Amended Safety Assessment of Achillea Millefolium-Derived Ingredients as Used in Cosmetics

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The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, 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 Lillian C. Becker, Scientific Analyst/Writer.

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Cosmetic Ingredient Review

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MEMORANDOM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: November 15, 2013

Subject: Draft Final Amended Safety Assessment of Achillea Millefolium-Derived Ingredients As Used In Cosmetics

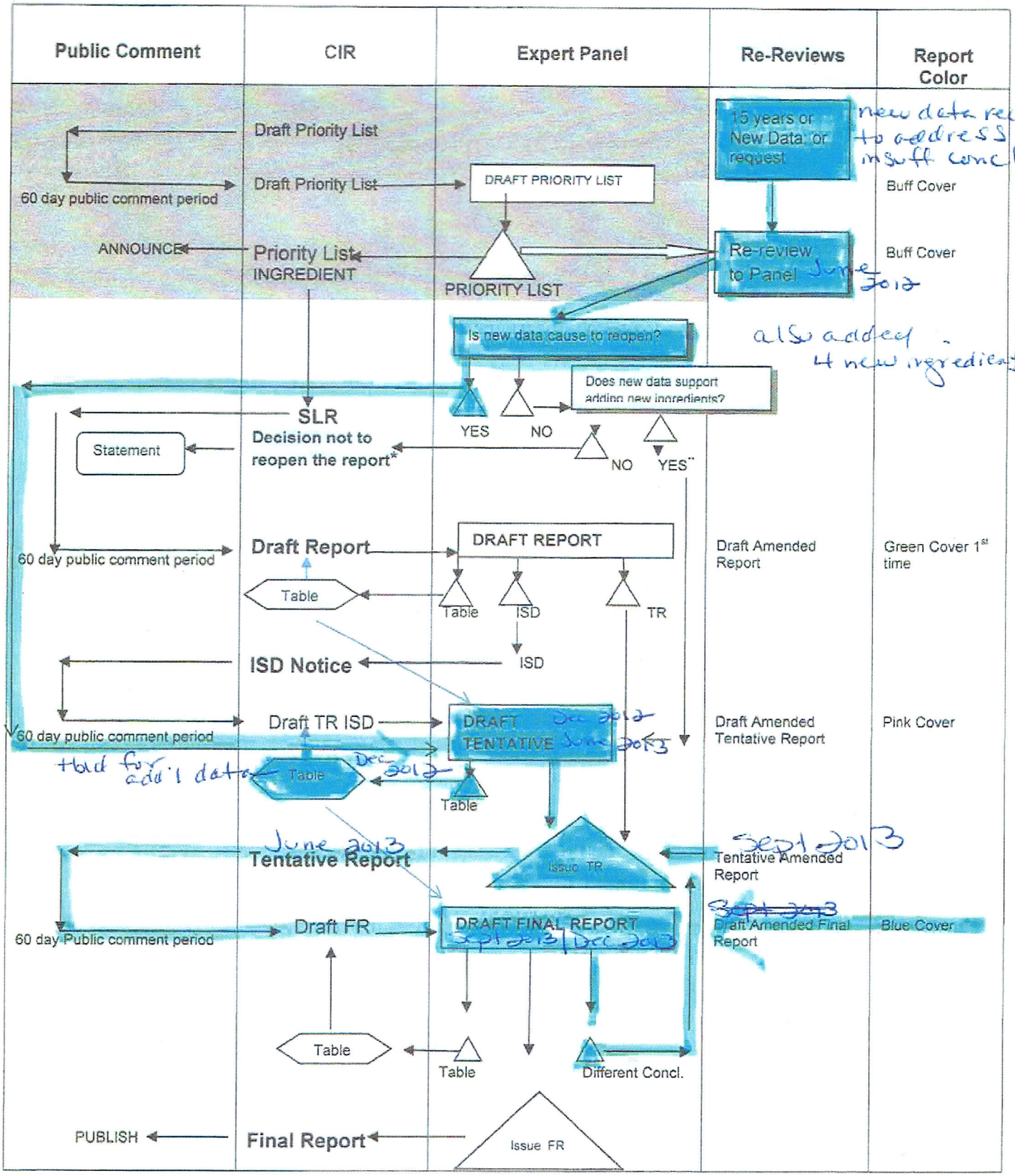
In September, 2013, the Panel changed the conclusion for Achillea millefolium-derived ingredients from safe as used to safe as used when formulated to be non-sensitizing. This change was to address the concern that plants of the Compositae family, of which *A. millefolium* is a member, are known sensitizers. Due to the change in conclusion, the safety assessment was issued for public comment.

Comments from industry have been addressed. No comments from the public have been submitted. There were no new data submitted.

The Panel should review the draft final amended report and ensure that the Abstract, Discussion and Conclusion reflect the Panel's thinking. The Panel is to issue a final amended report.

Achillea Millefolium — Dec 2013

SAFETY ASSESSMENT FLOW CHART



History of *Achillea millefolium* (Yarrow)– Derived Ingredients

2001 - CIR Expert Panel published its review of the safety of Achillea Millefolium concluding that the available data were insufficient to support the safety of this ingredient and identifying a list of 5 data needs.

- UV absorption data; if absorption occurs in the UVA or UVB range, photosensitization data are needed.
- Gross pathology and histopathology in skin and other major organ systems associated with repeated exposures.
- Reproductive/developmental toxicity data.
- Two genotoxicity studies, one using a mammalian system; if positive. a 2-year dermal carcinogenicity assay performed using National Toxicology Program (NTP) methods may be needed.
- Clinical sensitization testing (repeated-insult patch test with ISO subjects) at maximum concentration of use.

June, 2012 – The Panel examined the summaries of new data submitted by industry to address the data needs. The Panel decided to reopen the safety assessment to examine the data possibly change the conclusion.

December, 2012 - The Panel tabled the report after examining the Tentative Amended Report with the new data. The sensitization data were sufficient only up to 0.02%. The Use data show that these ingredients are used up to 0.04%. The Panel gave industry a chance to provide data at this level.

The Panel removed two ingredients from this report (the oil and flower water).

June, 2013 – Data were provided by industry in Wave 2. The Panel examined the data and came to a safe as used conclusion. There was discussion about how to handle LLNAs of mixtures.

September, 2013 – The Panel changed the conclusion to safe as used when formulated to be non-irritating at the suggestion of the Council. This takes into account that not all extracts of *A. millefolium* are the same and sensitizing constituents content may vary.

December, 2013 - The Panel is to review the Abstract, Discussion, and Conclusion to ensure that they reflect the Panel's thinking.

Achillea Millefolium (Yarrow)-derived ingredients Data Profile for December, 2013. Writer - Lillian Becker																		
	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
achillea millefolium extract			x	x			x			x	x		x	x	x	x		
achillea millefolium flower extract															x			x
achillea millefolium flower/leaf/ stem extract																		x

Data needs:

- UV absorption data; if absorption occurs in the UVA or UVB range, photosensitization data are needed.
- Gross pathology and histopathology in skin and other major organ systems associated with repeated exposures.
- Reproductive/developmental toxicity data.
- Two genotoxicity studies, one using a mammalian system; if positive. a 2-year dermal carcinogenicity assay performed using National Toxicology Program (NTP) methods may be needed.
- Clinical sensitization testing (repeated-insult patch test with ISO subjects) at maximum concentration of use.

Achillea Millefolium Transcripts
September, 2013
Dr. Marks' Team

DR. MARKS: Next, Achilea. So, in the June meeting we had a draft final amended safety assessment of achilea millefolium -- yarrow – and derived ingredients, with a "safe as used" conclusion.
Rons, Tom, comments?

DR. SHANK: I think the report's good as is. A minor little editorial thing --

DR. SLAGA: I agree. I think it's fine.

DR. MARKS: Halyna, can you comment on this -- or, Lillian Becker -- can you comment on this third paragraph, where it said, "comments from the CIR Science and Support Committee...suggested...safe when formulated to be non- sensitizing..."?
We had issued a draft final with "safe." We didn't feel it needed to be included "non-sensitizing," when the concentration is safe. You looked at the sensitization and the irritations study at 0.04 percent, and there was no irritation.
Is there a reason why that was added?

DR. BRESLAWEC: Yes, we thought that there are known sensitizers present in this particular botanical, and we felt that the change to "formulated to be non- sensitizing" was a safer way to go.
Carol --

MS. EISENMANN: Well, one of the issues with industry is that each botanical extract can be slightly different. And so they thought that for something like this, where you have a plant that is associated with sensitization, that maybe "safe when formulated to be non- sensitizing" would be a better conclusion, so that, you know, you're saying, industry, beware, this plant is an issue; that some extracts can be made without the sensitizing compounds, but some may have them. That's where they were coming from.

DR. HILL: To me, I thought since it's a request coming from industry that basically places a greater burden on industry, why would we not want to do that?
And I agree with their rationale, by the way.

DR. BERGFELD: We've never done it.

DR. MARKS: Yes, that's --

DR. BERGFELD: And we've done non-irritating, but not non-sensitive.

DR. BRESLAWEC: Oh, no, I think we have. CAPB, right?

DR. HILL: We sure did.

DR. BERGFELD: Did we do it once?

DR. BRESLAWEC: Yes.

DR. BERGFELD: But not very often.

DR. HILL: Not often.

DR. MARKS: So, cocamidopropyl betaine, because of the contaminants in it, we had that "safe when formulated to be non-sensitizing."
No, I liked the rationale. Was that capture in the discussion in this? Because that caught me a little bit by surprise.

And the other question, from a procedural point of view, does this need to go back out in comment? Does this change the conclusion significantly that we perhaps need to issue another tentative amended report, with this change and conclusion?

I think, since the 0.04 percent was safe, and that's the use, that perhaps it's not a drastic change in the conclusion. But I'm open for discussion.

So, Ron, Ron, and Tom? I heard, Ron Hill, you like the more restrictive, "when formulated to be non-sensitizing."

Now, is this going to be something you think is going to set as a precedent in all botanicals? Because we face this -- this is not the first, this may be the beginning of this is going to be the conclusion of all botanicals.

MS. EISENMANN: I don't know about all botanicals, but maybe asteraceae botanicals, for which you know -- I mean, they are known to have sensitizers, which there are others in this group today. But -- just a thought.

DR. SHANK: This ingredient has been tested for sensitization, and we have a level of use that is not sensitizing, enough to make the argument, well maybe if the manufacturer is different, than it could be, then we're in trouble.

DR. MARKS: I agree with you, because then you say, if it's different, how about the other potential ingredients? Would they now rise to a level? I mean, should you put "when formulated to be non- toxic?"

DR. SHANK: No, please.

DR. MARKS: I know -- but that's the extreme.

DR. HILL: But the point is, but the sensitizers act at -- can act at pretty low concentration. We're talking about a botanical here, where -- botanicals always vary in terms of -- unless you propose to make them measure the concentrations of those sensitizers, which we're not proposing, in each of these.

And so, I think -- I mean, they're coming from the industry perspective, and saying this might be a reasonable thing to do in this case, based on the known presence of sensitizers, and the fact that botanical extracts do vary, sometimes widely, in terms of content, based on source, growing season, phase of the moon – who knows what? I'm not even being that facetious when I say "phase of the moon."

So, I mean, I'm assuming the Belsito team will have some thoughts on this one.

DR. MARKS: Well, Don will be making a motion, but we better have our act together, too.

DR. HILL: You just heard what I think about it.

DR. MARKS: Yes, you like it. Ron Shank's a little bit on the other side of it, that we -- "safe." Tom, what do you feel?

DR. SLAGA: I'm with Ron Shank. I think it's safe the way it is. I mean, we definitely have concentrations that we can deal with, and we're below that (inaudible).

DR. MARKS: Then you would have language in the discussion, to be sure that this issue is well raised.

DR. SLAGA: Right.

DR. GILL: I was going to suggest that the language in the discussion captures what we've talked about here, and the conclusion as is.

DR. HILL: I would be okay with that, actually.

DR. MARKS: I like that, also.

DR. SHANK: Language is already in the discussion.

DR. HILL: I think it is.

DR. SHANK: About the sensitizer of these --

DR. MARKS: Is that page 26, 27? Which page are you on?

DR. SHANK: 27.

DR. MARKS: Yeah, okay.

DR. SHANK: The first complete paragraph, "The panel noted that among the constituents..." -- that's all about the sensitizers.

DR. MARKS: Right.

MS. EISENMANN: One thing to know about the "constituent" paragraph, thujone is discussed. And in the analysis of the aqueous extract – they did an analysis, and thujone was one of the materials they actually used. And they did not detect it a level of 300 ppm. I was thinking that that that needs to be changed to "constituents of concern in the plant," which may or may not be in the extract. If you still want to discuss thujone you can, but in the aqueous extract, which is the one that was most, there's the most data on in the report, there was no thujone at a level of 300 ppm -- which isn't a sensitizer issue, but it's in that paragraph.

DR. MARKS: So, Ron Shank, you're -- which paragraph was that again? You said 27 --

DR. HILL: It's the first full paragraph on that page, I think.

DR. SHANK: Top of the page.

DR. MARKS: Under "Discussion?"

DR. SHANK: Yes.

DR. HILL: Yes.

DR. MARKS: Yes, okay.

DR. SHANK: It starts, "The panel noted that among the constituents of these botanical ingredients..."

DR. MARKS: Oh, yes. Okay. Mm-hmm.

MS. EISENMANN: So, it shouldn't be "of these botanical ingredients," "of these plants." Because those are the constituents of the plants. I don't think, if you look back at the analytical work, those were actually in the ingredients. And I know, especially, thujone was not at a level of 300 ppm.

DR. SHANK: Yes, that's a good change.

DR. MARKS: Okay. Any other comments? So, tomorrow I'm going to move as "safe." And we've captured the non-sensitizing concern in the Discussion, and it will be handled there.

DR. HILL: One follow-up comment, though, to what she just said is that I don't think we have -- one of the ingredients that's included here is the achillea millefolium flower/leaf/stem extract. And I don't think we have full data on contents of that. So that's -- that's why I think that we -- but I do agree that something needs to be changed to better reflect the situation.

DR. MARKS: Lillian? Do you have that? Captured that?

MS. BECKER: Yes, I have it. Thanks.

DR. MARKS: Okay. So, presumably, I'll move a "safe," second a "safe" conclusion tomorrow. And, if there's discussion about changing the conclusion to "formulated to be non-sensitizing, I'll present our team feels that's been captured in the discussion. And I won't even get into the issue of whether this needs to be sent out again, whether it's a significantly different conclusion. Okay.

Any other comments? Next are hair dyes.

Dr. Belsito's Team

DR. BELSITO: Okay. Achillea, so in June we got new sensitization data at point oh four percent, seems to satisfy the safety. The highest use concentrations concluded they were safe as used. We discussed the LLNA and expressed concerns about using LLNA for mixtures. Council has made some changes in the conclusion and abstract formulated to be non-sensitizing. And so now we're being asked to look at this document and see is everything intact the way we want it.

I guess first and foremost just as a matter of corrections, I mean the genus should always be capitalized. So Achillea should be capitalized throughout.

I had on page 26 of the pdf document going on to page 27 we mention at the bottom in our summary about constituents of concern. I think we should include pesticides and heavy metals as well as the sensitizers.

Then on page 27 of the pdf on the panel, the incidental inhalation, we have one, two, three, four, five, six, seven, eight, nine lines down, it says, respiratory tract present no toxicological concerns based upon the chemical and biological properties. It should be, "of these ingredients." And I think that was all I had.

Otherwise, I thought it looked good. Paul?

DR. SNYDER: Yes, I just had a few editorial things.

DR. LIEBLER: Minor edits, nothing else to add.

MR. ANSELL: We would like to raise a comment concerning the conclusion that since the material contains non-sensitizers that the formulated to be non-sensitizing phrase be added.

DR. BELSITO: So in present practice of use in concentrations in cosmetics when formulated to be non-irritating?

MR. ANSELL: Non-sensitizing.

DR. BELSITO: Non-sensitizing rather.

DR. SNYDER: If we had HRIPT of the use concentrations that were negative.

MS. LORETZ: That's because it's a botanical and known sensitizers in it so it's -- it would only be that circumstance.

DR. BELSITO: Well, I guess looking at what you have the highest thing that would bother me so far is linalool at 4,000 parts per million. So that's what, point oh four percent of a plant? And then the concentration of use is I thought very low.

MS. BECKER: Zero point zero four percent.

DR. BELSITO: Zero point zero four?

MS. BECKER: Percent is the highest --

DR. BELSITO: Highest concentration and the concentration of linalool is point --

MS. BECKER: In the plant before processing at max 4,000 ppm.

DR. BELSITO: Right. So 4,000 ppm is point oh four percent, correct? One, two, three, four, five, six, point four percent. So point four percent and the highest concentration of use is?

MS. BECKER: Zero point zero four.

DR. BELSITO: Point oh four percent. So you got point zero zero one six. Pretty low percentage of a sensitizer to be concerned about plus as Paul said we have HRIPT data.

MR. ANSELL: I guess the consensus was that the inclusion of the phrase would highlight or underline the presence of the material and make sure manufacturers were aware.

DR. BELSITO: Well, I mean I'm more concerned that we get the boilerplate in there, that it not be combined with other things that contain linalool that then create a concentration of linalool in the finished product that are issues which, you know, is my concern. So my concern isn't with this as used if it's the only linalool containing ingredient in the finished product I'm not concerned. I mean, if you want to say and that's going to be an issue for all the botanicals is when you're adding botanicals that you could get to levels of an ingredient that could then sensitize.

If you want to put when formulated to be non- sensitizing, I'm very happy to do that. And then that would reinforce the boilerplate that we'll be raising when we see other botanicals that have sensitizers which is going to be pretty much true for all the botanicals we look at.

DR. LIEBLER: I mean if you do it for this one, why not do it for all botanicals? Because they'll all essentially have sensitizers in them.

DR. SNYDER: And we addressed it pretty good in the summary. I mean we say that we acknowledge they're in there. So we say that there are levels below.

DR. BELSITO: Right and then we need to discuss the boilerplate about stacking them on top of each other. I mean, I'm fine putting it --

MS. EISENMANN: I thought it might be useful for all the botanicals that are asteraceae family because they have a known issue of being sensitizers themselves.

DR. BELSITO: Right.

MS. EISENMANN: Not necessarily other plants but that one family.

DR. BELSITO: Right.

MS. EISENMANN: It doesn't include what these other that you reviewed, too.

DR. BELSITO: Right. I'm fine with putting that in.

DR. LIEBLER: Okay, but that's a different kettle of fish because the way it was pitched to us just now is that they have sensitizers in them. Well, so do all the botanicals. So.

MS. EISENMANN: But I mean that family in particular has issues.

DR. LIEBLER: Right, that makes more sense to me.

DR. BELSITO: And I'm fine since we're going to be creating a boilerplate. I think whenever we have a boilerplate that we'll say you need to use caution when combining this with other botanicals that might contain linalool or cinnamal or whatever the ingredient sensitizer of concern is. That we then put in the conclusion when formulated to be non-sensitizing, I'm very happy with that. I think it really reinforces what do they mean not sensitizing and when they read the discussion they'll clearly see, you know, particularly the ingredients we're

concerned about. I'm fine. Dan? Paul?

DR. LIEBLER: If we do that we just need to add a sentence to the discussion.

DR. BELSITO: Yes, for the others.

DR. LIEBLER: To explain that we were -- that that family --

DR. BELSITO: Well, there will be a sentence in this discussion because we're going to have the botanical boilerplate coming up in a few more so that's something that needs to be added to the discussion.

DR. LIEBLER: But do we have any language in here, Carol, that already refers to the family that you're referring to? Or is this going to hit people kind of out of left field if we mention it in the discussion?

DR. SNYDER: I think we can add that right at that last sentence here.

MS. EISENMANN: I think it was a description of the plant in the beginning I think that puts it in that family with the historical name of the compositae.

DR. LIEBLER: I'm not seeing it.

DR. BELSITO: Summary of the original.

DR. LIEBLER: It's only mentioned in passing in provocative testing. This is on pdf page 22 under the summary, the original safety assessment second paragraph. In provocative testing a number of patients reacted to a compositae mix that contained yarrow. Is that what you're referring to compositae?

MS. EISENMANN: It's also earlier I think there's a little description of the plant right here in the front. It's like in the chemistry section.

DR. BELSITO: I'm looking. I don't see it.

DR. LIEBLER: I don't see it.

MS. BECKER: It might be in the original safety assessment not this one.

DR. BELSITO: No, I don't see it, Carol.

MS. EISENMANN: Okay. It must have been in one of the other plant reports.

MS. BECKER: I think it is in the original.

DR. LIEBLER: So if you -- so the suggestion to add the non-sensitizing now makes more sense in light of what you just said as opposed to the logic of well, these contain sensitizers because almost all botanicals do. So but we need to have enough of a description so that we can mention it first in the chemistry section and then mention it in the discussion that botanicals of that family have been associated with sensitization and provide a reference.

So then do we say even though we have an HRIPT at highest use that was negative we still raise the concern?

DR. BELSITO: Yes, because the formulation needs to ensure that this product when combined with potentially other botanicals or other sources of linalool or whatever happens to be the allergen of concern will be non-sensitizing.

MR. ANSELL: Right, it can be used safely.

DR. LIEBLER: Okay.

MS. EISENMANN: Well and then also the variability within one.

DR. BELSITO: I understand, right.

MS. EISENMANN: And the extracts, too.

DR. BELSITO: So we need to put somewhere I don't know that we need to introduce, we can just put it in the discussion that, you know, the panel is aware that as a member of the compositae family this contains sesquiterpene lactones that have been shown to be sensitizing. You know, at the levels of reported use of Achillea millefolium this should not be an issue, however, when blended with other botanicals, you know, whatever the boiler plate we decide and then that would be the way we'd introduce it.

DR. SNYDER: I think we have the place to do it right here already in the discussion because we talk about the idea that the cosmetic formulation can contain multiple botanicals.

DR. BELSITO: Right.

DR. SNYDER: I think we need to and this is what I was thinking about in the (inaudible). I mean we can make it specific to this, whatever family the constituents in and this case is a good example because here we can say, we should identify the constituent concerns. We identify them in the report and then the use of other botanical ingredients to make it plain these constituents or concern in combination with milleform could result.

DR. BELSITO: Well, we have it in the next paragraph. The panel noted that among the constituents are these botanical ingredients, were linalool, thujone, quercetin and hydroquinone.

MS. EISENMANN: One comment. Instead of ingredients it's components of the plant.

DR. BELSITO: Components, right.

MS. EISENMANN: Because there was some analytical data that showed thujone was not present in at least one of the ingredients at a level of 300 ppm.

DR. BELSITO: Right.

MS. EISENMANN: So the components there are what's in the plant rather than ingredients. We don't know for sure. I mean they may or may not be in the ingredients.

DR. BELSITO: Right, I understand but I mean my thinking was this whole section starting on 26 of the pdf with the cosmetic formulation may contain multiple botanicals, through the first full paragraph on page 27 is going to need to be readjusted depending upon how we agree on the boilerplate. So I wouldn't waste time with this. At this point we've agreed when formulated to be non- sensitizing and then the conclusion we'll worry about wordsmithing the discussion once we get to the botanical boilerplate. Does that make sense?

Okay, should we take like a five minute break?

DAY TWO

DR. BERGFELD: Moving onto the next ingredient then, achillea. Dr. Belsito?

DR. BELSITO: Yeah. The June meeting, we had some new sensitization data, .04 percent, which allowed us to evaluate the safety of these ingredients at their highest use concentration. And we agreed that they were "safe as used." We also discussed the LLNA on a mixture and felt that that was somewhat of a problematic way of assessing sensitization of mixtures.

We then raised the issue of having multiple botanicals in a single product that may contain things like sensitizers, that the total impact might cause problems in a final formulation, heavy metals, et cetera, things like that. And we looked at some boilerplates, which I guess we'll get to later.

Having said all that, we felt that the conclusion that we reached was "safe in the present practice of use, and concentration, and cosmetics." The Council raised the issue of addending a bit by saying when formulated to be non-sensitizing, and our team actually thought that was a good idea because it will reflect back to the discussion regarding potential allergens, sensitizing allergens, in that botanical product that could be stacked upon other botanicals to create an issue.

So a little bit of a change in the conclusion, "safe when formulated to be non-sensitizing." I'm not a legal expert, so I don't know if this has to go out for another 60-day final or whether we are done with it.

DR. BERGFELD: Well, let us make a ruling on the safety, and then we'll discuss that.

DR. BELSITO: Okay. "Safe when formulated to be non-sensitizing."

DR. BERGFELD: Is there a second?

DR. MARKS: Second.

DR. BERGFELD: All right. I'm going to call for the vote then. All those in favor of "safe?" Okay, unanimous. Can we get an opinion on whether it has to go out again for comment? Halyna maybe or Lillian?

DR. GILL: I think we've changed that conclusion. It went out originally as a safe conclusion, and with the change of "conclusion," I think we will have to re-issue that for comment.

DR. BERGFELD: So this will go out again with the change of "conclusion." I think that's reasonable.

DR. BELSITO: Uh-huh.

DR. BERGFELD: I'd like to point out, too, that we had this discussion yesterday that this is only the second time that we have put the restriction into the conclusion of "non-sensitizing." Before it's been "non-irritating," but this is "non-sensitizing," a little bit different to make everybody aware of that.

DR. MARKS: Yeah, and our team really wanted to have that elucidated, as you've explained, Don, in the discussion, because it is unusual to say. The idea of combining botanicals and the level of an ingredient might then rise to the threshold of being sensitizing, I think, is important to explain in the discussion.

DR. HILL: I also liked it because it picked up the possibility of variations in source materials that some -- potentially could occur in this case.

DR. BERGFELD: Any other comment regarding this? None? All right. We've ruled on that as "safe," and we're going to send it out again for a second look at the conclusion.

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ABSTRACT

Cosmetic ingredients derived from *Achillea millefolium* function in cosmetics as skin-conditioning agents – miscellaneous, skin-conditioning agents – humectants; and fragrance ingredients. The CIR Expert Panel reviewed relevant animal and human data to determine their safety in cosmetics. Because formulations may contain more than one botanical ingredient, caution was urged to avoid reaching levels of toxicity for constituents. Industry should use good manufacturing practices to limit impurities. The Panel concluded that achillea millefolium extract, achillea millefolium flower extract, and achillea millefolium flower/leaf/stem extract are safe in the present practices of use and concentration in cosmetics when formulated to be non-sensitizing.

INTRODUCTION

This is an amended safety assessment of *Achillea millefolium* (yarrow)-derived ingredients. These ingredients function in cosmetics as skin-conditioning agents – miscellaneous, skin-conditioning agents – humectants; and fragrance ingredients (Table 1).[1] The three ingredients in this safety assessment are:

- achillea millefolium extract
- achillea millefolium flower/leaf/stem extract
- achillea millefolium flower extract

In 2001, the Cosmetic Ingredient Review (CIR) published a safety assessment of achillea millefolium extract as used in cosmetics.[2] The CIR Expert Panel (Panel) concluded that there were insufficient data to determine the safety of this ingredient. The data needs were:

- UV absorption data; if absorption occurs in the UVA or UVB range, photosensitization data.
- Gross pathology and histopathology of skin and other major organ systems in a repeated exposure study.
- Reproductive/developmental toxicity data.
- Two genotoxicity studies, one using a mammalian system; if positive, a 2-year dermal carcinogenesis bioassay performed using National Toxicology Program (NTP) methods may be needed.
- Clinical sensitization testing (repeated-insult patch test with 150 subjects) at maximum concentration of use.

Data have been submitted to meet these needs and are summarized below along with new data discovered in the literature.

Summary of Original Safety Assessment

Yarrow (*Achillea millefolium*) is an extract of the yarrow, *A. millefolium*, and functions as a biological additive in cosmetic products.[2] Sesquiterpene lactones, polyacetylenes, and flavonoids have been identified as components of *A. millefolium*, and chamazulene can exist in the essential oil. In 1998, it was reported to the FDA that yarrow (*Achillea millefolium*) extract was used in 65 cosmetic formulations. In 1984, yarrow extract was reported to be used at concentrations of ≤ 25%. Submissions from suppliers indicate that yarrow (*Achillea millefolium*) extract (actual yarrow extract content of 2% to 25%) is used at concentrations of 0.5% to 10%.

The oral and subcutaneous LD_{50} of yarrow (*Achillea millefolium*) extract were both 1 g/kg for the mouse. Guinea pigs were sensitized to crude extracts (using peroxide-free diethyl ether) of the whole plant and the flowers of *A. millefolium*. *A. millefolium* tea was weakly genotoxic in a somatic mutation and recombination test using *Drosophila melanogaster*. In clinical testing, product formulations containing 0.1% to 0.5% yarrow (*Achillea millefolium*) extract (2% extract) were generally not irritating. In provocative testing, a number of patients reacted to a Compositae mix that contained yarrow, as well as to yarrow itself. Also in clinical testing, a formulation containing 0.1% yarrow (*Achillea millefolium*) extract (2% yarrow in propylene glycol and water) was not a sensitizer and alcoholic extracts of dried leaves and stalks of *A. millefolium* did not produce a sensitization response.

CHEMISTRY

Definition

The definitions and functions of *A. millefolium* – derived cosmetic ingredients are listed in Table 1.

A. millefolium is an herbaceous plant with characteristic narrow, oblong, multiple pinnate leaves.[3] The flower heads are small, made up of five white or pink florets with a few yellow tubular florets. The plant grows to ~ 70 cm tall.

A. millefolium is a member of the Asteraceae (formerly Compositae) family, which is known to be sensitizing.[4]

Physical and Chemical Properties

UV absorbance of a 1% aqueous water achillea millefolium extract peaked at ~ 260 nm with small shoulders at 270 nm and ~320 nm.[5]

Constituents

The constituents of *A. millefolium* are listed in Table 2.

A sample of an achillea millefolium extract (aqueous) mixture (water 73.5%, butylene glycol 20%, pentylene glycol 5%, achillea millefolium extract 1%, xanthan gum 0.5%) contained 3.37% polyphenols, 61.25% proteins, and 38.12% sugars.[5] An assay for nitrogen compounds of the same sample showed the possible presence of pipecolic acid, L-alanine, and phenylalanine but not betaine, betonicine, betaine HCl, trigonelline, and stachydrine HCl. An analysis for phenolic compounds detected luteolin (a few ppm) and apigenin, but not gallic acid, chlorogenic acid, caffeic acid, coumaric acid, kaempferol, and quercetin. Another assay for terpenes and steroids, including thujone, guaizulene, ursolic acid, and β-sitosterol, was negative. Coumarin was not detected.

β-sitosterol, 3β-hydroxy-11α,13-dihydro-costunolide, desacetylmatricarin, leucodin, achillin, 8α-angeloxy-leucodin, and 8α-angeloxy-achillin were isolated from the flower heads of *A. millefolium* plants.[6]

The essential oil content of *A. millefolium* was lower in the vegetative stage (0.13%) than the full bloom stage (0.34%).[7] Changes in the content of essential oil was found to be related to the maturation of the plant, with increasing amounts of monoterpenes in relation to the sesquiterpene as the plant matures. However, a clear trend could be detected only for the monoterpenic compounds with increasing levels of α- and β-pinene and α-thujone and decreasing levels of sabinene, borneol, and bornyl acetate. Previously reported as major compounds, chamazulene and gernacrene D, could be found only in trace amounts. The terpenic compounds (sesquiterpenic compounds such as β-bisabolene, α-bisabolol, and δ-cadinene) were detected in greater amounts when using solid-phase microextraction when compared to amounts found in steam-distilled samples.

GC-MS analysis of the essential oil of *A. millefolium* identified 36 compounds constituting 90.8% of the total oil. Eucalyptol, camphor, α-terpineol, β-pinene, and borneol comprised 60.7% of the oil.[8]

A comparison of the aerial parts of *A. millefolium* plants that grew in the Indian Andes at altitudes of 1600 m and 2850 m was conducted.[9] Of the constituents tested, these sets of plants had considerable overlap in the content ranges of the major constituents; for example: β-pinene (10.6% - 17.7%), 1,8-cineole (3.0% - 15.1%), borneol (0.2% - 12.1%).

Constituents of Concern

A. millefolium is reported to contain linalool (1 – 4000 ppm), thujone, quercetin, α-peroxyachifolid, and hydroquinone.[10] The potential adverse effects of exposures to these constituents are summarized in Table 3.

Method of Manufacture

Achillea millefolium extract is processed from the stem, leaves, and other aerial parts of the plant.[5] Under controlled temperature, time, pressure and pH conditions (not provided), the plant parts are milled before an aqueous extraction. The extract is filtered then combined with butylene glycol (preservative) and xanthan gum. Other solvents (e.g., alcohols, propylene, butylene glycol), or series of solvents and additives (preservatives), have also been reported.[2]

USE

Data on ingredient usage were provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 4).[11] A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for these ingredients.[12]

The VCRP had an entry for “achillea millefolium”. It was assumed that this entry was actually “achillea millefolium extract” and data from that entry was combined with the extract data.[11]

Achillea millefolium extract was reported to be used in 135 cosmetic products; these include 83 leave-on products and 47 rinse-off products. Leave-on products were reported to be used up to 0.04% and rinse-off products were reported to be used up to 0.03%. The extract is reported to be used in eye makeup products up to 0.03%, hair preparations up to 0.03%, lipstick up to 0.00001%, and skin care products up to 0.03%.

There was no use information reported for achillea millefolium flower extract or achillea millefolium flower/leaf/stem extract.

Achillea millefolium extract was reported to be used in perfumes and face powders, and could possibly be inhaled. This ingredient was reportedly used in face powders at concentrations up to 0.00005% and in perfumes up to 0.0001%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[13-16] 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.[17,18]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

No new toxicokinetics data were identified or made available for review. However, since botanical extracts are mixtures, toxicokinetic data would only have meaning for individual constituents of the extract, not for the extract as a whole.

Cytotoxicity

ACHILLEA MILLEFOLIUM EXTRACT

A product containing an aqueous extract of *A. millefolium* (5.0 µL/mL) was not cytotoxic to L5178Y cells after 3 h of incubation.[19]

TOXICOLOGICAL STUDIES

Acute Toxicity

Oral – Non-Human

ACHILLEA MILLEFOLIUM EXTRACT

The oral LD_{50} of the mixture containing an aqueous extract of *A. millefolium* was reported to be > 2000 mg/kg in female rats.[20]

There were no mortalities when an aqueous *A. millefolium* extract (10 g/kg; leaves, stalks, stems) was orally administered to male and female Wistar rats.[21]

Intraperitoneal

ACHILLEA MILLEFOLIUM EXTRACT

There were no mortalities when an aqueous *A. millefolium* extract (3 g/kg; leaves, stalks, stems) was intraperitoneally (i.p.) administered to male and female Wistar rats.[21]

Repeated Dose Toxicity

Oral – Non-Human

ACHILLEA MILLEFOLIUM EXTRACT

An aqueous *A. millefolium* extract (0.3, 0.6, 1.2 g/kg/d; leaves, stalks, stems) orally administered to male and female Wistar rats (n = 10/sex) for 28 or 90 consecutive days produced no signs of toxicity.[21] The rats were observed for clinical signs and necropsied at the end of the treatment period or after a 30-day recovery period. All rats survived until the end of both treatment periods. Rats in both treatment time groups had mobility, reflex responses, muscular tone and breathing patterns similar to rats in the control group treated with water. Weight gain was similar in all groups. There were no changes in organ weight observed with the exception of a decrease in liver weights in females in the long-term/low-dose group, in males in the long-term/mid-dose group, and in both sexes in the mid-dose/long-term group and the high-dose/short- and long-term groups. Histopathological examination was unremarkable. The authors concluded that the rats exhibited no treatment-related toxicological or histopathological abnormalities.

An ethanol (60%) multi-herb mixture (20 mg/kg/d) that included achillea millefolium extract (3.5%; 0.7 mg/kg), orally administered to CBA/HZb mice (n = 6) for up to 6 months, caused no clinical signs.[22] Body weights were similar to controls. No differences were observed in the spleen, kidney, testicles, or liver weights when compared to controls. There was an increase in the serum activity of aspartate aminotransferase (AST) on day 7 compared to the levels at 24 h of treatment. Comparison of the serum activity of AST between the control and experimental group of rats on day 7 revealed an increase in the experimental group. The serum activity of alanine aminotransferase (ALT) and the concentration of cholesterol showed no changes during the treatment period. The authors concluded that the test mixture was not toxic to the liver, kidney, spleen, pancreas, testes and lungs. This mixture also contained *Vaccinium myrtillus, Taraxacum officinale, Cichorium intybus, Juniperus communis, Centaurium umbellatum, Phaseolus vulgaris, Morus nigra, Valeriana officinalis,* and *Urtica dioica.*

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

ACHILLEA MILLEFOLIUM EXTRACT

An ethanol (45%) *A. millefolium* extract (2.8 g/kg/d; 56 times the equivalent of a human dose of 50 mg/kg/d) was not maternotoxic when orally administered to Sprague-Dawley rats (n = 5) but caused decreased body weights in fetuses.[23] The dams were orally administered the test material during gestational days (GD) 1 – 8 or 8 – 15. The dams were killed on gestational day 20 and necropsied. There was no increase in pre- or post-implantation losses. Placental weights were increased in dams treated with achillea millefolium extract on GD 8–15 compared to the water and ethanol controls and on GD 1–8 compared to water control fetuses. Body weights were reduced in fetuses exposed to achillea millefolium extract on GD 8–15 compared to the water controls. There was no difference in the incidences of external or internal malformations.

An aqueous *A. millefolium* leaf extract (0.3, 0.6, 1.2 g/kg/d) orally administered to male Wistar rats (n = 10) for 90 days was not toxic nor caused any clinical or behavioral signs, but there was an increase in abnormal sperm in the males in the high-dose group.[24] The rats were killed and necropsied after 90 days, focusing on the testes, epididymis, prostate, and seminal vesicles (including coagulating glands). Daily sperm production and number of sperm were not affected. Body weight gain was similar in all groups.

An aqueous *A. millefolium* extract (1.0, 5.0, and 10.0 mL/100 mL feed) fed to Oregon-R strain of fruit flies (*Drosophila melanogaster*) resulted in F1 offspring with a dose-dependent increase in the number of malformations.[25] There

were no changes in the number of offspring.

ACHILLEA MILLEFOLIUM FLOWER EXTRACT

An ethanolic *A. millefolium* flower extract (200 mg/kg/d) i.p. administered to male Swiss albino mice (n = 6) for 20 days and an hydroalcoholic extract (300 mg/kg/d) orally administered for 30 days caused exfoliation of immature germ cells, germ cell necrosis, and seminiferous tubule vacuolization.[26] Mice in the treatment groups had an increased number of metaphases in the germ epithelium that might be due to cytotoxic substances or substances stimulating cell proliferation. Neither extract caused any differences in body weight gain or in testis and seminal vesicle weight.

An ethanolic *A. millefolium* flower extract (200, 400, 800 mg/kg) i.p. or orally administered to male albino Wistar rats (n = 5) every other day for 22 days caused no changes in the low-dose i.p. group and the low- and mid-dose oral groups; however, there were abnormalities in the development of sperm in the mid- and high-dose groups.[27] There were scattered immature cells on basal membrane in seminiferous tubules in the i.p. mid-dose group. A decrease in cell accumulation and vacuolization in seminiferous tubules was observed. In the i.p. high-dose group, thickened seminiferous tubules on basal membrane, decreased cell accumulation in seminiferous tubule, severe disarrangement, degenerative cells, and severe decrease in sperm count were also observed. At the oral high-dose, basal membranes were thickened and disarrangement in cells was observed. After a 40-day recovery period, normal physiology was observed in the low- and mid-dose groups compared with controls: however, there continued to be abnormal and damaged cells in the high-dose groups.

GENOTOXICITY

In Vitro

ACHILLEA MILLEFOLIUM EXTRACT

In an Ames test using *Salmonella typhimurium* (TA98, TA100, TA102, TA1535, TA1537), the mixture containing an aqueous extract of *A. millefolium* (0.06 – 5 µL) was not mutagenic with or without metabolic activation.[28]

In two micronucleus tests using V79 cells, the mixture containing an aqueous extract of *A. millefolium* (up to 15,000 µg/mL) was not clastogenic or aneugenic with or without metabolic activation.[29]

In a gene mutation assay using mouse lymphoma L5178Y $TK^{+/-}$, a product (up to 5 µL/ml) that contained an aqueous extract of *A. millefolium* (0.5%) was not mutagenic with or without metabolic activation.[19] The controls had the expected results.

IRRITATION AND SENSITIZATION

Irritation

Ocular

ACHILLEA MILLEFOLIUM EXTRACT

In an Epiocular Human Cell Construct assay, a product containing a mixture of an extract of *A. millefolium* (0.00045%) was found to not have irritation potential.[30]

Sensitization

Dermal – Non-Human

ACHILLEA MILLEFOLIUM EXTRACT

In a local lymph node assay using mice, a mixture containing an aqueous extract of *A. millefolium* (25%, 50%, and 100% in dimethylformamide) was not a sensitizer.[31] Because this assay was performed on a mixture where the substance of interest was less than 80% of the mixture, the results do not permit a quantitative evaluation of the sensitization potential of achillea millefolium extract.[32]

Dermal – Human

ACHILLEA MILLEFOLIUM EXTRACT

In a patch test of subjects with atopic dermatitis (n = 9), there were no positive reactions to *A. millefolium* extract (1% in petrolatum).[33] Finn chambers were used and the test sites were observed on days 2 and 3.

In a human repeated insult patch test (HRIPT; n = 107), a face moisturizer with self-tanner product containing an extract of *A. millefolium* (0.00045%; 0.2 mL) applied neat was not irritating or sensitizing.[34] The test material was applied to a 2 cm^2 occlusive patch. There were transient, barely perceptible to mild nonspecific and specific responses, occasionally accompanied by mild/moderate edema or mild dryness in nine test subjects. Five subjects had mild hyperpigmentation without erythema during the induction phase.

In an HRIPT (n = 108), a body splash product containing an extract of *A. millefolium* (0.001133%) applied neat was not irritating or sensitizing.[35] The test material was applied to an occlusive patch and allowed to dry for 20 min before administration to the scapula area. There were no adverse events reported.

In an HRIPT (n = 53) of a body lotion containing achillea millefolium extract (0.04%), it was concluded that the body lotion was neither irritating nor sensitizing.[36]

CLINICAL USE

Case Studies

A 44-year-old woman with a history of rhinoconjunctivitis and asthma developed rhinitis, asthma, and urticaria symptoms after working seasonally with dried flowers for 6 years.[37] The skin prick test was positive for pollen from *Cupressus semipervirens, Olea europaea, Lolium perenne, Salsola kali, Ariemisia vulgaris,* and *Parietaria judaica* as well as to cat and dog epithelium. Skin prick tests of aqueous extracts of the dried flowers were positive for *A. millefolium* and safflower. An asthmatic response resulted from a specific inhalation bronchial challenge.

SUMMARY

This is an amended safety assessment of *Achillea millefolium* (yarrow)-derived ingredients. New data were submitted to address the needs of the insufficient data conclusion enumerated in the previous safety assessment and are presented here. These ingredients function in cosmetics as skin-conditioning agents – miscellaneous, skin-conditioning agents – humectants; and fragrance ingredients.

UV absorbance peaked at ~ 260 nm with small shoulders at 270 and 320 nm using a 1% aqueous water extract.

A. millefolium extract was reported to be used in 134 cosmetic products, 84 leave-on products and 48 rinse-off products with use concentrations up to 0.04% in body and hand skin care products. There was no use information reported for: achillea millefolium flower extract, and achillea millefolium flower/leaf/stem extract.

A. millefolium extract was not cytotoxic to L5178Y cells.

The oral LD_{50} for achillea millefolium extract is > 2000 mg/kg for rats; no mortalities were reported at 10 g/kg. There were no mortalities to rats administered i.p. 3 g/kg achillea millefolium extract.

An aqueous *A. millefolium* extract was well tolerated by rats at up to 1.2 g/kg/d for up to 90 days. An ethanol extract of an herbal mixture that included *A. millefolium* at 3.5% was not toxic to mice when administered orally for up to 6 months. There were no effects to the major organs.

Oral administration of an ethanol *A. millefolium* extract was not maternotoxic at 2.8 g/kg/d when administered on GD 1 - 8 but did cause reduced body weight in the fetuses when administered on GD 8 - 15. There was no increase in external or internal malformations.

Oral administration of an aqueous *A. millefolium* leaf extract caused an increase in abnormal sperm at 1.2 g/kg/d in rats. Daily sperm production and number of sperm were not affected. Aqueous *A. millefolium* extract caused an increase in the number of malformations in *D. melanogaster* offspring.

A. millefolium flower extract administered i.p. caused damage to the reproductive organs of male mice at 300 mg/kg/d. An ethanolic *A. millefolium* flower extract i.p. or orally administered to male rats every other day for 22 days caused no changes at 200 mg/kg i.p. and the 200 and 400 mg/kg oral groups. There were abnormalities in the development of sperm in the 400 and 800 mg/kg i.p. groups. After a 40-day recovery period, there continued to be abnormal and damaged cells in the 800 mg/kg groups.

A. millefolium extract was not genotoxic in an Ames test, two micronucleus tests, and a gene mutation assay.

A. millefolium extract was not irritating to subjects with atopic dermatitis at 1%.

An Epiocular Human Cell Construct assay of a product that contained an extract of *A. millefolium* at 0.00045% was negative for ocular irritation.

An aqueous *A. millefolium* extract was not a sensitizer in a local lymph node assay at 1%.

Two products containing achillea millefolium extract up to 0.001133% were not sensitizing in HRIPTs. A product containing achillea millefolium extract at 0.04% was neither irritating nor sensitizing.

A woman was reported to develop an allergic reaction to *A. millefolium* after working with dried flowers.

DISCUSSION

Achillea millefolium extract is reported to be used up to 0.04% in body and hand creams, lotions and powders and in eye lotion. An LLNA was performed on an aqueous *A. millefolium* extract at 1%, and an HRIPT was performed at 0.04%. The Panel, however, considered that LLNA testing of mixtures containing a small fraction of any constituent of concern may not readily predict sensitization. HRIPT data were available at use concentrations demonstrating an absence of dermal irritation and sensitization.

The Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

A cosmetic formulation may contain multiple botanical ingredients, each of which can contribute to the total concentration of constituents of concern in the botanical ingredients. The use of other botanical ingredients that may contain constituents of concern in combination with *A. millefolium* ingredients in a single formulation could result in exposures that exceed levels of concern. For example, other constituents that may be of concern include potential sensitizers. Thus, cosmetic products containing multiple botanical ingredients should be formulated to ensure that total exposures to such constituents remain below levels of toxicological concern when used as intended.

The Panel noted that plants in the Asteraceae (formerly Compositae) family, such as *A. millefolium,* are associated

with dermal sensitization. Among the constituents of *A. millefolium* plants are linalool (1 – 4000 ppm), thujone, quercetin, α-peroxyachifolid, and hydroquinone. Linalool and α-peroxyachifolid are dermal sensitizers. Thujone has been reported to cause neurological toxic effects; the suggested acceptable daily intake was not more than 3 - 7 mg/kg/d. Quercetin has been reported to have some genotoxic effects in in vitro assays. Hydroquinone has been reported to cause skin depigmentation. These constituents are present in the plant. Data were presented shows that thujone and other constituents were not present in an extract. The levels of constituents of concern in the cosmetic ingredients derived from plants can vary widely, and may even be undetectable in the ingredients, depending on the growing conditions of the plant, the methods of manufacturing of the ingredient, and other factors. The maximum concentration of use of *A. millefolium*-derived extracts in cosmetics was reported to be 0.04%. This indicates that exposures to these constituents in cosmetics containing *A. millefolium* would be below levels of concern for these known effects.

However, manufacturers should employ good manufacturing practices to ensure that constituents of concern are below levels of toxicological concern, including sensitization. It is important for formulators to be aware that even though the assays in this report revealed no sensitizers, these ingredients may still contain sensitizers, such as sesquiterpene lactones. Products that contain such sensitizers need to be formulated at non-sensitizing levels.

The Panel discussed the issue of incidental inhalation exposure from perfumes and face powders. There were no inhalation toxicity data available. However, the Panel believes that the sizes of a substantial majority of the particles of the products containing these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. However, these ingredients are reportedly used at concentrations up to 0.0001% in cosmetic products that may be aerosolized and up to 0.00005% in other products that may become airborne. The Panel noted that 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the very low 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.

The Panel considered other data available to characterize the potential for *A. millefolium*-derived ingredients to cause irritation, sensitization, reproductive and developmental toxicity, and genotoxicity. They noted the lack of systemic toxicity at high doses in acute and subchronic oral exposure studies, no irritation or sensitization in tests of dermal and ocular exposure, as well as the absence of genotoxicity in an Ames test, two micronucleus tests, and a gene mutation assay. While *A. millefolium*-derived ingredients caused an increase in abnormal sperm and damage to male organs in rats, these effects were observed at levels much greater than any from exposure to cosmetics.

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 achillea millefolium extract, achillea millefolium flower extract*, and achillea millefolium flower/leaf/stem extract* are safe in the present practices of use and concentration in cosmetics when formulated to be non-sensitizing.

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

TABLES

Table 1. CAS Nos., definitions, and functions of *A. millefolium* – derived ingredients.[1]

Ingredient	Definition	Function
Achillea millefolium extract 84082-83-7	The extract of the whole yarrow plant, *A. millefolium*	Fragrance ingredient, skin-conditioning agent – miscellaneous
Achillea millefolium flower extract	The extract of the flowers of the yarrow plant, *A. millefolium*	Antioxidants, skin-conditioning agent – humectant
Achillea millefolium flower/leaf/stem extract	The extract of the flowers, leaves, and stems of the yarrow plant, *A. millefolium*	Skin-conditioning agent – miscellaneous

Table 2. Constituents of *Achillea millefolium*.[10]

Chemical	Part	Range (ppm)
Essential oil	Flower	700 – 5000
Thiophenes	Flower	167
(*E*)-nerolidol	Leaf	
1,8-cineole	Leaf	24 -1680
8-acetylagelolide	Leaf	
Allo-ocimene	Leaf	4 - 140
α-bisabolol	Leaf	1 - 915
α -cadinol	Leaf	1 -15
α -copaene	Leaf	
α -curcumene	Leaf	
α a-humulene	Leaf	
α -muurolene	Leaf	
α -phellandrene	Leaf	
α -pinene	Leaf	1 – 1000
α -terpinene	Leaf	2 -1120
α -terpineol	Leaf	1 – 80
α -thujene	Leaf	
α -thujone	Leaf	3 - 240
Artemisia-alcohol	Leaf	1 – 80
Artemisia-ketone	Leaf	
Artemisiatriene	Leaf	1 – 65
Ascaridole	Leaf	120 -6600
Ascaridole-isomer	Leaf	5 - 335
Ascorbic acid	Leaf	580 - 3100
Azulene	Leaf	0 - 8000
β-caryophyllene	Leaf	1 - 65
β-caryophyllene-oxide	Leaf	1 - 30
β-cubebene	Leaf	1 - 15
β-elemene	Leaf	
β-farnesene	Leaf	
β-pinene	Leaf	1 - 720
β-thujone	Leaf	1 - 30
Borneol	Leaf	6 - 275
Camphene	Leaf	2 - 600
Camphor	Leaf	20 - 2880
Carvacrol	Leaf	
Caryophyllene	Leaf	4 – 160
Chrsanthenyl acetate	Leaf	
cis-chrsanthenol	Leaf	1 – 30
cis-dehydromatricaria ester	Leaf	
cis-jasmone	Leaf	2 - 125
cis-sabinene hydrate	Leaf	1 - 80
Copaene	Leaf	1.5 - 60
Cuminaldehyde	Leaf	0.3 - 11
Deacetylmatricaine	Leaf	
δ-4-carene	Leaf	
δ cadinene	Leaf	0.2 – 8
Desacetylmatricin	Leaf	
Dihydroparthenolide	Leaf	
Essential oil	Leaf	250 – 16000
Folic acid	Leaf	
γ-cadinene	Leaf	
γ-terpinene	Leaf	9 – 370
Geranial	Leaf	1 – 50

Table 2. Constituents of *Achillea millefolium*.[10]

Chemical	Part	Range (ppm)
Germacrene-d	Leaf	
Humulene	Leaf	0.5 - 22
Isoartemisia-ketone	Leaf	20 – 16000
Isoborneol	Leaf	5 – 320
Lavandulol	Leaf	1 – 15
Limonene	Leaf	1 – 170
Linalool	Leaf	1 – 4000
Linoleic acid	Leaf	
Myrcene	Leaf	0.5 - 20
Octen-3-ol	Leaf	
p-Cymene	Leaf	9 – 1185
Sabinene	Leaf	1 – 1225
Saponins	Leaf	
Succinic acid	Leaf	
T-cadinol	Leaf	1 - 15
Terpinen-4-ol	Leaf	3 - 175
Terpinolene	Leaf	1 – 50
Thiophenes	Leaf	167
Thymol	Leaf	1 - 15
trans-dehydromatricaria ester	Leaf	
Tricyclene	Leaf	0.6 - 27
Yomogi alcohol	Leaf	5 - 270
(-)-Betonicine	Plant	
(-)-Viburnitol	Plant	
2,3-dehydroxydesacetoxymatricin	Plant	
2,3-dihydroacetoxymatricin	Plant	
2-pentyl-5-propylresorcinol	Plant	70
3-oxaguaianolide	Plant	
4-oxo-3,4-dihydro-2,3-diazaphenoxanthin	Plant	36
5-hydroxy-3,6,7,4'-tetramethoxyflavone	Plant	
6,10,14-trimethyl-pentadecan-2-one	Plant	32
8-acetocyartabsin	Plant	
8-anelooxyartabsin	Plant	
Acetylbalchanolide	Plant	
Achiceine	Plant	
Achilleine	Plant	
Achilletine	Plant	
Achillicin	Plant	
Achillin	Plant	
Aconitic acid	Plant	
Adenine	Plant	
α-patchoulene	Plant	90
α-peroxyachifolide	Plant	
Aluminum	Plant	6 – 34
Apigenin	Plant	
Apigenin-7-*O*-glucoside	Plant	
Arabinose	Plant	
Artemitin	Plant	
Ascorbic acid	Plant	119 -672
Ash	Plant	17700 -

Table 2. Constituents of *Achillea millefolium*.[10]

Chemical	Part	Range (ppm)
		125,000
Asparagine	Plant	
Austricin	Plant	
Balchanolide	Plant	
Balchanolide acetate	Plant	
Benzaldehydecyanhydringlycoside	Plant	
β-Carotene	Plant	
β-Himachalene	Plant	50
β-Sitosterol	Plant	
β-Sitosterol acetate	Plant	
Betaine	Plant	
Betonicine	Plant	
Bornyl-acetate	Plant	50
Butyric-acid	Plant	
Caffeic-acid	Plant	
Calcium	Plant	1535 - 8670
Campherenone	Plant	70
Capric acid methyl ester	Plant	
Caprylic acid methyl ester	Plant	
Carbohydrates	Plant	133104 – 752,000
Casticin	Plant	
Cerotinic acid	Plant	
Chamazulene	Plant	0 – 4845
Chamazulene carboxylic acid	Plant	
Chlorogenic acid	Plant	
Choline	Plant	
Chromium	Plant	0.4 – 2.5
Cineole	Plant	
cis-β-Farnesene	Plant	110
cis-Carveol	Plant	200
cis-nerolidol	Plant	230
cis-Sabinol	Plant	100
Cobalt	Plant	0.6 – 3.1
Cosmosiin	Plant	
Coumarins	Plant	3500
Dextrose	Plant	
Dulcitol	Plant	
Essential oil	Plant	177 – 14000
Eucalyptol	Plant	
Eugenol	Plant	
Farnesene	Plant	
Fat	Plant	7080 – 40000
Ferulic acid	Plant	
Fiber	Plant	69000 – 201,000
Fiber(crude)	Plant	69000
Fiber(dietary)	Plant	412,000
Folacin	Plant	
Formic acid	Plant	
Furfural	Plant	
Furfuryl alcohol	Plant	
Galactose	Plant	
Gallic acid	Plant	
Geranyl acetate	Plant	36
Glucose	Plant	
Glutamic acid	Plant	
Glycine	Plant	
Guaiazulene	Plant	
Heptadecane	Plant	
Histidine	Plant	
Homostachydrine	Plant	
Hydroquinone	Plant	
Hydroxyachillin	Plant	
Inositol	Plant	
Inulin	Plant	
Iron	Plant	

Table 2. Constituents of *Achillea millefolium*.[10]

Chemical	Part	Range (ppm)
Isobutyl acetate	Plant	
Isorhamnetin	Plant	
Isoschaftoside	Plant	
Isovaleric acid	Plant	
Kilocalories	Plant	2900
Leucodin	Plant	
Linoleic acid ethyl ester	Plant	
Linoleic acid methyl ester	Plant	
Linolenic acid methyl ester	Plant	
Luteolin	Plant	
Luteolin-7-*O*-beta-D-glucopyranoside	Plant	
Luteolin-7-*O*-glucoside	Plant	
Lysine	Plant	
Magnesium	Plant	340 - 1920
Maltose	Plant	
Mandelic acid	Plant	
Mandelonitrile glucoside	Plant	
Manganese	Plant	1 - 5
Mannitol	Plant	
Matricin	Plant	0
Menthol	Plant	
Millefin	Plant	
Millefolide	Plant	
Moschatine	Plant	
Myristic acid	Plant	
Neryl-acetate	Plant	28
Niacin	Plant	
Niacin	Plant	
Oleic acid	Plant	
Palmitic acid	Plant	
Palmitic acid ethyl ester	Plant	
Palmitic acid methyl ester	Plant	
Pentacosane	Plant	
Phenol	Plant	155
Phloroglucinol	Plant	
Phosphorus	Plant	522 - 2950
Ponticaepoxide	Plant	
Potassium	Plant	3151 - 17800
Proazulene	Plant	
Prochamazulene	Plant	
Protein	Plant	19116 - 144000
Protocatechuic acid	Plant	
Prunasin	Plant	
Pyrocatechol	Plant	
Quercetin	Plant	
Quercetin glycoside	Plant	
Quercitrin	Plant	
Resin	Plant	6000
Riboflavin	Plant	1 - 6
Rutin	Plant	
Salicylic acid	Plant	
Selenium	Plant	0.3 - 1.6
Silicon	Plant	1 - 4.5
Sodium	Plant	15 – 82
Spathulenol	Plant	495
Stachydrine	Plant	
Stearic acid	Plant	
Stigmasterol	Plant	
Sucrose	Plant	
Swertisin	Plant	
Tannic acid	Plant	
Tannin	Plant	28000 - 40000
Terpineol	Plant	
Thiamin	Plant	
Thiamine	Plant	
Thujone	Plant	

Table 2. Constituents of *Achillea millefolium*.[10]

Chemical	Part	Range (ppm)
Tin	Plant	5 - 26
trans-carveol	Plant	150
trans-*trans*-farnesol	Plant	160
Tricosane	Plant	
Trigonelline	Plant	
Undecylenic acid methyl ester	Plant	
Vanillic acid	Plant	
Vicenin-2-schaftoside	Plant	

Table 2. Constituents of *Achillea millefolium*.[10]

Chemical	Part	Range (ppm)
Water	Plant	823000
Zinc	Plant	
Anacyclin	Root	
Fat	Seed	223,000 - 334,000
Protein	Seed	286000

Table 3. Constituents of concern in *A. millefolium*.

Constituent	Effects	Reference
Linalool	Dermal sensitizer. Safe at up to 4.3% (20% in a consumer fragrance)	38
Thujone	α,β-Thujone was not mutagenic in the Ames test; in the micronucleus test, negative in male and positive in female mice; β-thujone: *some evidence of carcinogenicity in male rats* – significant incidence of cancers of the preputial gland in male rats given 25 mg/kg by gavage, and an increase in adrenal gland tumors in male rats may have been due to β-thujone; no increase in in cancer incidence in female rats (dosed with up to 50 mg/kg by gavage) or male or female mice (dosed with up to 25 mg/kg by gavage); all rats dosed with 50 mg/kg and all female mice dosed with 25 mg/kg died. Neurological toxic effects; the suggested acceptable daily intake was 3 - 7 mg/kg/d	39,40
Quercetin	Positive genotoxic effect in an Ames assay Consistently genotoxic in in vitro tests and in some in vivo studies of i.p. exposures, but was consistently nongenotoxic in oral exposure studies	41 42
Hydroquinone	Causes skin depigmentation. Prescriptions for medical skin lighteners start at 0.4%.	43
α-peroxyachifolid	Sensitizer to guinea pigs at 0.01%	44

Table 4. Frequency of use according to duration and exposure of *A. millefolium* extract.

Use type	Uses	Maximum Concentration (%)
	Achillea millefolium extract[1]	
Total/range	**135**	**0.000005-0.04**
Duration of use		
Leave-on	83	0.00001-0.04
Rinse-off	47	0.000005-0.03
Diluted for (bath) use	5	0.0001
Exposure type		
Eye area	2	0.00002-0.03
Incidental ingestion	NR	0.00001-0.01
Incidental Inhalation-sprays	3	0.0001
Incidental inhalation-powders	3	0.00005
Dermal contact	94	0.00002-0.04
Deodorant (underarm)	NR	NR
Hair-noncoloring	40	0.000005-0.006
Hair-coloring	NR	0.00001-0.00002
Nail	1	0.00002-0.0002
Mucous Membrane	11	0.00001-0.0001
Baby	NR	NR

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

[1] There was a VCRP entry for achillea millefolium with 3 shampoos listed. This was combined with achillea millefolium extract.

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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Personal Care Products Council
Committed to Safety, Quality & Innovation

TO: Lillian Gill, Ph.D.
Director – Cosmetic Ingredient Review
Cosmetic Ingredient Review Expert Panel
Liaisons to the Cosmetic Ingredient Review Expert Panel

FROM: Cosmetic Ingredient Review Science and Support Committee (CIR SSC) of the Personal Care Products Council

DATE: July 23, 2013

SUBJECT: Comments on the Tentative Report on *Achillea millefolium*-Derived Ingredients

The CIR SSC appreciates the opportunity to comment on the tentative report on the *Achillea millefolium*-derived ingredients.

The CIR SSC recognizes the potential of plant-derived ingredients to be potential sensitizers, especially those plants such as *Achillea millefolium* that are known to contain sesquiterpene lactones. We also recognize the potential for variability in the composition of plant extracts used in cosmetics. Because no information on the composition of the Achillea Millefolium Extracts included in the products tested in HRIPTs was provided, we suggest that the conclusion of this report be changed to: "safe when formulated to be non-sensitizing." We believe that this conclusion would encourage companies formulating products with Achillea Millefolium Extract to either learn more about the composition of the specific preparation they are using, or to complete human repeat insult patch tests on products containing these ingredients.

We are also concerned with the following sentence in the Abstract: "Because more than one botanical ingredient may be used in formulation, caution was urged to avoid reaching levels of concern from an accumulation of toxicological and allergenic constituent chemicals and impurities such as pesticides." We understand the concern about constituent chemicals coming from multiple botanical ingredients. Pesticides are not constituent chemicals and should not be treated in the same manner as constituent chemicals. The statement in the Discussion that "the cosmetics industry should continue to use the necessary procedures to limit these impurities [pesticides and heavy metals] before blending into cosmetic formulation" is appropriate. If pesticides/impurities are mentioned in the Abstract, it should be consistent with this statement in the Discussion.

Personal Care Products Council
Committed to Safety, Quality & Innovation

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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 3, 2013

SUBJECT: Comments on the Revised Tentative Amended Report on *Achillea millefolium*-Derived Ingredients

Key Issues

Please check the April 18, 2012 memo from the CIR SSC again. This memo indicates that 5 studies were on the aqueous extract. These 5 studies do not include any studies on finished products containing the ingredient. The type of extract included in the finished products containing Achillea Millefolium Extract is not known. Therefore, it is wrong to say that an aqueous extract as "described in Physical and Chemical Properties" was tested in the Epiocular assay, or the HRIPTs of the moisturizer with self-tanner, or the body splash product.

Regarding the aqueous extract, the Constituents section correctly states that "Another assay for terpenes and steroids was negative." Because thujone is considered a constituent of concern in the Discussion, and because this assay of the aqueous extract specifically looked for thujone and did not find it at a detection limit of about 300 ppm, more information about the assay for terpenes and steroids should be included in this report. As there are data to suggest that thujone is not in the aqueous extract of *Achillea millefolium* at a detection limit of 300 ppm, the Discussion should state that thujone was not found in the aqueous extract, and that thujone and the other constituents of concern may or may not be found in the cosmetic ingredients depending on the growing conditions and the methods used to produce the ingredients.

The Discussion should include information as to why the CIR Expert Panel concluded that the *Achillea millefolium*-derived ingredients are safe when formulated to be non-sensitizing. Although there are sensitization data on Achillea Millefolium Extract, plant preparations are known to have variable composition based on growing conditions and extraction methods, so that studies on one or two extracts may not represent the complete variability that might be found among plant extracts. In addition, *Achillea millefolium* 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.

Additional Comments

p.3 - As there was only one ingredient in the original report, please correct "safety of these ingredients" in the Introduction.

p.3 - Summary of Original Safety Assessment - The summary of the original safety assessment does not need to be provided verbatim. The information in the original report relevant to the current safety assessment should be presented. For example, re-stating the function of biological additive, a function which is no longer used, is unnecessary.

p.4 - As noted above, in the Constituents section, please provide more details on the assay used to assess terpenes and steroids in the aqueous extract. As thujone is considered a constituent of concern and it was used as a standard in this assay, it would be helpful to note that it was not found.

p.4 - Hausen et al. (1991) (a paper cited in the original CIR report) identified α-peroxyachifolid as the specific sesquiterpene lactone responsible for the sensitization potential of *Achillea millefolium*. It is not clear why α-peroxyachifolid is not listed as a constituent of concern.

p.4 - In the Cosmetic Use section, please do not imply that use concentrations reported are for the products reported to the FDA VCRP. The FDA VCRP and the Council survey are two separate sources and it should not be implied that the concentrations reported to the Council survey are for the products that are included in the VCRP.

p.4 - Please give the FDA product category associated with the use concentration of 0.00005% (either a perfume or face powder?).

p.6 - As stated above, the type of *Achillea millefolium* extract used in the product tested in the Epiocular study was not stated. It is not correct to say that it was an aqueous extract.

p.6, Sensitization, Human - Please include more details such as test volume and patch size in the descriptions of the patch test studies.

p.6 - As stated above, the type of *Achillea millefolium* extract used in the product tested in the HRIPTs of products (references 33 and 35) was not stated. It is not correct to say that it was an aqueous extract.

p.6 - Please correct "In and HRIPT (n=53)..."

p.7 - In the Summary, please state the FDA product category associated with the maximum use concentration.

p.7 - In what species were abnormal sperm observed at a dose of 1.2 g/kg/day?

p.7 - Because no changes were observed in the 200 mg/kg dose groups (i.p. and oral) it is not necessary to also state that there "normal physiology" was observed in the 200 mg/kg dose groups after the 40-day recovery period.

p.8 - What concentration of hydroquinone is associated with skin depigmentation?

p.8 - As these extracts are liquids, it does not make sense to say: "the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation."

p.8 - As one ingredient has reported uses, the footnote to the conclusion needs to be changed from "comparable to others in the group" to "comparable to Achillea Millefolium Extract".

p.15, Reference 38 - Please correct "realted"