% anthemis nobilis flower extract were received. The Panel determined that these data are sufficient, together with other skin irritation and sensitization data in the safety assessment, for evaluating the skin irritation and sensitization potential of anthemis nobilis-derived ingredients over the range of reported use concentrations. In the absence of composition data on all anthemis nobilis-derived ingredients, except anthemis nobilis flower oil, the Panel agreed that the available data on the composition of anthemis nobilis flower oil provide a reasonable assumption relative to the composition of the remaining anthemis nobilis-derived ingredients. Additionally, the Panel stressed that products should be formulated to minimize the presence of pesticide and heavy metal impurities that could result from the presence of anthemis nobilis-derived ingredients.

The CIR Expert Panel concluded that anthemis nobilis flower extract, anthemis nobilis flower oil, anthemis nobilis flower powder, and anthemis nobilis flower water are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing. The issuance of a tentative report with this conclusion was approved.

Draft Final Report, Belsito and Marks Teams/Panel: December 9-10, 2013

Comments received from the Council have been addressed.

Chamomile Ingredients Check List for December, 2013. Analyst – Wilbur Johnson																				
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Anthemis Nobilis Flower Extract																				
Anthemis Nobilis Flower Oil				X		X							X	X	X	X		X		X
Anthemis Nobilis Flower Powder																				
Anthemis Nobilis Flower Water																				

Literature Searches on Chamomile Ingredients (09/27/2012)

SciFinder Searches

Search Terms

Anthemis Nobilis Flower Extract
Anthemis Nobilis Flower Oil
Anthemis Nobilis Flower Powder
Anthemis Nobilis Flower Water
Anthemis Nobilis
Chamaemelum Nobile
Chamomile

Search Updates

Search updated on 5/8/2013
Search updated on 6/27/2013
Search updated on 10/26/2013

Day 1 of the September 9 -10, 2013 CIR Expert Panel Meeting – Dr. Belsito's Team

Amnthemis Nobilis-Derived Ingredients

Now we move on to the other chamomile, anthemis nobilis. So, again, same thing basically. We split these into two and asked for additional data on the composition of the nobilis ingredients except the flower oil, skin irritation and sensitization data on the ingredients except the flower oil at use concentration of 10 percent. And we, again, have this issue of deciding what kamillosan is, so that will be an issue for this report. And also when we're talking about just chamomile without the species defined, we need to be very specific in those sections that we're not sure whether this is anthemis nobilis or chamomilla recutita.

So what we got was composition data, updated use concentration data, HRIPT, a leave-on skin lotion containing 3 percent, and that was in Wave 2. So the question is where are we with this? I thought that we still don't have the sensitization and irritation data -- well, no, I'm sorry. They were safe as used and, again, in the introduction we need to name the ingredients that we're looking at.

DR. LIEBLER: So we still don't have the composition on the flower extract, right? The chemical composition?

DR. SNYDER: All we have is on the flower oil.

DR. LIEBLER: Yeah, and that's got seven uses and the flower extract's got 423 uses.

DR. BELSITO: I guess my thinking here -- and I reviewed this a while ago -- was when we look at the -- we have stuff on the flower. What we sort of missing is -- I mean if you look at the two columns, we have flower oil and we have flower. I think what we're missing from the flower are basically the oil components, which in the whole flower are going to be less. So my thinking was if you put the two together, you know what the heck is in the flower, and, in fact, the composition of the oils in the flower as it is are going to be lower than what you're seeing in the more concentrated oil. So I didn't have an issue with that.

DR. LIEBLER: Well, if we take that view here, then I think we need to take that view with chamomilla recutita.

DR. BELSITO: We are. We're saying the flower is fine, but we have no data on the stem and leaf.

DR. LIEBLER: Oh, stem and leaf, I see.

DR. SNYDER: Anything that's added to the flower.

DR. LIEBLER: Okay, flower, flower oil, right. So there's no stem/leaf.

DR. BELSITO: For recutita.

DR. LIEBLER: For nobilis. Well, I agree. The thing that I think was sort of insufficient here or that are lacking information was on the organics. And, of course, the organics would be present in the oil because the flower had these ppms on inorganics primarily in things like fat and fiber and so forth, which wasn't terribly helpful. Okay, so I think I agree. We're no longer insufficient on composition. I think it's a reasonable assumption on the oil-to-flower comparison.

DR. BELSITO: And all we have here are flower- derived materials.

DR. LIEBLER: Yeah, that's the key.

DR. BELSITO: And then, again, we need to clarify that kamillosan, and in the introduction we need to list the ingredients we're reviewing. And then I just had some minor typographical --

DR. LIEBLER: Same here.

DR. GILL: So let me ask for clarification again. We do have the data, all of the composition data. We're satisfied with the composition data we've received.

DR. BELSITO: Yes.

DR. GILL: For flower and --

DR. LIEBLER: Or inferring the flower from the oil. So that's the cache that we're doing it.

DR. SNYDER: So I think it's important in the introduction to state that "all of the ingredients used in cosmetics are derived from the flower component of the plant; and,

therefore, this material related to the" dah, dah, dah, dah can be used to support all of those.

DR. LIEBLER: The composition data from the oil.

DR. SNYDER: Yeah. So I think you need to just capture that clearly in the introduction. That just sets the tone for the rest of the report.

DR. LIEBLER: Yeah.

DR. SNYDER: As opposed to the other report, we did the opposite. We say that "the ingredients used in cosmetics are derived from all components of the plant and only composition data is available for the flower."

So what is the highest concentration of use of this again? This is now 10 percent back down to --

DR. BELSITO: No, this is --

DR. SNYDER: So the 10 percent were the carryover --

DR. ANSELL: The maximum use of the flower extract in a leave-on is 0.05. There is one reported use at 10 percent, but that's not supported.

DR. LORETZ: It's flower water.

DR. SNYDER: So they're at 10 percent with flower water.

MR. JOHNSON: Jay, what do you mean by that as unsupported?

DR. ANSELL: That it was a single reported use of the flower water used at 10 percent.

DR. BELSITO: But it's also in a rinse-off.

DR. GILL: And that is specifically what the Panel asked for, the concentration at 10 percent of irritation and sensitization.

DR. ANSELL: Right. And if there's a concern, you're prepared to support 0.05 percent?

DR. GILL: Uh-huh, so at the highest.

DR. ANSELL: It's really not the highest. It's a single report. And we confirmed that is the right number, but there's only one use at that level. And if the Panel is concerned with a use at that level, we'd be willing to accept a lower threshold.

DR. BELSITO: On the Leave-On section -- you know, the 10 percent is in a rinse-off, so I'm not getting excited about that. I guess I'm more interested in what's in a leave-on, and you have 4 percent for the flower water. But I don't see where that's coming from. You have dermal contact 1 to 10, and you have a bunch of others that are not reported. So where is that 4 for leave-on coming from because I just see --

DR. SNYDER: There is a deodorant, a dermal contact deodorant underarm at 1 to 10 percent, so it's more than rinse-off.

DR. BELSITO: Okay, so --

DR. SNYDER: For the flower water.

DR. BELSITO: But then it says rinse-off is 2 to and the dermal underarm deodorant --

DR. SNYDER: So that's wrong. That should be 1 to 10.

DR. BELSITO: It's dermal contact. For the dermal underarm deodorant there's no concentration reported. Either my.pdf or your Word is dermal underarm, nothing -- there's one ingredient for flower extract, but the concentration is --

DR. SNYDER: Well, what's the dermal contact 1 to 10? That includes the rinse-off.

DR. BELSITO: The 10 is rinse-off.

DR. SNYDER: Gotcha.

DR. BELSITO: But I don't know where the 4 is coming from.

MR. JOHNSON: There's a 4 percent of anthemis nobilis flower water used in foundations at 4 percent.

DR. SNYDER: So that's not in Table 5, so where did you get it? That's raw data that you have from the --

MR. JOHNSON: Yes, from the Council.

DR. SNYDER: So Table 5 needs to be updated?

MR. JOHNSON: Yes.

DR. GILL: There is a leave-on at 1 to 4 percent in Table 5.

MR. JOHNSON: Yeah, and that's at 4 percent.

DR. BELSITO: Yeah, but it's not clear where that is coming from. So what we're saying is it's a foundation.

MR. JOHNSON: A foundation, yes.

DR. BELSITO: And that is for the flower water?

MR. JOHNSON: The flower water, yes.

DR. ANSELL: Isn't it.4?

MR. JOHNSON: No, it's 4. That's on page 8 of the use concentration data received from the Council.

DR. BELSITO: What page of the.pdf?

MR. JOHNSON: 46.

DR. BELSITO: 4 percent, yeah, foundation. Got it. Okay, so let's just -- we have sensitization for the anthemis flower oil at 4 percent. And then we have flower oil 4 percent for petrolatum. I mean I think that the water extract is going to be much less sensitizing than the flower oil. We have 4 percent. I mean, again, I think we're fine, particularly since the 10 percent is in a rinse-off. I'm not going to argue with that. We have 4 percent oil, so I think these are safe as used. We'll have to attach whatever we agree on for the botanical boilerplate.

Ingredients of concern here for the discussion obviously are going to be the usual heavy metals, pesticides, whatever botanical combination boilerplate we come up with. In looking at what's in here, I didn't really flag anything for this one unless I'm missing something. I mean we're -- pretty much what's in this isn't really anything of significance in terms of allergens that I've heard coming out of the oil industry. So I mean I don't really even think there's anything to flag in terms of ingredients of concern.

DR. LIEBLER: Safe as used.

DR. BELSITO: Okay. Paul?

DR. SNYDER: Yup.

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Anthemis Nobilis-Derived Ingredients

DR. MARKS: So this is the second time seeing this report, we now have the Roman chamomile split out, we issued a tentative, the oil is safe, insufficient for other ingredients. We wanted composition, we wanted the HRIPT for the floral extract, we got that in Wave 2, 3 percent HRIPT of the flower water. HRIPT at 3 percent, flower water was 4 percent in a leave on, 10 percent in a rinse-off, so I still thought that's probably going to be okay. It's used in baby's, also there's inhalation. So, comments, Rons, Tom?

DR. SHANK: I had --

DR. MARKS: I think it was Don that wanted a composition. But, at any rate, we still didn't get the composition, right?

SPEAKER: Here it is, Table 3.

DR. SHANK: I had we still needed HRIPT on the water extract at 10 percent.

DR. MARKS: Percent.

DR. BERGFELD: Doctor?

DR. SHANK: Did we get that?

DR. BERGFELD: No, and you will not.

DR. SHANK: And we will not?

DR. BERGFELD: No.

DR. SLAGA: I said we need that, too, but they have sufficient for the oil.

DR. BERGFELD: There's no change in the concentration, Carol, this one because it was split off from the other.

MS. EISENMANN: No, that one, there is no change with the water, and I haven't been able to get the data on it, but there's still a possibility that I could get lower concentrations on the extract. I have to keep going lower to see if I can rattle up some data, but the water, I'm not going to get any data on it. So you could go insufficient, safe for the oil and insufficient for the other two.

DR. MARKS: Okay. So we still need the composition, correct?

DR. SLAGA: Uh-huh. Well, I doubt if we get it.

DR. MARKS: So if we -- how do you feel, Ron and Tom, in terms of composition? Should we have, now, an insufficient, a tentative report with an insufficient data (inaudible) composition?

DR. SLAGA: To me, if we have the one thing that Ron wanted, we wouldn't need the composition because we could say that the oil is already sufficient data, and if we have that for the extract, then I think it's sufficient without composition.

DR. MARKS: Ron Shank?

DR. SHANK: I'm still trying to find just what are grass, so just as the spice is grass, so I guess that's the whole thing. So, again, we're down to skin data, and the oil/skin data, the skin data on oil seems to be okay, but not on the water extract.

DR. SLAGA: Yeah.

DR. SHANK: So we could split it, the oil is safe as used and the water extract is insufficient with a need for human sensitization data if you use concentration.

DR. MARKS: How about the flower powder and the flower extract? We don't have data on that. Let's see, the flower extract, we got 3 percent HRIPT was okay. Flower -- so, Ron Hill, what we were discussing earlier is, we have the composition for the oil. Do we want to move forward with a tentative report that the oil is safe and the others are insufficient?

DR. HILL: That's what I was expecting to see.

DR. BERGFELD: For a non chemist, what's the difference between the oil and the water in penetration? I would think the oil would penetrate easier.

DR. HILL: Yes, I would expect components of the oil to be more penetrable but to be different, so I just, this is a case where I think, personally, the absence of data isn't the same as data that shows the absence of effect, that's all. I mean, it would be sensitization that actually, to me, would be about the only concern in this case. And if that's not a concern with these guys, then --

DR. MARKS: No, I think that's exactly right. We do have the flower extract up to 3 percent, we could put a limit on flower extract, if we wanted to. Oil is safe, we could say the others are insufficient and need for sensitization, or we could say the flower extract up to 3 percent -- what was the use concentration of flower extract?

DR. BRESLAWEC: I think it was 0.1 percent.

DR. MARKS: 0.1, okay. So then that would mean the flower extract should be okay, am I interpreting that correctly? I think that's what I had, here, the extract was okay, but we don't have composition, so is that necessary for the flower extract?

DR. HILL: I was sort of assuming that Dr. Belsito was wanting that to assess the possibility of additive effects when this is used with other botanicals in the same formulations. And so, without that compositional ingredient, he could -- I don't know, I highlighted a bunch of stuff on the transcript, I could have a look, but that was my general sense is that enough information to know the additivity issue.

DR. BERGFELD: I have another question on the penetration. If it's in water, it's trapped in the stratum corneum, so all of your chemical ingredients articles would be at the outer layer of the skin. The oil would penetrate supposedly a little deeper, so the affects of absorption, you would think, would be much less with the water, if it is the same plant part.

DR. HILL: I --

DR. BERGFELD: That's a different vehicle.

DR. HILL: Well, because you're going to get, with that water extract, you're going to get a different array of components, and the sorts of things that would be penetrable should be there at much lesser concentrations, probably even negligible. So I think it's a matter of what's going to be present in what amounts based on having oil versus having water extract. And then, yes, in general, I think the things that would show up in the water extract --

MS. EISENMANN: What -- water, I mean, it's not a water extract, it's when you --

DR. HILL: I know --

MS. EISENMANN: -- fill it. I mean, it can be a water extract, but when, in key names, things that are named as water is part of distillation process, and, again, you might know better once you take off the oil soluble part or, and then the water part comes up. I mean, it's all in that distillation process.

DR. HILL: All right, okay. So you do a steam distillation --

MS. EISENMANN: So it's not an extract -- right --

DR. HILL: This was probably the second organic lab I did in college, and you get oils, but then, yes, they come to where you can easily remove the oils and you're left with whatever's there in the water, and that's what I'm assuming we're assessing, here.

MS. EISENMANN: Right, right. And so it's not water --

DR. HILL: That's --

MS. EISENMANN: -- I mean, than the other extract, if you put some plant material and put water in it and stir it around --

DR. HILL: I misstated --

MS. EISENMANN: -- that's a water extract.

DR. HILL: I misstated when I said water extract, but effectively, that's what you get, because once you do a steam distillation, cool everything down, then you have oil and you're going pull that off and you'll have whatever stays in the water, which would be why it would be awfully nice to have some composition database I think that would come out loud and clear, and we don't have that. But --

DR. MARKS: So let's get back, do we need the composition? We have it for oil, we don't have it for the flower, for the water, for the flower extract, the water. And then what was the last one, it was powder.

DR. HILL: And I'm putting words in Don's mouth that shouldn't be put --

DR. MARKS: Well, we'll find out what Don has to say tomorrow. What I want to get straight is --

DR. HILL: I just --

DR. MARKS: -- what our team is saying.

DR. HILL: I was just going by a sense of what I read in the transcripts from the

other group.

DR. MARKS: So, do we need composition?

DR. SLAGA: No.

DR. MARKS: No, okay. So we can move forward without composition. I have the oil and the flower extract safe, water and the powder insufficient --

DR. SHANK: Yes.

DR. MARKS: -- based on sensitization.

DR. SLAGA: Right.

DR. MARKS: Water and powder insufficient, need sensitization. Okay. So we'll see how this works tomorrow, but we'll be issuing a suspect tentative report, and at least our team feels the report's conclusion is going to be the oil and flower extract safe, the water and powder insufficient, and the insufficiency that's the need for sensitization data. Any other comments? There was, did -- Rons and Tom in the Wilbur's one, two, three, four -- one, two, third paragraph in Wilbur's memo, the August 16th memo, panel needs to consider whether these studies should remain in the report. And that was the trade case reports on pages 5 and 6 and two epidemiological studies relating to reproductive and developmental toxicity page 7 in his memo. How did you feel, did you want to keep these studies in or delete those?

DR. SHANK: Which page is this?

DR. MARKS: Wilbur, do you want to -- I'm looking at Wilbur's memo dated August 16th right in the beginning, and it's -- are the pages the PDF pages, or is it the pages of --

MR. JOHNSON: No, they aren't, I'll check from here.

DR. MARKS: So it's page 5, 6 and 7. I assume that's under the repro and development, there were two cases, and you said two epidemiologic studies were all done to repro and development. And you were wondering -- what was the question, why were you wondering whether they should remain in, Wilbur?

MR. JOHNSON: Because we didn't know whether or not they were Anthemis Nobilis or Chamomilla Recutita derived, that's the reason why.

DR. MARKS: Okay, now I understand.

DR. HILL: To me, if you don't know the source, at most you leave them in at a footnote of some sort.

DR. MARKS: I guess it gets back to, even if you leave them in, it did not --

DR. SLAGA: The report separate the three, you can't interpret the data, right?

DR. MARKS: That's what I would think. But it gets back with these, does it raise any toxicological concern for repro and development. I know, I can't overlook Wilbur's --

MR. JOHNSON: And that's starting on page 24 on the case reports.

DR. MARKS: Is that in the separated, is that also in the German chamomile report, these three cases and the two epidemiological studies?

MR. JOHNSON: Yes.

DR. MARKS: Yes. So we left it in that, okay, we leave it in since we can't separate it. Again, Ron and Ron, does this change or influence your conclusion at all?

DR. HILL: I don't think we had the discussion whether we left it in the chamomile report, did we? We just skipped right over that.

DR. MARKS: That's why I asked Wilbur that, because I think it's very important, if we leave it in, do we have to -- it seems to me we have to at least mention it in the discussion and explain why this is not of concern.

DR. HILL: What I would like to see in both of them is, this is my, I'm just tossing this out there, is have it summarized in a table, much the same way some of our other tox summaries show up, and then reference in the discussion, at most, or else we just take it out. I mean, which I'm fine with, I think we've lost some data, we don't know the source. We've lost some data if we just totally take it out, but yet, if you keep it in chamomile, you don't know if it's contributing to that, because you don't know if it's been done with the Recutita. If you keep it in the other one, you don't know if it's contributing to that assessment because you don't know if it's been done with Nobilis.

DR. MARKS: I've got to say, I'll ask Rachel, but I don't like the idea of leaving it out, I think it has to be addressed. And we can say we don't know which one of the chamomiles, whether it's German or Roman, but it gets back to, this, to me, is a hazard alert, how do we deal

with this.

MS. WEINTRAUB: I agree, I think that's a better way to address it.

MS. EISENMANN: For the epidemiology side, I believe most commercial chamomile teas, if that's what they were drinking, are German, I don't think that make much of the Roman chamomile, I think it's German that's sold as the tea. So I think it's more likely to be German than Roman, but I can't say that for sure, I haven't actually looked at the studies.

DR. MARKS: So what would we -- I mean, we've gotten to the point of saying safe, we've set some limits on sensitization, but going back, there's, presumably, there were no other alerts, as far as repro and development, so can we --

DR. HILL: Well, let me back up one step, then, because -- I'm sorry, I tend to make the mistake of over relying on the data table that you guys put at the beginning of the reports, because sometimes those don't get updated when we have additional data come in. But just looking at the data table, and you're familiar with this, so you could -- it's on page 4 of the PDF -- there's no chronic tox on any of the Anthemis Nobilis ingredients reported in here, there's no repro developmental toxicity on any of the Anthemis Nobilis ingredients listed in here. We have a genotox result on the flower oil, and that's all. Actually, we don't have any acute tox except for the flower oil, oral and dermal, but that's one of the reasons we'd like to have the composition, because then you at least have a better chance of thinking about read-across. Without that, you have zero chance, from where I sit.

DR. MARKS: Ron Shank, I think he made the comment earlier, well, this is grass. So even though these things are reported, it's a grass.

DR. SHANK: Correct.

DR. MARKS: So --

DR. SHANK: So this focuses on skin, not systemic toxicity.

DR. MARKS: How should Wilbur incorporate that in there, then? These studies should remain, should we just say it's a grass ingredient and it's not relevant? And that's for you, I know Ron Hill has a little different take about the skin exposure, but any rate, I think that's why we went right over the systemic tox, because it's a grass.

DR. HILL: We didn't know if Anthemis Nobilis was grass, I thought that was what was captured in the transcript.

DR. SHANK: It says it's grass now in the use part.

DR. HILL: Okay.

DR. SHANK: As far as case reports --

DR. HILL: Okay, they are, they both are.

DR. SHANK: To me, they're not helpful at all.

DR. MARKS: Yeah, your approach is the same as --

DR. SHANK: So, if you want to be inclusive, put them in, sometimes they're entertaining reading, but they certainly don't help me as a toxicologist. Because you really don't know what the case is, what else they were exposed to, a single person responding to whatever just doesn't help me. I have no objection to taking them out --

DR. MARKS: Interesting.

DR. SHANK: The only reason to include them is to be inclusive and show that we have looked at all the data.

DR. MARKS: How about the epidemiological studies? Well, I could let you off the hook on the case studies, I agree with you.

DR. SHANK: Oh, dear, I was hoping -- well, again, in most cases -- well, the epidemiology here did not help me, either.

DR. MARKS: Okay. And you would leave them out, Ron Shank.

DR. SHANK: As I said, it makes no difference to me, really.

DR. MARKS: Okay.

DR. SHANK: I don't object to them being in.

DR. MARKS: Perhaps this --

DR. SHANK: And it does show that we are aware of the literature, but it didn't help me.

DR. MARKS: And would you -- it didn't help you because? Again, these are grass substances, and --

DR. SHANK: Well, that, for sure, and then these case, someone developed rhinitis when smelling this.

DR. MARKS: Okay. Does that give you some direction, Wilbur? We're going to see this, we'll see this gun, and, Wilbur, don't hesitate to bring that up again in a memo. So, tomorrow, let me see, am I the one -- no, this is Belsito. So a tentative report, as you know, I have no hesitation in representing our team, so, tomorrow, I'm going to perhaps second a tentative report with a conclusion --

DR. SLAGA: Perhaps?

DR. MARKS: Well, I haven't seen the motion yet, so that's why I say perhaps. A motion that the oil and flower extracts are safe, that the water and powder are insufficient because of the need for sensitization data use concentration. Any other comments -- and, Wilbur, we'll let you deal with the case reports and the epidemiologic studies based on what Dr. Shank has said here. Any other comments?

Day 2 of the September 9 -10, 2013 CIR Expert Panel Meeting – Full Panel

Anthemis Nobilis-Derived Ingredients

Dr. Belsito, you started the discussion here, anthemis nobilis.

DR. BELSITO: Okay. Okay. So again, in this one, we need to clarify what chamilosin, and it's either anthemis nobilis or chamomilla recutita, and get it out of the inappropriate document and into the appropriate document.

And then having said that, we had extensive composition of the plant as a whole, as opposed to what we got with chamomilla recutita. And so, while we had lesser information about the flower, what we had was really the type of information we needed from the flower, which were the essential oils, and the potential fragrance ingredients, and sensitizers.

So for this particular group, the anthemis nobilis, we thought we could go "safe as used when formulated to be non-sensitizing." Again, a discussion, the pesticide boilerplate, and, you know, identifying those components of concern.

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

DR. MARKS: Yeah. Let me make a comment because that's -- we had not considered that conclusion. We felt we could say the linalool flower extracts are safe because we have the sensitization data to support that. We didn't have the sensitization for water and powder, so we thought we would split that out and make it "insufficient." But if you use the conclusion "non-sensitizing," I guess that covers it.

So with that in mind, just as long as it's captured in this discussion, we'll second the motion. Team?

DR. SLAGA: Yeah.

MR. JOHNSON: Can I ask a question?

DR. BERGFELD: Wilbur?

MR. JOHNSON: Dr. Belsito, I guess with respect to expansion of this discussion, do you have any specific components that you would like to be addressed in that discussion?

DR. BELSITO: Hold on, Wilbur. Actually for this one, there was nothing -- in terms of the components, the angelate, the tryglate, there was nothing that really jumped out. So, you know, I don't think we need to really mention any components. Just go with "formulated to be non-sensitizing."

MR. JOHNSON: Thank you.

DR. BERGFELD: Any other discussion, or needs, or edits? Ron Shank?

DR. SHANK: I'd like to make one comment. We're developing a clear pattern here saying when "formulated to be non-sensitizing." And what do we do about all the compounds that have -- reviewed before and we've said they're insufficient because we don't have sensitization data? Do we go back to all of those and say we've changed the conclusion to "safe if they're formulated to be non- sensitizing?"

DR. BELSITO: No, because I think the difference here, the only other time we did that was with cocoamidyl propyl betaine or betaine because of the issue of the impurities and the difficulties of really fully assessing that. But really to date, we've been dealing with a pure compound, you know? I mean, you know, either it contains so much iodopropynyl butylcarbamate or doesn't. And you're not going to get iodopropynyl butylcarbamate being brought into the formulation by some other product.

Here, you know, particularly with botanicals, I mean, read a label on some of these shampoos. I mean, you just start, and there are 10 in a row. And so, the concern with the botanicals are they're not a single pure ingredient, and you can stack component upon component upon component to get to a level in the finished product that is not safe.

So I think that's the twist here in the issue is that it's not a pure chemical that you can easily restrict.

DR. SNYDER: I think it goes to the very fact of the stacking of the different components within a final product. So you can say "safe as used," but that's taking only that single botanical. But the three botanicals in sum total, they exceed the levels which will cause sensitization, which we clearly have negative data on. I think that's what we're trying to alleviate.

We're trying to give them some guidance to make sure that they monitor the levels of known sensitizers in the final product.

DR. BERGFELD: Could I just ask a point of clarification. This word, "stacking," has been used a lot. The definition is? Is it scientific?

DR. SNYDER: I think it would be better to say the cumulative nature of the product formulation.

DR. BERGFELD: Okay, thank you.

DR. BELSITO: It's like bio handling.

(Laughter)

DR. HILL: If we're going to go there, then I like "aggregate" better than cumulative, but that's just me.

DR. BERGFELD: Okay.

DR. BELSITO: "Aggregate" is good. I like that.

DR. BERGFELD: Okay. I'm going to call for the question. All those in favor of the conclusion that's been proposed, please indicate by raising your hands.

Safety Assessment of Anthemis Nobilis-Derived Ingredients as Used in Cosmetics

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The 2013 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, 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 Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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ABSTRACT: Anthemis nobilis (Roman chamomile) flower extract, anthemis nobilis flower oil, anthemis nobilis flower powder, and anthemis nobilis flower water are ingredients that function as fragrance ingredients and skin conditioning agents in cosmetic products. These ingredients are being used at concentrations up to 10% (anthemis nobilis flower water) in cosmetic products. The available data indicate that these 4 ingredients are not irritating or sensitizing. Chemical compostion data and the low use concentrations suggest that systemic toxicity would not be likely if percutaneous absorption of constituents were to occur. Formulations may contain more than one botanical ingredient; each may contribute to the final concentration of a single component. Manufacturers were cautioned to avoid reaching levels of plant constituents that may cause sensitization or other adverse effects. Industry should continue to use good manufacturing practices to limit impurities in the ingredient before blending into cosmetic formulations. The Expert Panel concluded that these ingredients are safe in the present practices of use and concentration in cosmetics, when formulated to be non-sensitizing.

INTRODUCTION

This report presents information relevant to evaluating the safety of the following 4 Roman chamomile[1] or *Anthemis nobilis*-derived ingredients as used in cosmetics: anthemis nobilis flower extract, anthemis nobilis flower oil, anthemis nobilis flower powder, and anthemis nobilis flower water The Cosmetic Ingredient Review (CIR) is evaluating 11 *Chamomilla recutita* (German chamomile) derived ingredients in a separate report because the CIR Expert Panel thought that these two groups of botanical ingredients were substantially different and should not be addressed in the same report. These *Anthemis nobilis*-derived ingredients function as fragrance ingredients and skin conditioning agents in cosmetic products. Composition data are available on anthemis nobilis flower oil, as well as samples of the whole plant and the flower of *Anthemis nobilis*. The Panel agreed that these data are adequate to support assumptions about the likely compositions of other *Anthemis nobilis*-derived ingredients.

CHEMISTRY

The plant source of the ingredients reviewed in this safety assessment is *Anthemis nobilis* L. [Asteraceae]. Compositae family is the previous or historical name for the Asteraceae family. *Chamaemelum nobile* is a synonym for *Anthemis nobilis*.[1] The definitions of the 4 chamomile ingredients presented in this safety assessment are included in Table 1.

Physical and Chemical Properties

Anthemis nobilis flower oil is a light blue or light blue-green liquid with a specific gravity of between 0.892 and 0.910 (Table 2). Information on the remaining 3 ingredients was not found, nor was unpublished information provided.

Method of Manufacture

Anthemis Nobilis Flower Oil

The preparation of anthemis nobilis flower oil involves the steam distillation of the dried flowers of *Anthemis nobilis* as a key step.[2]

Composition/Impurities

A trade name material containing anthemis nobilis flower extract consists of the flower extract in propylene glycol and water (Table 3).[3] Heavy metals (in *Anthemis nobilis* flower only) and various other components of anthemis nobilis flower oil and the *Anthemis nobilis* plant and its flower are included in Table 4.

Anthemis Nobilis Flower Oil

According to the Personal Care Products Council (Council), the chamomile essential oil tested in the 2 skin irritation and sensitization studies summarized later in this report was derived from *Anthemis nobilis* L. The results of an analysis of this oil, provided by the Research Institute for Fragrance Materials (RIFM), are included below:[4]

- isobutyl angelate (30% to 35%)
- 2-methylbutyl angelate (15% to 20%)
- methallyl angelate (5% to 10%)

- isobutyl isobutyrate (5% to 10%)
- pinocarveol (1% to 5%)
- isoamyl angelate (1% to 5%)
- alpha-pinene (1% to 5%)
- unknown 71/43/100 mw = 170 (1% to 5%)
- pentan-2-yl butyrate (% to 5%)
- butyl methacrylate, iso-(2-propenoic acid, 2-methyl:isobutyl ester) (% to 5%)
- angelyl angelate (1% to 5%)
- propyl angelate (1% to 5%

Results from the nutritional characterization of *Anthemis nobilis* are stated as follows:[5] Carbohydrates are the most abundant macronutrients, followed by proteins. Ash and fat contents were low, and the energetic contribution was 389.88 kcal/100 g dry weight. The main sugar found in *Anthemis nobilis* was fructose, followed by glucose and sucrose. Trehalose was found in lower amounts. Polyunsaturated fatty acids (PUFA) predominated over saturated fatty acids (SFA) and monounsaturated fatty acids (MUFA). The fatty acids determined in higher percentages were linoleic acid (C18:2n6), oleic acid (C18 1n9), α-linolenic acid (C18:3n3), and palmitic acid ((C16:0). Regarding tocopherols, only α- and γ-tocopherols were found in *Anthemis nobilis*. β-Carotene and lycopene were also quantified in the sample studied.

USE

Cosmetic

The *Anthemis nobilis* ingredients function as fragrance ingredients and skin conditioning agents in cosmetic products.[6]

Information on uses of these ingredients as a function of product type was supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2013.[7] The Council conducted a survery of ingredient use concentrations in 2013, indicating use at concentrations up to 10% (anthemis nobilis flower water).[8]

As shown in Table 5, both VCRP use data and use concentration data were available for the following 3 ingredients:

- anthemis nobilis flower extract
- anthemis nobilis flower oil
- anthemis nobilis flower water

Neither VCRP data nor use concentration data were available for:

- anthemis nobilis flower powder

Cosmetic products containing *Anthemis nobilis*-derived ingredients may be applied to the skin and hair, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

The following ingredients are used in products that are sprayed (highest reported maximum use concentration = 2.8% anthemis nobilis flower oil in a potential spray product [perfume]): anthemis nobilis flower extract, anthemis nobilis flower oil, and anthemis nobilis flower water. Because these ingredients are used in products that are sprayed, they could possibly be inhaled. 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.[9,10,11,12] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[9,10]

Non-Cosmetic

Anthemis nobilis (Roman chamomile) is listed among the spices and other natural seasonings and flavorings that are generally recognized as safe (GRAS) for their intended use in food for human consumption.[13] It is also listed among the spices and other natural seasonings and flavorings that are GRAS for their intended use in animal drugs, feeds, and related products.[14]

Anthemis nobilis flowers are listed among the essential oils, oleoresins (solvent-free), and natural extractives (including distillates) that are GRAS for their intended use in food for human consumption.[15] They are also listed among the essential oils, oleoresins (solvent-free), and natural extractives (including distillates) that are GRAS for their intended use in animal drugs, feeds, and related products.[16]

FDA has determined that the available data are inadequate for establishing general recognition of safety and effectiveness of chamomile flowers as used in digestive aid drug products.[17]

The fragrant flowering heads of both German chamomile (*Chamomilla recutita*) and Roman chamomile (*Anthemis nobilis*) are collected and dried for use as teas and extracts.[18] Additionally, 2 ointments marketed under the name Kamillosan® are available in Europe, one containing German chamomile (also known as *Matricaria recutita* or *Chamomilla recutita*), and the other, containing Roman chamomile (also known as *Chamaemelum nobile* or *Anthemis nobilis*).[19]

TOXICOKINETICS

Data on the absorption, distribution, metabolism, and excretion of anthemis nobilis flower extract, anthemis nobilis flower oil, anthemis nobilis flower powder, or anthemis nobilis flower water were not found in the published literature, nor were unpublished data provided.

TOXICOLOGY

Acute Toxicity

Oral

Anthemis Nobilis Flower Oil

The acute oral toxicity of anthemis nobilis flower oil (dose = 5 g/kg) was evaluated using 10 rats (strain not stated).[20] Dosing was followed by a 14-day observation period. None of the animals died, and an LD_{50} of > 5 g/kg was reported.

Ocular Irritation

Anthemis Nobilis Flower Extract

One of the trade name mixtures associated with anthemis nobilis flower extract has the INCI name, propylene glycol (and) water (and) anthemis nobilis flower extract and contains 5%-9.9% anthemis nobilis flower extract (Table 3). It is also known as Vegetol® chamomile LC 376 hydro, and the extraction solvent is propylene glycol and water. The ocular irritation potential of this trade name mixture was evaluated using 6 New Zealand hybrid albino male rabbits.[21] The mixture (20% (v/v) solution in distilled water; volume = 0.1 ml) was instilled into the inferior conjunctival sac of the right eye. Reactions were scored 1 h post-instillation and then 1, 2, 4, and, possibly, 7 days post-instillation. The diluted mixture was classified as a very slight ocular irritant.

Skin Irritation

Animal

Anthemis Nobilis Flower Extract

One of the trade name mixtures associated with anthemis nobilis flower extract has the INCI name, propylene glycol (and) water (and) anthemis nobilis flower extract and contains 5%-9.9% anthemis nobilis flower extract (Table 3). It is also known as Vegetol® chamomile LC 376 hydro, and the extraction solvent is propylene glycol and water. The skin irritation potential of this mixture (20% v/v solution in distilled water) was evaluated using 6 New Zealand hybrid albino male rabbits.[21] The trade name mixture was applied to intact and scarified skin sites (on clipped flank) at a dose of 0.5 ml per area per animal. The test material remained in contact with the skin for 24 h. Reactions were scored approximately 30 minutes after patch removal and 48 h later. The trade name mixture was classified as a non-irritant.

Anthemis Nobilis Flower Oil

Undiluted anthemis nobilis flower oil was applied to the backs of hairless mice (number and strain not stated). Details relating to the test procedure were not reported. The oil was classified as non-irritating.[2] In another test, undiluted anthemis nobilis flower oil was applied (under occlusion) to intact or abraded skin of rabbits (number and strain not stated) for 24 h. The oil was classified as moderately irritating.[2]

Human

Predictive Testing

The skin irritation potential of anthemis nobilis flower oil (4% in petrolatum) was evaluated in a 48-h closed patch test involving human subjects (number not stated). Skin irritation was not observed.[2]

Skin Sensitization

Animal

Anthemis Nobilis Flower Oil

The skin sensitization potential of anthemis nobilis flower oil was evaluated in the open epicutaneous test on 6 guinea pigs (males and females).[22] Using a pipette or syringe, anthemis nobilis flower oil (4% solution, 0.1 ml) was applied epicutaneously to an 8 cm^2 area of the clipped flank daily, and the test site remained uncovered for 24 h. These induction applications were repeated daily for 3 weeks. Reactions were scored either at the end of the application period or at the end of each week. The guinea pigs were challenged with the oil (on contralateral flank) on days 21 and 25. Ten guinea pigs served as controls. The anthemis nobilis flower oil solution was not allergenic in this study.

Human

Predictive Testing

The skin sensitization potential of a leave-on skin care lotion containing 3% (0.03% solids) anthemis nobilis flower extract was evaluated in an HRIPT using 104 subjects (between 18 and 70 years old).[23] The test substance (0.2 ml, under patch [type not stated]) was applied to the upper back, between the scapulae, for 24 h on Mondays, Wednesdays, and Fridays. This procedure was repeated for a total of 9 induction applications (same test site). Reactions were scored 24 h after patch removal on Tuesdays and Thursdays, and, 48 h after patch removal, on Saturdays. Following a 2-week, non-treatment period, a challenge patch was applied for 24 h to a previously untreated site on the back. Reactions were scored at the time of patch removal and at 48 h and 72 h. No clinically significant dermal reactions were observed during the study. The authors concluded that the skin care lotion did not demonstrate a potential for eliciting dermal irritation or sensitization.

Anthemis Nobilis Flower Oil

The skin sensitization potential of anthemis nobilis flower oil (4% in petrolatum) was evaluated in the maximization test using 25 healthy volunteers (21 to 44 years old).[24] The test material (4% in petrolatum) was applied, under occlusion, to

the volar forearm of each subject for a total of 5 alternate-day 48-h periods. The test site was pre-treated with 5% sodium lauryl sulfate (24-h application, under occlusion) prior to application of the test material. A 10-day non-treatment period was observed after the induction phase. Challenge patches were then applied, under occlusion, to new test sites for 48 h. The application of challenge patches was preceded by a 1-h application of 10% aqueous sodium lauryl sulfate (under occlusion). Reactions were scored at the time of challenge patch removal and 24 h later. There was no evidence of contact sensitization in any of the subjects tested.

Anthemis Nobilis Essential Oil

In a skin irritation and sensitization study, anthemis nobilis essential oil (concentration not stated) was initially applied to 113 healthy subjects (13 men, 100 women;18 to 69 years old), 110 of whom completed the study.[25] Three subjects withdrew for reasons unrelated to conduct of the study. The oil was applied, under an occlusive patch (volume and area not stated), between the scapulae of the upper back. Patches were applied to the same site on Mondays, Wednesdays, and Fridays for a total of nine 24-h induction applications. Removal of patches on Tuesdays and Thursdays was followed by a 24-h non-treatment period. Patch removal on Saturdays was followed by a 48-h non-treatment period. Reactions were scored during non-treatment periods. The challenge phase was initiated at the end of a 2-week non-treatment period. Challenge patches were applied to new test sites, and reactions were scored at 24 h, 48 h, 72 h, and 96 h post-application. At most, mild erythema was observed in 5 subjects during the induction phase. During the challenge phase, 1 subject had mild erythema and edema at the 48-h reading. This reaction had increased to well-defined erythema by the 72-h reading, but had diminished to mild erythema by the 96-h reading. During re-challenge of this subject (semi-occlusive, occlusive, and open patches used), barely perceptible erythema was observed at 24 h (occlusive patch test only). There were no visible skin reactions at 48 h or 72 h following application of any of the 3 types of patches. It was concluded that chamomile essential oil did not demonstrate a potential for eliciting dermal irritation or sensitization.

The skin irritation and sensitization potential of anthemis nobilis essential oil (concentration not stated) was evaluated in an RIPT that initially involved 122 healthy subjects (90 women, 32 men; 18 to 68 years old), 104 of whom completed the study.[26] Eighteen subjects withdrew for reasons unrelated to conduct of the study, one of whom withdrew due to a generalized petechial response on most of the back. The oil (0.2 ml) was applied to a 2 cm x 2 cm semi-occlusive patch that was placed on the back (between the scapulae and waist, adjacent to the spinal midline) of each subject. The patches remained in place for 24 h. Removal of patches on Tuesdays and Thursdays was followed by a 24-h non-treatment period. Patch removal on Saturdays was followed by a 48-h non-treatment period. Reactions were scored during non-treatment periods. The test procedure was repeated on Mondays, Wednesdays, and Fridays for a total of 9 induction applications. The challenge phase was initiated at the end of a 2-week non-treatment period. Challenge patches were applied to new test sites, and reactions were scored at 24 h and 72 h post-application. Transient, barely perceptible erythema was observed in 8 of the 104 subjects during induction and/or challenge phases. These reactions were not classified as irritant or allergic in nature. It was concluded that chamomile essential oil did not induce skin irritation or allergenicity.

Provocative Testing

Anthemis Nobilis Extract

The sensitization potential of anthemis nobilis extract in patients sensitive to 5% Compositae mix (also contains anthemis nobilis extract) in petrolatum was evaluated using 76 patients. The extraction solvent was not stated. Anthemis nobilis extract (1% in petrolatum) was applied to the back of each of 29 patients (24 women [mean age = 56], 5 men [mean age = 55] for 2 days using Finn chambers on Scanpor® tape. Reactions were scored on days 3 to 5, and possibly, on day 7 according to ICDRG criteria. There were no positive reactions to anthemis nobilis extract.

Anthemis Nobilis

Up to 14 adult patients who had previously tested positive (at least a 2+ reaction) to ether extracts of *Chamomilla recutita* (2.5% in petrolatum) and/or *Arnica Montana* (0.5% in petrolatum) were patch tested with *Anthemis nobilis* (1% in petrolatum).[27] A patch (Finn chambers on Scanpor® tape) containing either of the test materials was applied to the back for 2 days. Reactions were scored on day 3, and, possibly, day 7 according to ICDRG recommendations. Of the 14 patients patch tested with *Anthemis nobilis* (1% in petrolatum), 6 had reactions that were described as follows: 2 with ++ reactions, 2 with doubtful positive follicular reactions, 1 with a + follicular reaction, and 1 with a doubtful positive reaction.

Case Reports

Chamomile/Chamomile Extract

Rapid onset of a transient rash, burning, stinging, and itching at the application sites were reported for a 24-year-old woman who had applied a cosmetic skin mask formulation to her face.[28] Components of the skin mask were as follows: whole egg, lecithin, allantoin, aloe gel, melissa extract, and chamomile extract (extraction solvent not stated). The genus and species of the chamomile extract were not stated. Open testing (i.e., without prick, scratch, or chamber) with 1% chamomile extract (in physiologic saline) produced an extensive wheal and flare reaction on intact forearm skin. Open test results were negative for the saline control and 1% chamomile extract in 10 control subjects. The authors concluded that the patient appeared to have developed immunologic contact urticaria.

A 20-year-old woman complained of a short-lasting cough and rhinitis after inhaling fragrance from a chamomile-scented toilet paper.[29] The genus and species of the chamomile were not stated. Chamomile allergenicity was evaluated in a prick test and radioallergosorbent test (RAST). Results for the prick test (wheal mean diameter = 12 mm) and RAST (Pharmacia ImmunoCAP system (CAP system): 12.9 KU/l (v.n. < 0.35) were positive. Results were also positive when the chamomile-scented toilet paper was evaluated in a prick-by-prick test (mean diameter of wheal = 9 mm (toilet paper) and 5 mm (histamine). Two atopic subjects and 2 healthy subjects served as controls for the prick-by-prick test, and results were negative for the chamomile-scented tissue.

Anthemis Nobilis Flower

Acute eczema on the forearms and hands was observed in a 50-year old metalworker after using a product for cleaning metallic items.[30] The patient had no personal or family history of atopy, but had psoriasis. Treatment of the eczema involved washing and applying compresses (over 2-month period) with chamomilla recutita (matricaria) tea (from flower heads) and, subsequently, with a tea made from chamomilla recutita (matricaria) (flower heads), anthemis nobilis (flower heads), and mallow herbs. Patch tests were performed using Finn chambers; neither the area of application nor test concentration was stated. Positive reactions to anthemis nobilis tea (++ on days 2 and 4) were reported. Negative results were reported for 5 control subjects tested with anthemis nobilis tea. It should be noted that the fragrant flowering heads of both German chamomile (*Chamomilla recutita*) and Roman chamomile (*Anthemis nobilis*) are collected and dried for use as teas and extracts.[18]

Anthemis Nobilis Flower Oil

Severe exudative eczema of both nipples and areolae was observed in a 32-year-old woman who had been applying Kamillosan® ointment (containing extracts and oil of *Anthemis nobilis* 10.5%) to treat cracked nipples.[19] It should be noted that 2 ointments marketed under the name Kamillosan® are available in Europe, one containing German chamomile (also known as *Matricaria recutita* or *Chamomilla recutita*) and, the other, containing Roman chamomile (also known as *Chamaemelum nobile* or *Anthemis nobilis*). Patch testing of the ointment (Finn chambers on Scanpor® tape) identified a 3+ reaction to the ointment at 2 days. A 3+ reaction was also observed after patch testing with 0.1% anthemis nobilis flower oil in petrolatum; results were negative in 10 control subjects. Bilateral eczema of the nipples and areolae was also observed in a 38-year-old woman who had used the same ointment. Patch testing also revealed a 3+ reaction to 0.1% anthemis nobilis flower oil in petrolatum at 2 days.

A 34-year-old woman with a history of atopic dermatitis was hospitalized with acute generalized eczema, accentuated on the face.[31] Prior to the onset of symptoms, the patient had applied compresses of chamomile tea to her face and neck. Additionally, she drank chamomile tea regularly. Patch test results were as follows: 25% anthemis nobilis flower oil in olive oil (++ on day 2; +++ on day 3) and 4% anthemis nobilis flower oil in petrolatum (++ on day 2; +++ on day 3).

Anthemis Nobilis and Anthemis Nobilis Extract

A 55-year-old male employee of a magnet factory presented with crops of disseminated confluent erythroderma, initially on sun-exposed areas (face, neck, V of neck and acral) and then spreading to the remainder of the skin.[32] The lesions were described as itchy and scaly. The patient experienced exacerbation of these reactions after visiting an area where there were many and varied plants, even though there was no direct contact with the plants. Patch testing with *the Anthemis nobilis* plant as is yielded a +++ reaction on days 2 and 4. The same reactions were reported after patch testing with *Anthemis nobilis* ethyl ether extracts (stem and leaves). Photopatch testing (Finn chambers, UVA exposure) also yielded a +++ reaction to the plant as is and its ethyl ether extracts.

Phototoxicity

Anthemis Nobilis Flower Oil

The phototoxicity of anthemis nobilis flower oil was evaluated using 12 Skh-1:hairless mice and 2 miniature swine.[33] The light source was a 6-kW long-arc xenon high pressure burner (UVA and UVB proportions approximated those found in mid-latitude summer sun spectrum) or a bank of 4 fluorescent F40BL black light lamps (UVA region, centered over 350 nm). The 12 mice and 2 swine were treated with the non-viscous oil, tested as received. A single application of the oil (20 µl) was made to an area of the back that was approximately 2 cm^2. Six mice and 1 swine were then exposed to one of the light sources, and, the remaining 6 mice and 1 swine, to the other light source at 30 minutes post-application of the oil. The duration of exposure to the fluorescent blacklight source was 1 h (integrated UVA intensity = 3 W/m^2), and 40 minutes (intensity of weighted erythemal energy = 0.1667 W/m^2) to the xenon lamp. If application of the oil elicited a response from skin exposure to the blacklight lamp or elicited more than a barely perceptible response to the xenon lamp, the oil was considered phototoxic. The area of skin treated with the oil, but not irradiated, served as the control for primary irritant reactions. One group of control mice was treated with 8-methoxypsoralen (8-MOP, 0.01% in methanol), and another group, with appropriate vehicle only. Exposure to the xenon lamp caused barely perceptible erythema in animals pretreated with vehicle only or with anthemis nobilis flower oil. Parallel results were obtained using the blacklight lamp. 8-MOP was phototoxic.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Chamomile

A case-control analysis of data from the Quebec pregnancy registry was performed. Data on 3183 pregnant females were collected, and multivariate logistic regression models were used for data analysis.[34] Cases were defined as women who delivered a newborn (< 2500 g), and 424 of the 3183 participants were classified as cases. After adjusting for potential confounders, there were no statistically significant associations found between the use of chamomile (*Anthemis nobilis*) tea (alone or in combination with other herbal products) during the last 2 trimesters of pregnancy and the incidence of low birth weight.

An epidemiology study examined the use of herbal products by pregnant women in Italy and pregnancy outcome.[35] The number of subjects (mostly between 31 and 40 years old) interviewed was 392. Of the 392 subjects, 109 reported having taken one or more herbal products during pregnancy; the remaining 283 were classified as non-users. The most frequently used herb was chamomile (48; 44% of the 109 subjects), followed by licorice (15; 13.8% of the 109 subjects). For the 37 regular users of chamomile and 14 regular users of licorice, there was a higher frequency of threatening miscarriages (21.6% and 35.7%, respectively) and preterm labors (21.6% and 16.7%, respectively) when compared to non-users. Whether or not the frequency of threatening miscarriages in users of chamomile versus non-users was statistically significant was not stated. An unspecified cardiac malformation (thought to have been related to Down's syndrome) and an enlarged kidney were diagnosed in 2 neonates, following regular maternal consumption of chamomile. Regarding pregnancy outcome in the study population, no statistically significant differences were evident between users and non-users, except for a higher incidence of newborns small for gestational age (11.9% vs. 5.3%; $p = 0.039$). However, after further analysis of the data, it was hypothesized that the regular intake of 2 herbs (chamomile and licorice, taken from the beginning of pregnancy) may have had an influence on threatening miscarriages and preterm labors of low birth weight infants.

GENOTOXICITY

Anthemis Nobilis Flower Oil

The genotoxicity of anthemis nobilis flower oil was evaluated in the rec-assay using *Bacillus subtilis* strains PB 1652 and PB 1791 and in the *Salmonella*/microsome reversion assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537.[36] In the rec-assay, 10-30 µl of the oil was applied to a sterile filter paper disk (9-mm diameter), placed on the surface of nutrient agar plates seeded with the tester strains. Following incubation, the diameter of the inhibition zones formed around the disk was measured. Methyl methanesulfonate (MMS), mitomycin C (MIT C), and adriamycin (ADR) served as positive controls. Ampicillin (AMP) and chloramphenicol (CAF) served as negative controls. Positive DNA-damaging activity was assumed if the ratio between the diameter of the inhibition zone of the rec^- mutant and that of the parental rec^+ strain exceeded a value of 1.2. Anthemis nobilis flower oil did not produce positive DNA-damaging

activity in either *Bacillus subtilis* strain. All positive controls had positive DNA damaging activity, whereas, the 2 negative controls did not. In the *Salmonella*/microsome reversion assay (with and without metabolic activation), the oil (in DMSO) was evaluated at doses up to 1 µl/plate and was not found to be genotoxic.

CARCINOGENICITY

Carcinogenicity studies on the *Anthemis nobilis*-derived ingredients reviewed in this safety assessment were not found in the published literature, nor were unpublished studies provided.

BIOLOGICAL ACTIVITY

Anti-inflammatory Activity

Anthemis Nobilis Flower Oil

The anti-inflammatory activity of anthemis nobilis flower oil was evaluated using groups of 6 adult male Wistar rats.[37] The oil from 2 varieties of *Anthemis nobilis* that have been cultivated in Italy under the names "white-headed" (WH) or "double-flowered roman chamomile" and "yellow-headed roman chamomile" (YH) was tested. The oil from each flower type was administered i.p. at a dose of 350 mg/kg, and the animals were then dosed orally (gavage) with 5 ml water. Of the 2 control groups, 1 was injected i.p. with normal saline (dose not stated), and the other, with indomethacin (14 µmol/kg). The dosing of control animals i.p. was followed by oral dosing with water. At 30 minutes post-treatment, the right hind paw was injected with 0.1 ml of a 1% suspension of carrageenan in normal saline to induce phlogosis. Each oil caused a considerable anti-inflammatory effect, particularly by 3 h post-injection. The oils caused 22.8 to 38.7% inhibition of the carrageenan-induced increase in paw volume. Indomethacin caused 73.7% inhibition.

SUMMARY

The safety of Roman chamomile [*Anthemis nobilis*]) ingredients is reviewed in this safety assessment. These ingredients function mostly as fragrance ingredients and skin conditioning agents in cosmetic products. The VCRP and Council survey data combined indicate that the following 3 chamomile ingredients have been used in cosmetic products: anthemis nobilis flower extract, anthemis nobilis flower oil, and anthemis nobilis flower water. Of the 3 ingredients, the highest ingredient use concentration has been reported as 10% for anthemis nobilis flower water in a skin cleansing product.

Anthemis nobilis flower oil is produced by the steam distillation of *Anthemis nobilis* flowers.

A UV spectral analysis indicated an absorption maximum of ~225 nm for anthemis nobilis flower oil.

Anthemis nobilis flower oil did not induce acute toxicity when administered orally to rats.

A trade name mixture associated with anthemis nobilis flower extract (propylene glycol (and) water (and) anthemis nobilis flower extract) was classified as a very slight ocular irritant in rabbits. The mixture contained 5%-9.9% anthemis nobilis flower extract and was tested as a 20% v/v solution in distilled water.

Anthemis nobilis flower oil was classified as non-irritating to the skin of hairless mice and irritating to the skin of rabbits. A trade name mixture associated with anthemis nobilis flower extract (propylene glycol (and) water (and) anthemis nobilis flower extract) was also non-irritating to the skin of rabbits. The mixture contained 5%-9.9% anthemis nobilis flower extract and was tested as a 20% v/v solution in distilled water.

Anthemis nobilis flower oil (4%) did not induce skin sensitization in guinea pigs. In a human predictive patch test, anthemis nobilis flower oil (4%) was not a skin irritant in subjects tested or skin sensitizer in a maximization test involving 25 subjects. In 2 other human repeated insult patch tests, anthemis nobilis essential oil did not induce skin irritation or sensitization in 110 and 104 subjects, respectively. A skin care lotion containing 3% anthemis nobilis flower did not demonstrate a potential for eliciting dermal irritation or sensitization in a predictive HRIPT.

Results were negative in 29 patients patch-tested with anthemis nobilis extract (1% in petrolatum). Provocative patch test reactions to *Anthemis nobilis* (plant part(s) not specified; 1% in petrolatum) were described as ++ reactions (2 of 14 patients) and doubtful positive follicular reactions (2 patients). Positive reactions to *Anthemis nobilis* ingredients were also observed in a number of case reports.

Barely perceptible erythema was observed in hairless mice and miniature swine treated with anthemis nobilis flower oil (20 µl/cm^2) in a phototoxicity study, and these results were classified as negative.

In a case-control study (424 cases), there were no statistically significant associations found between the use of chamomile tea (alone or in combination with other herbal products) during the last 2 trimesters of pregnancy and the risk of low birth weight. For 37 regular users of chamomile (herbal product, genus and species not stated), both the frequency of threatening miscarriages and the frequency preterm labors were 21.6% higher when compared to non-users (group of 283); many of the subjects also consumed licorice.

Anthemis nobilis flower oil was not genotoxic in the rec-assay (no positive DNA-damaging activity) or Ames test. Carcinogenicity data on chamomile ingredients were not found in the published literature.

The anti-inflammatory activity of anthemis nobilis flower oil has been demonstrated in rats dosed intraperitoneally.

DISCUSSION

Composition data are available on anthemis nobilis flower oil, as well as samples of the whole plant and the flower of *Anthemis nobilis*. The Panel agreed that these data are adequate to support assumptions about the likely compositions of other *Anthemis nobilis*-derived ingredients.

As botanical ingredients, derived from natural plant sources, are complex mixtures, the Panel expressed concern that multiple botanical ingredients may each contribute to the final concentration of a single constituent. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects.

In particular, the Panel was concerned that cosmetics containing these ingredients may contain potentially sensitizing levels of constituents, such as sesquiterpene lactones. The levels of these constituents can vary widely in cosmetic ingredients, depending on the growing conditions of the plant, the method of manufacturing of the ingredient, and other factors, and the reported results of the sensitization tests may not represent the complete spectrum of likely levels in cosmetic ingredients. Thus, the Panel concluded that cosmetics containing these ingredients should be formulated to be non-sensitizing.

The Panel expressed concern about pesticide residues and heavy metals that may be present in *Anthemis nobilis*-derived ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities in the ingredient before blending into cosmetic formulations.

The Panel noted that the highest use concentration reported for *Anthemis nobilis*-derived ingredients reviewed in this safety assessment is 10% anthemis nobilis flower water. Because use at this concentration was reported only for a single skin cleansing product in a survey of ingredient use concentrations, the Panel agreed that use at a concentratrion of 10% is not representative of typical use concentrations. Thus, the Panel determined that the negative HRIPT data on a product containing 3% anthemis nobilis flower extract are sufficient, together with other skin irritation and sensitization data in this safety assessment, for evaluating the skin irritation and sensitization potential of *Anthemis nobilis*-derived ingredients over the range of reported use concentrations. Although mammalian genotoxicity and carcinogenicity data were not available, the negative bacterial genotoxicity data, the available chemical composition data on these botanical ingredients, and the low use concentrations suggest that systemic toxicity would not be likely if percutaneous absorption of any of the constituents were to occur.

The Panel discussed incidental inhalation exposure from aerosol and pump hair sprays and foot powders and sprays. Inhalation toxicity data were not available. However, the Panel considered pertinent data indicating that incidental inhalation exposures to these ingredients in such cosmetic products would not cause adverse health effects, including data characterizing the potential for these ingredients to cause acute oral toxicity, and ocular or dermal irritation or sensitization. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount.

Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that anthemis nobilis extract, anthemis nobilis flower oil, anthemis nobilis flower powder, and anthemis nobilis flower water are safe in the present practices of use and concentration, described in this safety assessment, in cosmetics, when formulated to be non-sensitizing.

Table 1. Definitions and functions of the ingredients in this safety assessment[6]

Ingredient, CAS No.	Definition	Function
Anthemis Nobilis-Derived		
Anthemis Nobilis Flower Extract [84649-86-5]	Anthemis Nobilis Flower Extract is the extract of the flowers of the chamomile, *Anthemis nobilis.*	Fragrance ingredients; skin-conditioning agents-miscellaneous
Anthemis Nobilis Flower Oil [8015-92-7]	Anthemis Nobilis Flower Oil is the volatile oil distilled from the dried flower heads of *Anthemis nobilis.*	Fragrance ingredients; skin-conditioning agents-miscellaneous
Anthemis Nobilis Flower Powder	Anthemis Nobilis Flower Powder is the powder obtained from the dried, ground flowers of *Anthemis nobilis.*	Skin-conditioning agents-miscellaneous
Anthemis Nobilis Flower Water	Anthemis Nobilis Flower Water is an aqueous solution of the steam distillates obtained from the flowers of *Anthemis nobilis.*	Fragrance ingredients; skin-conditioning agents-miscellaneous

Table 2. Chemical and Physical Properties[38,39,40]

Properties	Anthemis Nobilis Flower Oil
Form	Light blue or light green-blue liquid with strong, aromatic odor
Specific gravity	Between 0.892 and 0.910
Refractive Index	Between 1.440 and 1.450 at 20°C
Solubility	Soluble in most fixed oils and almost completely soluble in mineral oil. Soluble in propylene glycol, but insoluble in glycerin
Acid value	Not more than 15.0
Ester value	Between 250 and 310
UV absorption maximum	~ 225 nm

Table 3. Composition Data on *Anthemis Nobilis* Trade Name Materrial[3,41]

Trade Name	INCI Name	Composition (%)	Extraction Solvent
Vegetol® roman chamomile LC 376 Hydro	Propylene glycol (and) water (and) Anthemis nobilis flower extract	> 50 %, 25% to 50%, 5% to 9.9%	Propylene glycol and water

Table 4. Composition of Anthemis Nobilis Plant and Components.[1,38,42,43,44,45,37]

Data	Plant Part/Derivative		
Components/Impurities	**Anthemis Nobilis Flower Oil**	**Anthemis Nobilis Flower**	**Anthemis Nobilis Plant**
Aluminum		27 ppm	
Angelyl angelate	1 to 5%		
Ascorbic Acid		267 ppm	
Ash		62,000 ppm	
Beta-carotene		2.2 ppm	
n-Butylangelate + hexyl acetate	14.5 to 34.2%		
Butyl methacrylate, iso-(2-propenoic acid, 2-methyl:isobutyl ether	1 to 5%		
Calcium		6,720 ppm	
Carbohydrates			785,000 ppm
Chromium		6 ppm	
Cobalt		58 ppm	
EO			6,000 to 17,500 ppm
Fat		39,000 ppm	
Fiber		72,000 ppm	
Iron		170 ppm	
Isoamyl angelate	1 to 22.8%		
Isoamyl tigliate	0.6 to 0.8%		
Isobutyl angelate	30 to 35%		
Isobutyl butyrate	0.6 to 1.5%		
Isobutyl isobutyrate	5 to 10 %		
Isobutyl isovalerate	3.5 to 3.8%		
Magnesium		2,920 ppm	
Manganese		52 ppm	
Methallyl angelate	5 to 10%		
2-Methylbutyl angelate	15 to 20%		
2-Methylbutyl-2-methylbutyrate	7.3% to 9.2%		
pentan-2-yl butyrate	1 to 5%		
Phosphorus		3,220 ppm	
α-Pinene	1 to 5%		
Pinocarveol	1 to 5%		
Potassium		13,200 ppm	
Propyl angelate	1 to 5%		

Table 4. Composition of Anthemis Nobilis Plant and Components.[1,38,42,43,44,45,37]

Data	Plant Part/Derivative		
Components/Impurities	**Anthemis Nobilis Flower Oil**	**Anthemis Nobilis Flower**	**Anthemis Nobilis Plant**
Protein		115,000 ppm	
Riboflavin		4.3 ppm	
Silicon		31 ppm	
Sodium		2,580 ppm	
Thiamin		0.8 ppm	
Tin		10 ppm	
Water		812,000 ppm	

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2013.[7,8]

	Anthemis Nobilis Flower Oil		**Anthemis Nobilis Flower Water**		**Anthemis Nobilis Flower Extract**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	NR	0.000057-0.01	1	1	44	0.001-0.025
Incidental Ingestion	NR	NR	NR	NR	5	NR
Incidental Inhalation- Sprays	NR	0.000039-2.8	NR	2	16	0.0004-0.03
Incidental Inhalation- Powders	2	NR	NR	NR	7	NR
Dermal Contact	6	0.000039-2.8	2	1-10	315	0.000001-0.05
Deodorant (underarm)	NR	NR	NR	NR	1	NR
Hair - Non-Coloring	1	0.00039-0.01	NR	NR	80	0.000025-0.1
Hair-Coloring	NR	NR	NR	NR	12	NR
Nail	NR	NR	NR	NR	3	NR
Mucous Membrane	2	0.00077-0.007	NR	NR	36	0.0003-0.01
Baby Products	3	NR	NR	NR	9	NR
Duration of Use						
Leave-On	3	0.000039-2.8	2	1-4	252	0.00004-0.05
Rinse off	2	0.0002-0.05	NR	2-10	155	0.000001-0.1
Diluted for (bath) Use	2	0.007	NR	NR	16	NR
Totals/Conc. Range	7	0.000039-2.8	2	1-10	423	0.000001-0.1

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.

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

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2013 FDA VCRP Data

Anthemis Nobilis Flower Extract

01A - Baby Shampoos	4
01B - Baby Lotions, Oils, Powders, and Creams	3
01C - Other Baby Products	2
02A - Bath Oils, Tablets, and Salts	2
02B - Bubble Baths	6
02D - Other Bath Preparations	8
03A - Eyebrow Pencil	2
03B - Eyeliner	4
03C - Eye Shadow	2
03D - Eye Lotion	14
03E - Eye Makeup Remover	7
03F - Mascara	8
03G - Other Eye Makeup Preparations	7
04A - Cologne and Toilet waters	1
04E - Other Fragrance Preparation	4
05A - Hair Conditioner	24
05B - Hair Spray (aerosol fixatives)	1
05F - Shampoos (non-coloring)	32
05G - Tonics, Dressings, and Other Hair Grooming Aids	9
05I - Other Hair Preparations	10
06A - Hair Dyes and Colors (all types requiring caution stater	10
06C - Hair Rinses (coloring)	1
06E - Hair Color Sprays (aerosol)	1
07A - Blushers (all types)	4
07B - Face Powders	4
07C - Foundations	5
07E - Lipstick	5
07H - Makeup Fixatives	1
07I - Other Makeup Preparations	2
08B - Cuticle Softeners	2
08C - Nail Creams and Lotions	1
10A - Bath Soaps and Detergents	8
10B - Deodorants (underarm)	1
10E - Other Personal Cleanliness Products	7
11E - Shaving Cream	1
11G - Other Shaving Preparation Products	4
12A - Cleansing	42
12C - Face and Neck (exc shave)	27
12D - Body and Hand (exc shave)	18
12E - Foot Powders and Sprays	1
12F - Moisturizing	47
12G - Night	10
12H - Paste Masks (mud packs)	15
12I - Skin Fresheners	17
12J - Other Skin Care Preps	32

13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	5
13C - Other Suntan Preparations	1
Total	**423**

Anthemis Nobilis Flower Oil

01A - Baby Shampoos	1
01B - Baby Lotions, Oils, Powders, and Creams	2
02A - Bath Oils, Tablets, and Salts	1
12C - Face and Neck (exc shave)	1
12F - Moisturizing	1
12H - Paste Masks (mud packs)	1
Total	**7**

Anthemis Nobilis Flower Water

03G - Other Eye Makeup Preparations	1
12C - Face and Neck (exc shave)	1
Total	**2**

Personal Care Products Council
Committed to Safety, Quality & Innovation
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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: July 22, 2013

SUBJECT: Updated Concentration of Use by FDA Product Category: Chamomile-Derived Ingredients

Concentration of Use by FDA Product Category - Chamomile-Derived Ingredients

Chamomilla Recutita (Matricaria) Extract
Chamomilla Recutita (Matricaria) Flower
Chamomilla Recutita (Matricaria) Flower Extract (alternate VCRP name Matricaria Chamomilla Flower Extract)
Chamomilla Recutita (Matricaria) Flower/Leaf Extract
Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Extract
Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Water
Chamomilla Recutita (Matricaria) Flower Oil
Chamomilla Recutita (Matricaria) Flower Powder
Chamomilla Recutita (Matricaria) Flower Water
Chamomilla Recutita (Matricaria) Leaf Extract
Chamomilla Recutita (Matricaria) Oil
Anthemis Nobilis Flower Extract
Anthemis Nobilis Flower Oil
Anthemis Nobilis Flower Powder
Anthemis Nobilis Flower Water

Ingredient	FDA Code†	Product Category	Maximum Concentration of Use
Chamomilla Recutita (Matricaria) Extract	03A	Eyebrow pencil	0.0001%
Chamomilla Recutita (Matricaria) Extract	03B	Eye liner	0.071%
Chamomilla Recutita (Matricaria) Extract	03C	Eye shadow	0.02%
Chamomilla Recutita (Matricaria) Extract	03D	Eye lotion	0.4%
Chamomilla Recutita (Matricaria) Extract	07B	Face powders	0.0004%
Chamomilla Recutita (Matricaria) Extract	07C	Foundations	0.002-0.4%
Chamomilla Recutita (Matricaria) Extract	07E	Lipstick	0.002%
Chamomilla Recutita (Matricaria) Extract	10A	Bath soaps and detergents	0.61%

Chamomilla Recutita (Matricaria) Extract	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.01-0.1%
Chamomilla Recutita (Matricaria) Extract	12C	Face and neck products not spray spray	 0.0025-0.13% 0.1%
Chamomilla Recutita (Matricaria) Extract	12D	Body and hand products not spray	 0.0009-0.13%
Chamomilla Recutita (Matricaria) Extract	12F	Moisturizing products not spray	 0.002%
Chamomilla Recutita (Matricaria) Extract	13A	Suntan products not spray	 0.13%
Chamomilla Recutita (Matricaria) Flower	05D	Permanent waves	0.5%
Chamomilla Recutita (Matricaria) Flower	05E	Rinses (noncoloring)	0.02%
Chamomilla Recutita (Matricaria) Flower	06A	Hair dyes and colors (all types requiring caution statement and patch test)	0.3%
Chamomilla Recutita (Matricaria) Flower	06E	Hair color sprays aerosol	 0.02%
Chamomilla Recutita (Matricaria) Flower Extract	01A	Baby shampoos	0.0097%
Chamomilla Recutita (Matricaria) Flower Extract	02A	Bath oils, tablets and salts	0.00051%
Chamomilla Recutita (Matricaria) Flower Extract	02B	Bubble baths	0.00051%
Chamomilla Recutita (Matricaria) Flower Extract	03B	Eye liner	0.064-0.2%
Chamomilla Recutita (Matricaria) Flower Extract	03C	Eye shadow	0.0001-0.2%
Chamomilla Recutita (Matricaria) Flower Extract	03D	Eye lotion	0.02%

Chamomilla Recutita (Matricaria) Flower Extract	03E	Eye makeup remover	0.02%
Chamomilla Recutita (Matricaria) Flower Extract	03F	Mascara	0.005-0.02%
Chamomilla Recutita (Matricaria) Flower Extract	04A	Colognes and toilet waters	0.01%
Chamomilla Recutita (Matricaria) Flower Extract	04E	Other fragrance preparations not spray	 0.02%
Chamomilla Recutita (Matricaria) Flower Extract	05A	Hair conditioners	0.000025-0.12%
Chamomilla Recutita (Matricaria) Flower Extract	05B	Hair sprays aerosol pump sprays	 0.00001-0.00003% 0.0001-0.01%
Chamomilla Recutita (Matricaria) Flower Extract	05C	Hair straighteners	0.0007%
Chamomilla Recutita (Matricaria) Flower Extract	05D	Permanent waves	0.00001%
Chamomilla Recutita (Matricaria) Flower Extract	05E	Rinses (noncoloring)	0.00004%
Chamomilla Recutita (Matricaria) Flower Extract	05E	Shampoos (noncoloring)	0.00006-0.25%
Chamomilla Recutita (Matricaria) Flower Extract	05G	Tonics, dressings and other hair grooming aids spray	0.00001-0.0075% 0.0002-0.002%
Chamomilla Recutita (Matricaria) Flower Extract	06A	Hair dyes and colors (all types requiring caution statement and patch test)	0.0005-0.005%
Chamomilla Recutita (Matricaria) Flower Extract	06C	Hair rinses (coloring)	0.00001%
Chamomilla Recutita (Matricaria) Flower Extract	06F	Hair lighteners with color	0.00005-0.02%
Chamomilla Recutita (Matricaria) Flower Extract	06G	Hair bleaches	0.02%
Chamomilla Recutita (Matricaria) Flower Extract	07A	Blushers (all types)	0.00032-0.02%
Chamomilla Recutita (Matricaria) Flower Extract	07C	Foundations	0.003-0.025%

Chamomilla Recutita (Matricaria) Flower Extract	07E	Lipstick	0.0002-0.5%
Chamomilla Recutita (Matricaria) Flower Extract	07F	Makeup bases	0.2%
Chamomilla Recutita (Matricaria) Flower Extract	07H	Makeup fixatives	0.0005-0.1%
Chamomilla Recutita (Matricaria) Flower Extract	07I	Other makeup preparations	0.00032-0.086%
Chamomilla Recutita (Matricaria) Flower Extract	08B	Cuticle softeners	0.01-0.3%
Chamomilla Recutita (Matricaria) Flower Extract	08F	Nail polish and enamel removers	0.002%
Chamomilla Recutita (Matricaria) Flower Extract	08G	Other manicuring preprations	0.3%
Chamomilla Recutita (Matricaria) Flower Extract	09A	Dentifrices (aerosol, liquid, pastes and powders)	0.002%
Chamomilla Recutita (Matricaria) Flower Extract	09B	Mouthwashes and breath fresheners (liquids and sprays)	0.002%
Chamomilla Recutita (Matricaria) Flower Extract	10A	Bath soaps and detergents	0.0001-0.034%
Chamomilla Recutita (Matricaria) Flower Extract	10D	Feminine hygiene deodorants aerosol	0.0004%
Chamomilla Recutita (Matricaria) Flower Extract	10E	Other personal cleanliness products	0.000025-0.02%
Chamomilla Recutita (Matricaria) Flower Extract	11A	Aftershave lotions	0.009-0.2%
Chamomilla Recutita (Matricaria) Flower Extract	11E	Shaving cream (aerosol, brushless and lather)	0.00017-0.00019%
Chamomilla Recutita (Matricaria) Flower Extract	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0002-0.02%
Chamomilla Recutita (Matricaria) Flower Extract	12B	Depilatories	0.0075-0.2%
Chamomilla Recutita (Matricaria) Flower Extract	12C	Face and neck products not spray	0.002-0.088%

Chamomilla Recutita (Matricaria) Flower Extract	12D	Body and hand products not spray spray	 0.0002-0.02% 0.01%
Chamomilla Recutita (Matricaria) Flower Extract	12F	Moisturizing products not spray	 0.01-0.1%
Chamomilla Recutita (Matricaria) Flower Extract	12G	Night products not spray	 0.002-0.05%
Chamomilla Recutita (Matricaria) Flower Extract	12H	Paste masks and mud packs	0.0075-0.038%
Chamomilla Recutita (Matricaria) Flower Extract	12J	Other skin care preparations	0.005-0.15%
Chamomilla Recutita (Matricaria) Flower Extract	13A	Suntan products not spray	 0.2%
Chamomilla Recutita (Matricaria) Flower/Leaf Extract	05G	Tonics, dressings and other hair grooming aids spray	 0.0001%
Chamomilla Recutita (Matricaria) Flower/Leaf Extract	07B	Face powders	0.002%
Chamomilla Recutita (Matricaria) Flower/Leaf Extract	07C	Foundations	0.02%
Chamomilla Recutita (Matricaria) Flower/Leaf Extract	07E	Lipstick	0.01%
Chamomilla Recutita (Matricaria) Flower/Leaf Extract	08B	Cuticle softeners	0.01%
Chamomilla Recutita (Matricaria) Flower Oil	03E	Eye makeup remover	0.001%
Chamomilla Recutita (Matricaria) Flower Oil	05B	Hair sprays aerosol	 0.007%

Chamomilla Recutita (Matricaria) Flower Oil	05G	Tonics, dressings and other hair grooming aids	0.1%
Chamomilla Recutita (Matricaria) Flower Oil	06A	Hair dyes and colors (all types requiring caution statement and patch test)	0.06%
Chamomilla Recutita (Matricaria) Flower Oil	07E	Lipstick	0.03%
Chamomilla Recutita (Matricaria) Flower Oil	10A	Bath soaps and detergents hand soap	 0.0001%
Chamomilla Recutita (Matricaria) Flower Oil	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.012%
Chamomilla Recutita (Matricaria) Flower Oil	12C	Face and neck products not spray	 0.001%
Chamomilla Recutita (Matricaria) Flower Oil	12D	Body and hand products not spray spray	 0.2% 0.066%
Chamomilla Recutita (Matricaria) Flower Powder	12H	Paste masks and mud packs	1%
Anthemis Nobilis Flower Extract	03B	Eye liner	0.001-0.025%
Anthemis Nobilis Flower Extract	03D	Eye lotion	0.02%
Anthemis Nobilis Flower Extract	03E	Eye makeup remover	0.003%
Anthemis Nobilis Flower Extract	05A	Hair conditioners	0.000025-0.001%
Anthemis Nobilis Flower Extract	05F	Shampoos (noncoloring)	0.000025-0.1%
Anthemis Nobilis Flower Extract	05G	Tonics, dressings and other hair grooming aids spray	0.0002% 0.0004%
Anthemis Nobilis Flower Extract	10A	Bath soaps and detergents	0.003%

Anthemis Nobilis Flower Extract	10E	Other personal cleanliness products	0.002-0.01%
Anthemis Nobilis Flower Extract	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.002-0.0075%
Anthemis Nobilis Flower Extract	12C	Face and neck products not spray	0.01%
Anthemis Nobilis Flower Extract	12D	Body and hand products not spray	0.00004%
Anthemis Nobilis Flower Extract	12E	Foot powders and spray spray	0.03%
Anthemis Nobilis Flower Extract	12F	Moisturizing products not spray	0.0028-0.03%
Anthemis Nobilis Flower Extract	12H	Paste masks and mud packs	0.000001%
Anthemis Nobilis Flower Extract	12J	Other skin care preparations	0.007-0.05%
Anthemis Nobilis Flower Oil	02A	Bath oils, tablets and salts	0.007%
Anthemis Nobilis Flower Oil	03D	Eye lotion	0.000057-0.01%
Anthemis Nobilis Flower Oil	04B	Perfumes	2.8%
Anthemis Nobilis Flower Oil	04E	Hair conditioners	0.000039%
Anthemis Nobilis Flower Oil	05F	Shampoos (noncoloring)	0.00033-0.004%
Anthemis Nobilis Flower Oil	05G	Tonics, dressings and other hair grooming aids spray	0.0006-0.01% 0.006%
Anthemis Nobilis Flower Oil	07C	Foundations	0.02%
Anthemis Nobilis Flower Oil	10A	Bath soaps and detergents	0.00077%

Anthemis Nobilis Flower Oil	11E	Shaving cream (aerosol, brushless and lather)	0.0002%
Anthemis Nobilis Flower Oil	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.001-0.0063%
Anthemis Nobilis Flower Oil	12C	Face and neck products not spray	 0.0063-0.5%
Anthemis Nobilis Flower Oil	12D	Body and hand products not spray spray	 0.0063-0.5% 0.006-0.37%
Anthemis Nobilis Flower Oil	12G	Night products not spray	 0.5%
Anthemis Nobilis Flower Oil	12H	Paste masks and mud packs	0.05%
Anthemis Nobilis Flower Oil	12J	Other skin care preparations	0.0063%
Anthemis Nobilis Flower Water	03B	Eye liner	1%
Anthemis Nobilis Flower Water	07C	Foundations	4%
Anthemis Nobilis Flower Water	11A	Aftershave lotions	2%
Anthemis Nobilis Flower Water	11E	Shaving cream (aerosol, brushless and lather)	2%
Anthemis Nobilis Flower Water	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	10%
Anthemis Nobilis Flower Water	12C	Face and neck products not spray	 3%
Anthemis Nobilis Flower Water	12F	Moisturizing products not spray	 1%
Anthemis Nobilis Flower Water	12J	Other skin care preparations	

		rinse-off	3%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

†Product category codes used by FDA

Information collected in 2013

Table prepared: May 2, 2013

Updated May 10, 2013: Chamomilla Recutita (Matricaria) Flower Extract: body and hand products: changed high concentration from 0.5 to 0.02%; skin cleansing: changed 0.001-2% to 0.0002-0.02%; hair conditioners: changed high concentration from 1% to 0.12%; aerosol hair spray: changed 0.00003-10% to 0.00001-0.00003%; hair straighteners: changed 7% to 0.0007%; hair grooming aids: changed 0.00024-10% to 0.00001-0.0075%; feminine hygiene deodorants: changed 0.4% to 0.0004%; shampoo changed 0.00006-1% to 0.00001-0.25%

Updated July 22, 2013: deleted Chamomilla Recutita (Matricaria) Flower: hair grooming aids; Chamomilla Recutita (Matricaria) Flower Extract: hair sprays aerosol changed high concentration from 0.0003% to 0.00003%; shampoos changed high concentration1% to 0.25%; Anthemis Nobilis Flower Extract: other skin care preparations high concentration changed from 1% to 0.05%

Personal Care Products Council
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Memorandum

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

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

DATE: October 4, 2013

SUBJECT: Comments on the Tentative Report on *Anthemis nobilis*-Derived Ingredients

Key Issues

Although it is mentioned in the Discussion, the HRIPT of a skin care lotion containing 3% of the flower extract (provided August 5, 2013) still needs to be added to this report in the Skin Sensitization section.

The Discussion should include information as to why the CIR Expert Panel concluded that the ingredients derived from *Anthemis nobilis* are safe when formulated to be non-sensitizing (rather than a conclusion of safe as used). Although there are sensitization data on a some of the ingredients in the report, plant preparations are known to have variable composition based on growing conditions and extraction methods, so that studies on one preparation may not represent the complete variability that might be found among plant-derived ingredients. In addition, *Anthemis nobilis* is in the Asteraceae family, a family of plants that contains sesquiterpene lactones which are known to be sensitizers. The CIR Expert Panel also thought the "safe when formulated to be non-sensitizing" conclusion would reinforce their concern about products that contain plant-derived ingredients from multiple species.

The first paragraph of the Discussion is not appropriate for a report on plant derived ingredients. The ingredients are grouped together in this report because they are expected to have similar composition because they are derived from the same plant. There is no information included in the report on "structure-property relationships" of the complex mixtures that are reviewed in this report.

Additional Comments

p.1 - The Abstract incorrectly states that "Three ingredients are being used at concentrations up to 10%". Only one ingredient (Anthemis Nobilis Flower Water) has a reported use at 10%.

p.1 - In the abstract, please state that this plant is Roman chamomile.

p.1 - Please see the Dictionary definitions of the chemical classes for a description of methods of manufacture for essential oils and waters. It is not necessary to use "reportedly"; Anthemis Nobilis Flower Oil is prepared by steam distillation.

p.1 - Although Table 4 indicates that some metals are found in *Anthemis nobilis* flowers, none of the metals are listed as being in Anthemis Nobilis Flower Oil. Therefore, the Composition/Impurities section is wrong when it states: "Heavy metals and other components have been reported in anthemis nobilis flower oil..."

p.1 - Although there was a Council cover memo, the composition data on the Anthemis Nobilis Flower Oil came from RIFM. They confirmed that it was this oil that was tested in the irritation and sensitization studies they provided.

p.3 - These ingredients are mixtures. Therefore, it is not possible to study the kinetics of mixtures. It is possible to study the kinetics of components of mixtures. The statement that no data on the absorption, metabolism, and excretion of Roman chamomile ingredients were found in the published literature is misleading, as search terms did not included components of this plant.

p.3, 4 - It is not necessary to include the trade name of the ingredient in the text (Ocular Irritation, Skin Irritation sections).

p.5 - Please include the species of arnica that was studied in reference 26.

p.7 - The abstract of reference 33 indicates that the subjects used tea made from *Anthemis nobilis*.

p.8 - Please correct "othe,"

p.8 - In the Summary, please indicate the FDA product category in which 10% Anthemis Nobilis Flower Water was used.

p.8 - Please indicate the dose/concentration of Anthemis Nobilis Flower Oil used in the phototoxicity study.

p.9 - The Discussion should also note that in addition to the essential oil, composition information on the flower and plant are available.

p.10, Table 2 - If no saponification number is available, the row label should be deleted from Table 2.