BLUE

Safety Assessment of Achillea Millefoluim-Derived Ingredients as Used in Cosmetics

CIR EXPERT PANEL MEETING

JUNE 10-11, 2013

Cosmetic Ingredient Review

Commitment & Credibility since 1976

June 17, 2013

MEMORANDOM

To: CIR Expert Panel and Liaisons

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

Subject: Tentative Amended Safety Assessment of Achillea Millefolium (Yarrow)-Derived Ingredients As Used In Cosmetics

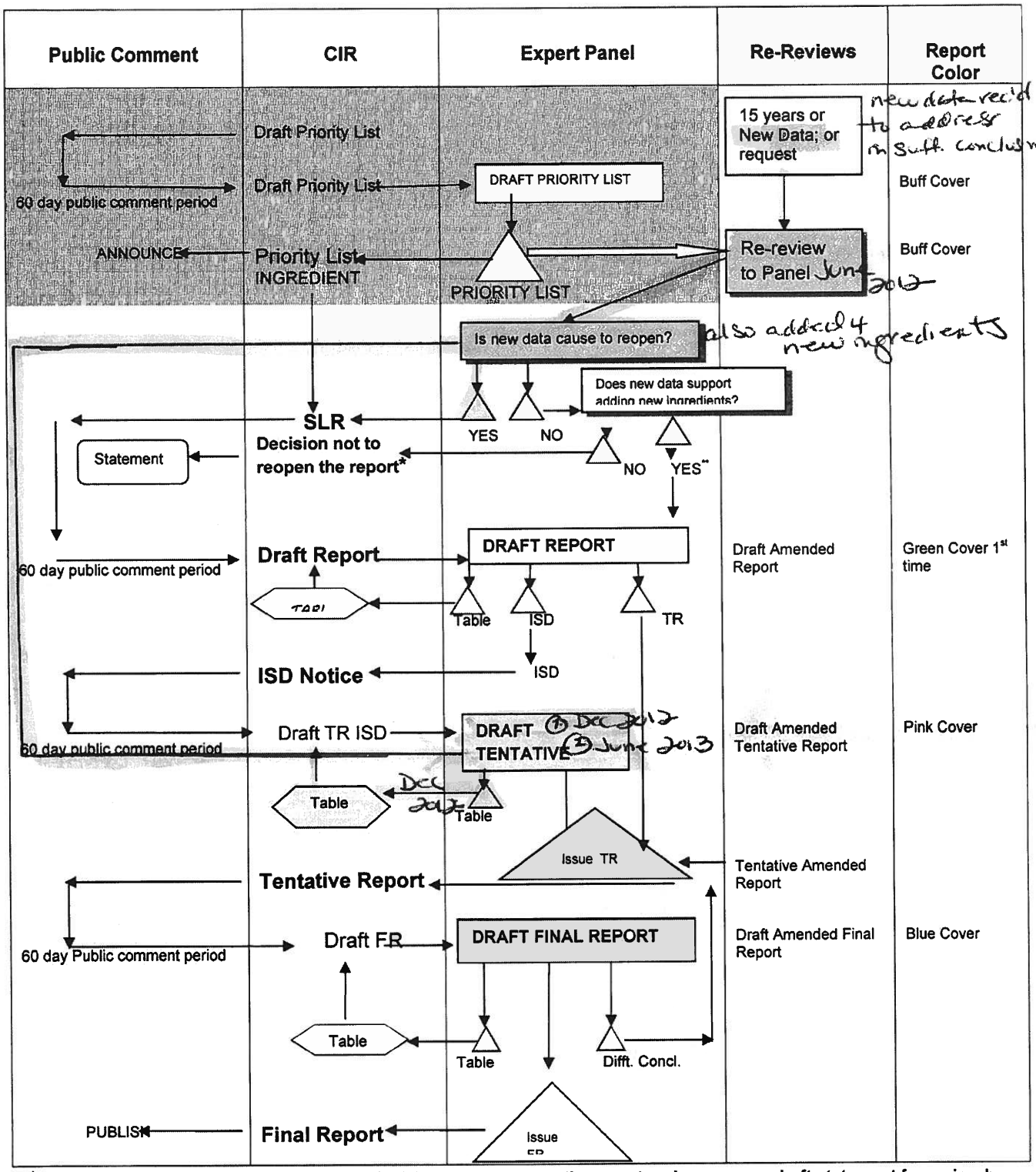
In December, 2012, the Panel examined data submitted from industry to possibly address the insufficient data conclusion from the original report issued in 2001. The Expert Panel decided to table the safety assessment to provide industry the opportunity to provide sensitization data at or above the highest reported use concentration. No new data have been submitted.

Comments from industry have been addressed. The 2013 VCRP data have been incorporated into the report; there were no substantial changes in the reported use. The new botanical language framework was applied in the Discussion and Abstract sections.

The Panel should review the tentative amended report and decide how to proceed with the new data. The Panel may issue an insufficient data conclusion or place a limit on the concentration of use.

1101 17th Street, NW Suite 412, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

SAFETY ASSESSMENT FLOW CHART



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

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

Expert Panel Decision

Document for Panel Review

Option for Re-review

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 – No new data have been provided by industry. The Panel will examine the data and provide a conclusion, possibly with a limit.

Achillea Millefolium (Yarrow)-derived ingredients Data Profile for December, 2012. 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 millefoium (Yarrow) Minutes
December, 2012

Day 1
Dr. Belsito's Team

DR. BELSITO: Okay. Any other comments? Okie-doke. So, moving down to the last one. Achillea millefolium, a.k.a. yarrow, right? So, in June we again agreed that new data would likely address our data insufficiencies of 2001. And so, we re-opened the safety assessment. And so, the use concentration is to 0.04 percent, is that the?

MS. BRESLAWEC: Sorry, could you repeat that?

DR. BELSITO: The current use concentration -- you know, again --

MS. BRESLAWEC: .03.

DR. BELSITO: .03. Okay, I had.04. In this report it was tested at.01 but in the old report we had.1 percent of a 2 percent extract, which was.002. So, this is one where I didn't see that it was tested at concentration of use.

And then, thujone comes into play here, but we deal with that with low use, et cetera. Which just brought up the fact that, you know, granted when we're -- these have been reported and reported as insufficient, but gosh, it would have been so much easier for me when I was reviewing it if there was a summary of the data that we had looked at before in terms of sensitization and irritation so I wouldn't have to go back and open up the old report and look at it if it were just in the new report. Just as an FYI.

I just found it, you know -- this is a waste of time when you're going back and forth. You know, so it would be a nice summary. Previously looked at it, at concentrations of this, this, and this and found to be negative or, you know -- I don't know. I know it's an issue with the publishers that were recycling old data, but you know maybe it could be put in and then deleted when we publish it or done in some way that it just makes it easier when we're re-reviewing.

MR. ANDERSEN: I think we get it.

DR. BELSITO: Yeah. But anyway, I didn't see that there was any testing at concentration of use. Maybe I missed it?

DR. EISENMANN: You do have a local lymph node assay, to 100 percent of that aqueous extract.

DR. BELSITO: Yeah. You know, we've dealt with -- you know, local lymph node assays of mixtures in the RIFM panel, and they can be a little bit unreliable. Yeah, there have been cases where we've looked at, you know, assays of individual constituents and then assays of the mixture itself, and you would think that they don't come out together, necessarily, all the time. So if you read review articles and critiques of local lymph node assays, they will say that there are issues with assessing mixture toxicity. So, I don't know that a local lymph node assay satisfies me in terms of a mixture. I mean, it's just -- and maybe it's just me. Maybe other people have different opinions.

I would like to see an HRIPT. It would make me feel a little bit more comfortable.

MR. ANDERSEN: Don, is there -- from the testing that you do have, is there concentration at which you were comfortable? Like, .01 percent you said was the highest?

DR. BELSITO: No, it's.001.

MR. ANDERSEN: Okay.

DR. BELSITO: Oh, .002 in the old report. It was .1 percent of a 2 percent extract, and then in this report the highest was .001 percent. Correct?

MR. ANDERSEN: Yes.

MS. BECKER: Yeah, correct.

MR. ANDERSEN: Why couldn't you pick the highest of those available data and set a concentration limit?

DR. BELSITO: I mean, I could and then ask industry to come back and support -- I wrote down.04, but maybe my writing was wrong. So, it's.03 is the highest leave-on?

MS. BECKER: Leave-on I got.04.

DR. BELSITO: Yeah, that's what I have. But someone down there said.03.

DR. EISENMANN: Are you looking at the new --

MS. BECKER: Yes, let me pull up the data and I can double-check the source..

DR. BELSITO: No, it's -- yeah, I think you're right. Well, it's.04 in Table 3.

DR. SNYDER: It's Wave 2.

DR. BELSITO: It's Wave 2 is also.04.

MS. BECKER: Yes.

DR. BELSITO: Okay. Yes.

MR. ANDERSEN: Well, again regardless of --

DR. BELSITO: Body and hand cream, lotion, and spray.

MR. ANDERSEN: If you have data at.002, that's where you can set the limit. We've done it before.

DR. BELSITO: You know, then we don't say safe as used. Safe up to.002 and provide us the data at.04 if you want to go there.

It's just that these botanicals are so, so difficult to deal with as a dermatologist. And this is one, I should point out, that is going to have fragrance oils like linalool that can oxidize and create issues. The leaf has up to 4,000 parts per million of linalool. It has limonene and it has a good number of terpenes that can be issues for contact sensitization, which is why I'm not comfortable signing off on something that they don't have data at their use concentration.

DR. LIEBLER: We also asked for UV absorption, and there's a spectrum on Panel Book Page 32 that plainly shows UVB absorption.

DR. BELSITO: Panel Book 32. It tells us so much.

DR. LIEBLER: You got -- it's always misleading when they show the -- you know, the band that's 190 because it makes everything look small. But you know, there are two bands there. There's one at about 280 -- that's not the UVB, but there's another one at about 280 and another one at around 320, 330. Anyway, there's --

DR. BELSITO: Yeah, I mean --

DR. LIEBLER: UVB-absorbing stuff in this mixture.

DR. BELSITO: Of course.

DR. LIEBLER: So the question I had was, what is our trigger for then -- given data like this, what's our trigger for asking for photo-tox or photosensitization? You know, historically? Has there been any kind of?

DR. BERGFELD: It's the peak. There's basically where the peaks were.

MR. ANDERSEN: I don't think there's ever been a number that has ever been linked to it, but where the panel has been comfortable is where that keeps going down and there's no shoulder.

DR. LIEBLER: I see two shoulders.

MR. ANDERSEN: Me, too.

DR. BELSITO: Yeah, and the second one certainly is way out in the UVA range, and when you're worried about photo- toxicity it's usually UVA you're worried about, not UVB. You know?

We certainly can ask for it at concentration of use. I mean, I guess looking at the --

DR. LIEBLER: If you put a botanical extract in a cuvette, I would be willing to bet you the house payment this is what you get every time, something that looks like this.

DR. BELSITO: Yeah.

DR. LIEBLER: So, I guess the short answer is there's been no clear-cut trigger, historically, based on a UV spectrum for requesting photosensitization or photo-tox data.

DR. BELSITO: No.

MR. ANDERSEN: But in this case, those data were part of the original insufficiency. And at this point, you have a couple of things you can legitimately do. One is to wonder what the significance of that absorption spectrum is and ask for either more clarification or real photo-tox data to back it up. And you do that by tabling it and asking for that.

Or, you could make a judgement that you still don't have sufficient photo-tox data or UV absorption, and declare it to still be insufficient.

DR. BELSITO: Well in the spirit of moving it on, why don't we declare it insufficient both for concentration, for lack of sensitization and irritation data up to.04, and for photosensitization data, and let industry know that right now we're comfortable with a.002 for sensitization and maybe they can finesse the absorption spectrum in ways that will make us less concerned about photosensitization.

But I mean, go ahead without because someone's using it at.04, and hopefully they have some data that will tell us that it's okay to be used there.

It's just that, you know -- I mean, now we're getting really high into the terpenoid ingredients here and you know, linalool, a lot of things that get oxidized -- limonene -- and make them much more allergenic. So I think we need to take a little more, greater caution than we did with St. John's Wort.

MR. ANDERSEN: Okay -- go ahead.

MS. BECKER: I just want to point out that the limonene and the linalool -- I'm not sure how to say it.

DR. BELSITO: Linalool.

MS. BECKER: Yeah. That they're both in the leaf but not in other plant parts. And of your ingredients, only one of them has the leaf and it's a flower/leaf/stem extract. So we're talking about it's not even part of the whole extract, it's a smaller part. Just to throw that in the hopper.

DR. BELSITO: Right. The whole thing is in the hopper.

MR. ANDERSEN: The -- proceeding from here gives me a little bit of pause. Where we were before September is that this ingredient was insufficient. So, if you decide to just not do anything further, it's already insufficient.

DR. BELSITO: So we need to table it and ask for the data, is what you're saying?

MR. ANDERSEN: Well, if you want to really stimulate interest and say that this isn't a lost cause, tabling it might be the right message to send.

DR. BELSITO: That's fine.

MR. ANDERSEN: I think -- Halyna can opine as far as what the industry reaction is going to be to whatever we do. Your discussion sends some pretty clear signals, so maybe we don't have to label it anything.

DR. BELSITO: So, you know, I guess I agree with you. Thinking about it, we already said it was insufficient. It's still insufficient. When that happens, the whole thing goes away until industry re-submits another thing to us. So, I don't have a problem with saying table it. You know, industry is on alert that we, you know, may re-look at the UV data and find out we don't need photosensitization but right now we'd like to see if there's any photosensitization data out there and any data that would support leave-on use up to.04 percent.

Okay?

MR. ANDERSEN: You get to move it tomorrow. So --

DR. BELSITO: Wow.

MR. ANDERSEN: See what happens..

DR. BELSITO: Good.

Dr. Mark's Team

DR. MARKS: In achillea millefolium aka yarrow was assessed and reported in 2001 with an insufficient data conclusion. In June of this year, we reopened it and in light of having a number of new data. And so, on the memo from Lillian the data needs work. Bulleted on her memo and then the question is are the -- is the new data okay? Can we move forward with a safe or do we still have insufficient data needs?

DR. SHANK: For sensitization, I couldn't find the lymph node assay study. The conclusion says it's okay but I wasn't able to review the study.

DR. MARKS: Yeah. I have 100 percent assay it was okay. So, Lillian -- so, I thought that was the last bullet. Clinical sensitization, repeat insult patch, but I thought the local lymph node assay where it was okay at 100 percent would really would not -- we would not need an RIPT say at that point. So, it would indicate that it's virtually a non- sensitizer or almost non-sensitizer.

Okay, continue, Ron, while Lillian's looking..

MS. BECKER: Okay. The mouse lymphoma is on panel book 43.

DR. MARKS: No, that's --

MS. BECKER: Oh, sorry.

DR. MARKS: -- a --

MS. BECKER: Oh here we go. I'm sorry. 37. Yeah, local lymph --

DR. MARKS: Pardon?

MS. BECKER: 37. Panel book 37.

DR. SHANK: Okay. That's all there is.

MS. BECKER: That's all they gave us, yes.

DR. SHANK: Okay.

DR. MARKS: That's -- I trusted them. So, that was okay. Particularly in my clinical experience even these have become very common, these botanicals in personal care products. I can't remember seeing that, the yarrow and the case reports would pick up things too. And again, you just don't see much.

DR. SHANK: Okay.

DR. MARKS: So, we'll say the last bullet is okay. How about the UV absorption? It's minimal above 290 it looks like? Is that okay at this point? Do we need --

DR. SLAGA: It absorbs at 360 right?

DR. MARKS: Yeah.

DR. SHANK: Actually, the reference shows a single absorption peak at 190. Nothing at 260. That's on panel book page 32.

DR. MARKS: Yes. So --

DR. HILL: Well, no. There are minor absorption bands at 260 and another one at 330. I mean there's not as -- the e-max is not as high. There's still absorption going on clear out to 390 which I would expect from a plant extract because there are going to be some --

DR. SHANK: But our tech says there was a peak at 260.

DR. HILL: Oh, there is a peak. Well, it's a shoulder at 270, 265, something like that.

DR. MARKS: No, I think what you said, 190 didn't you? It's below 200.

MS. BECKER: Yeah. It's 190. I reworded that, yes.

DR. MARKS: So, are --

DR. HILL: There are shoulders. There's a shoulder at 265 and there's another shoulder at 330ish.

DR. MARKS: Okay, so is there -- even though there's some absorption in the ultraviolet range -- concerns? I think it's small.

DR. HILL: I didn't because the concentrations of use are so low.

DR. MARKS: Right. Okay.

DR. HILL: That was where I landed on that one.

DR. MARKS: How about these other, gross pathology histopath?

DR. SLAGA: There's no histopath of the skin but I don't know if that's needed.

DR. MARKS: This point it --

DR. SLAGA: From repeated applications but I don't have a concern for it.

DR. SHANK: I don't think we need it.

DR. SLAGA: -- toxicity. I don't -- there's oral repeated.

DR. MARKS: Repro development tox?

DR. SHANK: We have that.

DR. SLAGA: We have that.

DR. MARKS: That's okay.

DR. SLAGA: Genotox I think we have.

DR. MARKS: And the geno is okay. So, it looks like we could move forward to a safe but now we have include the oils, page --

DR. HILL: I was going to say, can we go to page 3 and have a look quickly cause --

DR. MARKS: Yes. That's -- you're ahead of me, Ron, but good. Thank you.

MS. BECKER: 3 in the report or 3 in the book?

DR. HILL: Panel book page 3.

DR. MARKS: 3. So, we have other ingredients in here now.

DR. HILL: Yeah.

DR. MARKS: So, do we want to include and I question the oils.

DR. HILL: I'm not sure why the oil is here. You know, that, to me belongs, if it's truly an oil that belongs in vegetable oils and we had a whole other -- I don't know if we picked that one up back when we did that. Probably not or else it probably wouldn't have landed here but we don't have any data on it. And I question whether it even belonged in here given its dissimilarity from the other extracts I'm almost certain.

DR. MARKS: So, your sense would be that was what I was questioning. Is the oil the same as a water extract? No. That's what -- So, Ron and Tom, would you include or delete the oil? Because we have the opportunity now to -- and I guess it's an -- if we use that this is going to be an amended report, this should be a no brainer if we add ingredients. And it doesn't like the oil is a no-brainer.

DR. HILL: This doesn't belong with the others from where I see it. If it's truly an oil it doesn't go with --

DR. MARKS: Okay. So, we will have one, two, three, four ingredients.

MS. BECKER: Well, according to the definition it is an oil. It's oil obtained from the herb so --

DR. HILL: All right. So that shouldn't go here in my opinion.

DR. MARKS: Yeah. So, four ingredients. Safe.

MS. BECKER: And what would you like me to mention in the discussion besides the UV?

DR. MARKS: Well, obviously convention. All these things that were safety needs before that now we feel are met. I think that would be important. Do we have, again, since these are plants, do we have the heavy metals and pesticides boiler plate?

MS. BECKER: Yes, we do. Put that in.

DR. MARKS: Okay. And then I had a question, page panel book 16. And I forget. I

should have looked it up but quercitin is one of the ingredients and that just rung a bell. Was there safety concerns in the past about quercitin or not?

MS. BECKER: Don't know.

DR. SLAGA: Yes. It was sold over the counter --

MS. BECKER: It's an OTC drug? Oh, good.

DR. SLAGA: I mean there is some toxological but it's extremely at high doses.

DR. MARKS: Okay. Okay, good.

DR. HILL: That's what I was going to say. And the extracts are used at small concentrations and then amount here is -- I mean none's listed which means that should be small.

DR. MARKS: Right. I had the same. I had hydroquinone as listed as an ingredient and of course that's a feed pigmenter but it's such a small amount that it seems like that would be un -- that was on page 15. Okay.

MS. BECKER: Would you like me to mention this?

DR. MARKS: What does the team feel? No?

DR. SLAGA: It's such small amounts.

MS. BECKER: Well, that would be why I'd mention.

DR. SHANK: I would just say these minor components are not a concern because of the low use concentration via extract.

DR. HILL: Right. And if we want to pick on something then we should pick on isoartemisia-ketone. When you get down to the --

DR. MARKS: Yeah, so I would probably not mention it. I just wanted to bring it up now to make sure that there weren't any alerts there.

Okay, so let me see. This is Belsito. I will move, I presume he'll move, it will be safe. We want to have the four ingredients, not the oil and this would move on to a final. To a draft amended final report. Okay. Any other comments? Lunch?

DAY TWO

DR. BERGFELD: … Moving on to the next botanical, Dr. Belsito.

DR. BELSITO: This is achillea millefolium-derived ingredients. This was another one that we looked at back in 2001 with this insufficient data and a number of data needs. Industry has come back with some of that information; however, we noted that it is used up to 0.04 percent, and the highest level of sensitization data that we have is 0.002 percent. So we are going insufficient for sensitization concentration of use.

DR. MARKS: We felt -- so that's a motion?

DR. BERGFELD: A motion. That's a motion.

DR. MARKS: Discussion now?

DR. BERGFELD: Yes.

DR. MARKS: We felt that we could actually move on to a safe conclusion. I'm not sure if I heard you correctly; that would be 2,000th difference -- a difference between.002 and.004 percent?

DR. BELSITO: .04.

DR. MARKS: .04, okay.

DR. BELSITO: It is not a small difference.

DR. MARKS: No.

DR. BELSITO: So we could table it. I guess we talked about this. We really can't go insufficient because we were asked to reopen it. So we can either table it and ask for the data from industry, or I'm comfortable going ahead and saying safe up to.002 percent. And if industry wants to respond, that's fine, but I don't have the data to justify going that high with a

plant-derived material.

DR. MARKS: So I guess, Don, my response was it was not an irritant in humans, and then the local lymph node assayed at 100 percent did not show it was a sensitizer.

DR. BELSITO: Yeah.

DR. MARKS: In the clinical experience -- we don't have case reports in here, so for me that difference in the RIPT, even though it wasn't up to use concentration, I thought the other supporting data was enough to overcome that.

DR. BERGFELD: Don?

DR. BELSITO: I'm in the process of reviewing botanicals to give a talk at the academy. And we don't have case reports because we don't have the material to test for it, and we really don't understand what we're testing for in these mixtures. It's a real issue for all of them because they can differ depending upon how they're extracted and what's in them. So number 1, number 2, maybe we should have Anne-Marie or David Basketter come back and talk to us about the local lymph node assay, but it is very unreliable for mixtures. There are a number of different types of products where it doesn't necessarily predict the sensitization and that's been looked at in the fragrance industry because, of course, they have a lot of essential oils. And they've taken the individual components of essential oils, done those LLNAs, and then compared them to the response of an LLB-essential oil, and it doesn't necessarily tally together. So the LLNA for a mixture like this, an extract, doesn't give me any confidence. I would like to see data in animals or an HRIPT in humans.

DR. BERGFELD: So there is a motion, but it has not been seconded. Will you repeat your motion?

DR. BELSITO: Well, I guess my motion -- because we can't go insufficient -- is to say safe as used up to.002 percent, or table it to give industry a chance to respond to.04 percent.

DR. BERGFELD: Is that two motions or one motion? Which would you prefer?

DR. BELSITO: Let's table it and give industry a chance to respond and see. I mean it may be that no one's using it at.04 percent and it's moot. I don't know.

DR. BERGFELD: It's a motion to table. Is there a second? There's no discussion. Are you motioning to second?

DR. MARKS: Yes, second to table.

DR. BERGFELD: All those in favor, please indicate by raising your hand. This ingredient has been tabled.

DR. HILL: We had talked about removing the oil from this category.

DR. MARKS: Yes.

DR. HILL: What did we decide?

DR. MARKS: This would be a follow-up discussion, Ron. Thanks for bringing it up. I was going to mention that. We felt that we would delete the oil from the amended report because it was different the way it would be derived and the safety data's basically on the extracts, not the oil. So that's just -- it's been tabled, but consider that and capture that in the minutes, and we'll see how this plays out. But just so the Belsito Team's aware that our team felt the oil probably should be deleted.

DR. BERGFELD: Any other comments while this is under consideration, this particular ingredient? Don?

DR. BELSITO: Maybe we should just discuss that so that --

DR. BERGFELD: Okay.

DR. BELSITO: I mean if we're going to delete the oil, let's do it.

DR. BERGFELD: Please go forward then.

DR. BELSITO: The issue was is the oil used in cosmetics? It has four reported uses in leave-ons. And your concern was because the manufacturing was different?

DR. BERGFELD: Ron Hill, you want to respond?

DR. HILL: We just thought that the nature of that compared to the other extracts is expected to be quite different, meaning if it's an oil then it's an oil. And second of all there is no safety data whatsoever on that oil, so read-across for me was impossible.

DR. BERGFELD: Comment from the Belsito Team? Dan or Paul?

DR. SNYDER: So in the frequency of use table, we just have the -- oh, I see it. We have it. I'm sorry. Never mind.

DR. BERGFELD: Dan?

DR. LIEBLER: I don't object to deleting the oil.

DR. BERGFELD: Okay. Any other discussion? Halyna?

DR. BRESLAWEC: I note that the only function listed for the oil and for the flower water is as fragrance ingredients.

DR. BERGFELD: Don, do you want to comment on that?

DR. BELSITO: If it's a fragrance ingredient, it's not under our purview. It's under RIFMs and IFRAs, so can't object to removing it. And if the water -- you said the flower water extract also?

DR. BRESLAWEC: Correct. We would not object to removing both of them..

DR. BELSITO: So both of them should be removed.

DR. BERGFELD: So it will be removed. So the discussion will reflect this discussion in the minutes, correct? And then when we come back, this will be included in the packets for the Panel members. All right. Thank you very much.

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

Status: Tentative Amended Report for Panel Review
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The 2012 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 F. Alan Andersen, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

1101 17th Street, NW, Suite 412 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢ cirinfo@cir-safety.org

TABLE OF CONTENTS

ABSTRACT

Cosmetic ingredients derived from *Achillea millefolium* function in cosmetics as skin-conditioning agents – miscellaneous, skin-conditioning agents – humectants; and fragrance ingredients. The Panel reviewed relevant animal and human data to determine their safety in cosmetics and concluded that these *Achillea millefolium*-derived ingredients were safe as cosmetic ingredients in the present practices of use up to 0.02%. Because formulators may use more than one botanical ingredient in a formulation, caution was urged to avoid reaching levels of concern for constituent chemicals and impurities such as pesticides.

[*This Abstract will be edited and confirmed at the June, 2013 meeting*.]

INTRODUCTION

This is a draft tentative 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. The three ingredients in this safety assessment are:

- achillea millefolium extract,
- achillea millefolium flower/leaf/stem extract, and
- achillea millefolium flower extract.

In 2001, the Cosmetic Ingredient Review (CIR) published a safety assessment of achillea millefolium extract as used in cosmetics.[1] The CIR Expert Panel concluded that there were insufficient data to determine the safety of these ingredients. The data needs were:

- 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.

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

Original Safety Assessment

This is a summary of the data in the original safety assessment.

Yarrow (achillea millefolium) is an extract of the yarrow, *A. millefolium*, and functions as a biological additive in cosmetic products.[1] 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 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 pinnately divided leaves.[2] 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.

Physical and Chemical Properties

UV absorbance of a 1% aqueous water extract peaked at ~ 260 nm with small shoulders at 270nm an ~320 nm.[3]

Constituents

The constitiuents 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.[3] An assay for nitrogen compounds of the same sample showed the possible presence of pipecolic acid, L-alamine 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 quercetine. Another assay for terpenes and steroids 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.[4]

The essential oil content of *A. millefolium* was lower in the vegetative stage (0.13%) than the full bloom stage (0.34%).[5] 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.[6]

A comparison of the arial parts of *A. millefolium* plants that grew in the Indian Andes at altitudes of 1600 m and 2850 m was conducted.[7] 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%), borneaol (0.2% - 12.1%).

Method of Manufacture

Achillea millefolium extract is processed from the stem, leaves, and aerial parts of the plant.[3] 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 zantham gum.

Impurities

A mixture containing hypericum perforatum extract (1%-5%), olive (*Olea europaea*) oil (>50%), and tocopherol (0.1 %) contained < 10 ppm heavy metals and <0.0 1 ppm organochlorines; organophosphoric compounds were not detectable.[8]

USE

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 4).[9] A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for these ingredients.[10]

VCRP had an entry for achillea milefolium. It was assumed that this was achillea millefolium extract and was combined with that data.[9]

Achillea millefolium extract was reported to be used in 135 cosmetic products; these include 83 leave-on products up to 0.04% and 47 rinse-off products up to 0.03%. %. The extract is also 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 and achillea millefolium flower/leaf/stem extract.

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

No new toxicokinetics data were identified or made available for review.

Cytotoxicity

ACHILLEA MILLEFOLIUM EXTRACT

A product containing an aqueous extract of A. millefolium (described in Physical and Chemical Properties; 5.0 μL/mL) was not cytotoxic to L5178Y cells after 3 h of incubation.[11]

TOXICOLOGICAL STUDIES

Acute Toxicity

Oral – Non-Human

ACHILLEA MILLEFOLIUM EXTRACT

The oral LD_{50} of the mixture containing an aqueous extract of A. millefolium (described in Physical and Chemical Properties) is > 2000 mg/kg in female rats.[12]

There were no mortalities when an aqueous achillea millefoium extract (10 g/kg; leaves, stalks, stems) was orally administered to male and female Wistar rats.[13]

Intraperitoneal

ACHILLEA MILLEFOLIUM EXTRACT

There were no mortalities when an aqueous achillea millefolium extract (3 g/kg; leaves, stalks, stems) was intraperitoneally administered to male and female Wistar rats.[13]

Repeated Dose Toxicity

Oral – Non-Human

ACHILLEA MILLEFOLIUM EXTRACT

An aqueous achillea 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.[13] 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 similar mobility, reflexes, muscular tone and breathing patterns 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 weight 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 rats exhibited no treatment-related toxicological or histopathological abnormalities.

An ethanol (60%) multi-herb mixture (20 mg/kg/d), that includes 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.[14] Body weights were similar to controls. No differences were observed in the weight of the spleen, kidney, testicles, or liver 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%) achillea millefolium extract (2.8 g/kg/d; 56 times the equivalent human dose of 50 mg/kg/d) was not maternotoxic when orally administered to Sprague-Dawley rats (n = 5) but caused reduced body weights in fetuses.[15] 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 fetuses 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 weight was reduced in fetuses exposed to achillea millefolium extract on GD 8–15 compared to the water controls. There was no difference in incidence of external or internal malformations.

An aqueous achillea 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.[16] The rats were killed and necropsied after 90 days, concentrating 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 achillea millefolium extract (1.0, 5.0, and 10.0 mL/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.[17] There were no changes in the number of offspring.

ACHILLEA MILLEFOLIUM FLOWER EXTRACT

An ethanolic achillea millefolium flower extract (200 mg/kg/d) intraperitoneally (i.p.) administered to male Swiss albino mice (n =) 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.[18] 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 achillea millefolium flower extract (200, 400, 800 mg/kg/d) 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 group.[19] However, there were abnormalities in the development of sperm in the mid- and high-dose groups. 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 *Salmonell typhimurium* (TA98, TA100, TA102, TA1535, TA1537), the mixture containing an aqueous extract of A. millefolium (described in Physical and Chemical Properties; 0.06 – 5 µL) was not mutagenic and non-promutagenic.[20]

In two micronucleus tests using V79 cells, the mixture containing an aqueous extract of A. millfolium (described in Physical and Chemical Properties; up to 15,000 µg/mL) was not clastogenic or aneugenic with or without metabolic activation.[21]

In a gene mutation assay using mouse lymphoma L5178Y $TK^{+/-}$, a product (up to 5 µL/ml) that contained the an aqueous extract of A. millefolium (0.5%) was not mutagenic with or without metabolic activation.[11] The controls had the expected results.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

ACHILLEA MILLEFOLIUM EXTRACT

In a patch test of subjects with atopic dermatitis (n = 9), there were no positive reactions to achillea millefolium extract (1% in petrolatum).[22]

Ocular

ACHILLEA MILLEFOLIUM EXTRACT

In an Epiocular Human Cell Construct assay, a product containing a mixture of an aqueous extract of *A. millfolium* (described in Physical and Chemical Properties; 0.00045%) was found to not have irritation potential.[23]

Sensitization

Dermal – Non-Human

ACHILLEA MILLEFOLIUM EXTRACT

In a local lymph node assay using mice, a mixture containing an aqueous extract of *A. millfolium* (described in Physical and Chemical Properties; 25%, 50%, and 100% in dimethylformamide) was not a sensitizer.[24]

Dermal – Human

ACHILLEA MILLEFOLIUM EXTRACT

In a human repeated insult patch test (HRIPT; n = 107), a face moisturizer with self-tanner product containing an aqueous extract of *A. millefolium* (described in Physical and Chemical Properties; 0.00045%) applied neat was not irritating or sensitizing. 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.[25]

In an HRIPT (n = 108), a body splash product containing an aqueous extract of *A. millfolium* (described in Physical and Chemical Properties; 0.001133%) applied neat was not irritating or sensitizing.[26] There were no adverse events reported.

CLINICAL USE

Case Studies

A 44-year-old woman with a history of rhinononjunctivitis and asthma developed rhinitis, asthma, and urticaria symptoms after working seasonally with dried flowers for 6 years.[27] The skin prick test was positive for pollen from Cupressus semipervirens, Olea europaea. Lolium perenne. Salsola kali. Ariemisia vulgaris and Parietaria judaica and 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. 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 270nm an d320 nm using a 1% aqueous water extract.

Achillea 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%. There was no use information reported for: achillea millefolium flower extract, and achillea millefolium flower/leaf/stem extract.

Achillea 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 achillea 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 achillea 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 achillea 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 achillea millefolium leaf extract caused an increase in abnormal sperm at 1.2 g/kg/d. Daily sperm production and number of sperm were not affected. Aqueous achillea millefolium extract caused an increase in the number of malformations in *D. melanogaster* offspring. Achillea millefolium flower extract administered i.p. caused damage to the reproductive organs of male rats starting at 300 mg/kg/d.

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

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

An Epiocular Human Cell Construct assay was negative for ocular irritation at 0.00045%.

Achillea 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 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 powder and in eye lotion. While there is an LLNA irritation test of an *A. millefolium* extract at 1%, an HRIPT was performed only at 0.001133%. The Panel was concerned that LLNA assays are not considered reliable when testing mixtures (as plant extracts are) and can only be used as supporting evidence, not primary. So, the Panel considered that a finding that these ingredients would not be sensitizers was only supported up to the concentration of the HRIPT.

Formulators must minimize the overall concentrations of impurities and constituents of concern when more than one botanical ingredient is used in a cosmetic formulation. A cosmetic formulation may contain multiple botanical ingredients, each of which can contribute to the total concentration of pesticides, heavy metals, or other substances of concern in the botanical ingredients. As a result, industry must employ the procedures necessary to limit the concentrations of pesticide residues and heavy metals that result from combining botanical ingredients in the entire finished product, NOT just to each of the component ingredients in the formulation.

The Panel noted that among the constituents of these botanical ingredients were linalool (1 – 4000 ppm), thujone, quercetin, and hydroquinone. Linalool is a dermal irritant and has toxic effects to the liver and kidneys of rats. Thujone has neurological toxic effects; the suggested acceptable daily intake was 3 - 7 mg/kg/d.[28] Quercetin may be genotoxic. Hydroquinone causes skin depigmentation. However, the maximum concentration of use of *A. millefolium*-derived extracts in cosmetics was reported to be 0.04%. This indicates that exposures to these and other minor constituents of these ingredients in cosmetics would be below levels of toxicological concern.

However, the Panel also noted that the use of other botanical ingredients that may contain linalool, thujone, quercetin, and hydroquinone in combination with *A. millefollium* ingredients in a single formulation, could result in exposures that exceed levels of toxicological concern. 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.

[*This Discussion to be edited and confirmed at the June, 2013 Panel meeting.*]

DRAFT CONCLUSION

The following three achillea millefolium-derived ingredients are safe in the present practices of use in cosmetics up to 0.001133%:

Achillea millefolium extract,
Achillea millefolium flower extract*, and
Achillea millefolium flower/leaf/stem extract*.

*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.

[*This conclusion to be confirmed at the June, 2013 Panel meeting.*]

TABLES AND FIGURES

Table 1. CAS Nos., definitions, and functions of *A. millefolium* – derived ingredients.[29]

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*.[30]

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
Alpha-bisabolol	Leaf	1 - 915
Alpha-cadinol	Leaf	1 -15
Alpha-copaene	Leaf	
Alpha-curcumene	Leaf	
Alpha-humulene	Leaf	
Alpha-muurolene	Leaf	
Alpha-phellandrene	Leaf	
Alpha-pinene	Leaf	1 – 1000
Alpha-terpinene	Leaf	2 -1120
Alpha-terpineol	Leaf	1 – 80
Alpha-thujene	Leaf	
Alpha-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
Beta-caryophyllene	Leaf	1 - 65
Beta-caryophyllene-oxide	Leaf	1 - 30
Beta-cubebene	Leaf	1 - 15
Beta-elemene	Leaf	
Beta-farnesene	Leaf	
Beta-pinene	Leaf	1 - 720
Beta-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	
Delta-4-carene	Leaf	
Delta-cadinene	Leaf	0.2 – 8
Desacetylmatricin	Leaf	
Dihydroparthenolide	Leaf	
Essential oil	Leaf	250 – 16000
Folic-acid	Leaf	
Gamma-cadinene	Leaf	
Gamma-terpinene	Leaf	9 – 370
Geranial	Leaf	1 – 50
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	
Alpha-patchoulene	Plant	90
Alpha-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 - 125,000
Asparagine	Plant	

Austricin	Plant	
Balchanolide	Plant	
Balchanolide-acetate	Plant	
Benzaldehydecyanhydringlycoside	Plant	
Beta-carotene	Plant	
Beta-himachalene	Plant	50
Beta-sitosterol	Plant	
Beta-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-beta-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	
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	
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	
Water	Plant	823000
Zinc	Plant	
Anacyclin	Root	
Fat	Seed	223,000 - 334,000
Protein	Seed	286000

Table 3. 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.

REFERENCES

1. Andersen FA. Final report on the safety assessment of yarrow (Achillea millefoium) extract. *International Journal of Toxicology*. 2001;20(Suppl. 2):79-84.

2. Wichtl M. Herbal drugs and phytopharmaceuticals: A handbook for practice on a scientific basis. London: Medpharm Scientific Publishers, 1994.

3. Anonymous. 2011. Description of the product: Aqueous extract of *Achillea millefolium.*

4. Glasl, S., Mucaji, P., Werner, I., Presser, A., and Jurenitsch, J. Sesquiterpenes and flavonoid aglycones from a Hungarian taxon of the Achillea millefolium group. *Z.Naturforsch.C.* 2002;57(11-12):976-982.

5. Rohloff, J., Skagen, E. B., Steen, A. H., and Iversen, T. H. Production of yarrow (Achillea millefolium L.) in Norway: essential oil content and quality. *J.Agric.Food Chem.* 2000;48(12):6205-6209.

6. Candan, F., Unlu, M., Tepe, B., Daferera, D., Polissiou, M., Sokmen, A., and Akpulat, H. A. Antioxidant and antimicrobial activity of the essential oil and methanol extracts of Achillea millefolium subsp. millefolium Afan. (Asteraceae). *J.Ethnopharmacol.* 2003;87(2-3):215-220.

7. Agnihotri, V. K., Lattoo, S. K., Thappa, R. K., Kaul, P., Qazi, G. N., Dhar, A. K., Saraf, A., Kapahi, B. K., Saxena, R. K., and Agarwal, S. G. Chemical variability in the essential oil components of Achillea millefolium agg. from different Himalayan habitats (India). *Planta Med.* 2005;71(3):280-283.

8. Chemisches Laboraturium Dr. Kurt Richter GmbH. Raw material documentation on St. John's wort oil CLR (hypericum parforatum extract and olive (Olea europaea) oil and tocopherol. 1996. pp. 1-6.

9. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2011. Washington, DC: FDA.

10. Personal Care Products Council. 10-31-2012. Concentration of Use by FDA Product Category: *Achillea millefolium*-Derived Ingredients (August 2012 survey). 3 pages.

11. Labor L&S AG. 1998. Gene mutation assay in mouse lymphoma L5178Y TK+/- cells to trifluorothymidine-resistance with Extrapon 5-UK NEU (contains 0.5% Achillea Millefolium Extract). L+S Study Number: 10383997.

12. EVIC France. 2009. Summary of an acute oral toxicity study in the rat OECD 423 of a mixture containing an aqueous extract of *Achillea millefolium*.

13. Cavalcanti, A. M., Baggio, C. H., Freitas, C. S., Rieck, L., de Sousa, R. S., Da Silva-Santos, J. E., Mesia-Vela, S., and Marques, M. C. Safety and antiulcer efficacy studies of Achillea millefolium L. after chronic treatment in Wistar rats. *J.Ethnopharmacol.* 9-19-2006;107(2):277-284.

14. Petlevski, R., Hadzija, M., Slijepcevic, M., and Juretic, D. Toxicological assessment of P-9801091 plant mixture extract after chronic administration in CBA/HZg mice--a biochemical and histological study. *Coll.Antropol.* 2008;32(2):577-581.

15. Boswell-Ruys, C. L., Ritchie, H. E., and Brown-Woodman, P. D. Preliminary screening study of reproductive outcomes after exposure to yarrow in the pregnant rat. *Birth Defects Res.B Dev.Reprod.Toxicol.* 2003;68(5):416-420.

16. Dalsenter, P. R., Cavalcanti, A. M., Andrade, A. J., Araujo, S. L., and Marques, M. C. Reproductive evaluation of aqueous crude extract of Achillea millefolium L. (Asteraceae) in Wistar rats. *Reprod.Toxicol.* 2004;18(6):819-823.

17. Uysal, H., Kara, A. A., Algur, O. F., Dumlupinar, R., and Aydogan, M. N. Recovering effects of aqueous extracts of some selected medical plants on the teratogenic effects during the development of D. melanogaster. *Pak.J.Biol.Sci.* 5-15-2007;10(10):1708-1712.

18. Montanari, T., de Carvalho, J. E., and Dolder, H. Antispermatogenic effect of Achillea millefolium L. in mice. *Contraception*. 1998;58(5):309-313.

19. Takzare, N., Hosseini, M. J., Hamideh, Mortazavi S., Safaie, S., and Moradi, R. The effect of Achillea millefolium extract on spermatogenesis of male Wistar rats. *Hum.Exp.Toxicol.* 2011;30(4):328-334.

20. Vivotecnia Research SL. 2009. Summary of a bacterial reverse mutation assay of a mixture containing an aqueous extract of *Achillea millefolium*.

21. Anonymous. 2012. Summary of an *in vitro* micronucleus assay in V79 cells (mixed population method) of a mixture containing an aqueous extract of *Achillea millefolium.*

22. Jovanovic, M., Poljacki, M., Duran, V., Vujanovic, L., Sente, R., and Stojanovic, S. Contact allergy to Compositae plants in patients with atopic dermatitis. *Med.Pregl.* 2004;57(5-6):209-218.

23. Institute for In Vitro Sciences Inc. 2006. Topical application ocular irritation screening assay using the Epiocular™ human cell construct of an indoor tanning product containing 0.00045% Achillea Millefolium Extract. Study Number: 06AG64, 05AH41.015110. 11 pages.

24. Harlan. 2009. Summary of a local lymph node assay (LLNA) in mice of a mixture containing an aqueous extract of *Achillea millefolium.*

25. RTCS Inc. 2006. Clinical safety evaluation human repeated insult patch test (HRIPT) of an indoor tanning product containing 0.00045% Achillea Millefolium Extract. RCTS Study No. 2114.

26. Clinical Research Laboratories Inc. 2009. Repeated insult patch test of a body and hand spray containing 0.001133% Achillea Millefolium Extract. CRL Study Number: CRL41409-2.

27. Compes, E., Bartolome, B., Fernandez-Nieto, M., Sastre, J., and Cuesta, J. Occupational asthma from dried flowers of Carthamus tinctorious (safflower) and Achillea millefolium (yarrow). *Allergy*. 2006;61(10):1239-1240.

28. Pelkonen O, Abass K, and Wiesner J. Thujone and thujone-containing herbal medicinal botanical products: Toxicological assessment. *Regulatroy Toxicology and Pharmacology*. 2013;65(1):100-107.

29. Gottschalck TE and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 14 *ed*. Washington, DC: Personal Care Products Council, 2012.

30. Duke J. Dr. Duke's Phytochemical and Ethnobotanical Databases; Achillea millefolium L. - Asteraceae. http://sun.ars-grin.gov:8080/npgspub/xsql/duke/plantdisp.xsql?taxon=18. Date Accessed 10-30-2012.

Personal Care Products Council
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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: January 2, 2013

SUBJECT: Updated Concentration of Use by FDA Product Category: *Achillea millefolium*-Derived Ingredients

1101 17th Street, N.W., Suite 300 | Washington, D.C. 20036-4702 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Concentration of Use by FDA Product Category*

Achillea Millefolium Extract
Achillea Millefolium Flower Extract
Achillea Millefolium Flower/Leaf/Stem Extract
Achillea Millefolium Flower Water
Achillea Millefolium Oil

Ingredient	FDA Code†	Product Category	Maximum Concentration of Use
Achillea Millefolium Extract	02A	Bath oils, tablets and salts	0.0001-0.002%
Achillea Millefolium Extract	02B	Bubble baths	0.002%
Achillea Millefolium Extract	03D	Eye lotion	0.03%
Achillea Millefolium Extract	03F	Mascara	0.00002%
Achillea Millefolium Extract	04B	Perfumes	0.0001%
Achillea Millefolium Extract	05A	Hair conditioners	0.00004-0.005%
Achillea Millefolium Extract	05D	Permanent waves	0.00001%
Achillea Millefolium Extract	05E	Rinses (noncoloring)	0.00005%
Achillea Millefolium Extract	05F	Shampoos (noncoloring)	0.000005-0.006%
Achillea Millefolium Extract	05G	Tonics, dressings and other hair grooming aids	0.0006%
Achillea Millefolium Extract	05I	Other hair preparations (noncoloring)	0.0006-0.003%
Achillea Millefolium Extract	06A	Hair dyes and colors (all types requiring caution statement and patch test)	0.00001%
Achillea Millefolium Extract	06C	Hair rinses (coloring)	0.00001%
Achillea Millefolium Extract	06G	Hair bleaches	0.00002%
Achillea Millefolium Extract	07B	Face powders	0.00005%
Achillea Millefolium Extract	07C	Foundations	0.00002%
Achillea Millefolium Extract	07E	Lipstick	0.00001-0.01%
Achillea Millefolium Extract	07H	Makeup fixatives	0.0005%
Achillea Millefolium Extract	08C	Nail creams and lotions	0.00002%
Achillea Millefolium Extract	08E	Nail polish and enamel	0.0002%
Achillea Millefolium Extract	08F	Nail polish and enamel removers	0.00002%

Achillea Millefolium Extract	11A	Aftershave lotion	0.0002%
Achillea Millefolium Extract	11E	Shaving cream (aerosol, brushless and lather)	0.0002%
Achillea Millefolium Extract	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0005-0.03%
Achillea Millefolium Extract	12C	Face and neck creams, lotions and powder not spray	 0.01%
Achillea Millefolium Extract	12D	Body and hand creams, lotions and powder not spray spray	 0.01-0.04% 0.001%
Achillea Millefolium Extract	12F	Moisturizing creams, lotions and powders not spray	 0.0002%
Achillea Millefolium Extract	12G	Night creams, lotions and powders not spray	 0.03%

*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 2012

Table prepared October 25, 2012

Updated January 2, 2013: 02A added high concentration 0.002%; added 02B; added 07H; added 12D spray

VCRP Use Data for Achilea Millefolium 2013

05F - Shampoos (non-coloring)	ACHILLEA MILLEFOLIUM	3
02A - Bath Oils, Tablets, and Salts	ACHILLEA MILLEFOLIUM EXTRACT	4
02B - Bubble Baths	ACHILLEA MILLEFOLIUM EXTRACT	1
03D - Eye Lotion	ACHILLEA MILLEFOLIUM EXTRACT	1
03G - Other Eye Makeup Preparations	ACHILLEA MILLEFOLIUM EXTRACT	1
04C - Powders (dusting and talcum, excluding aftershave talc)	ACHILLEA MILLEFOLIUM EXTRACT	1
05A - Hair Conditioner	ACHILLEA MILLEFOLIUM EXTRACT	13
05B - Hair Spray (aerosol fixatives)	ACHILLEA MILLEFOLIUM EXTRACT	1
05C - Hair Straighteners	ACHILLEA MILLEFOLIUM EXTRACT	1
05F - Shampoos (non-coloring)	ACHILLEA MILLEFOLIUM EXTRACT	12
05G - Tonics, Dressings, and Other Hair Grooming Aids	ACHILLEA MILLEFOLIUM EXTRACT	7
05H - Wave Sets	ACHILLEA MILLEFOLIUM EXTRACT	1
05I - Other Hair Preparations	ACHILLEA MILLEFOLIUM EXTRACT	2
07B - Face Powders	ACHILLEA MILLEFOLIUM EXTRACT	2
08B - Cuticle Softeners	ACHILLEA MILLEFOLIUM EXTRACT	1
10A - Bath Soaps and Detergents	ACHILLEA MILLEFOLIUM EXTRACT	2
10E - Other Personal Cleanliness Products	ACHILLEA MILLEFOLIUM EXTRACT	4
12A - Cleansing	ACHILLEA MILLEFOLIUM EXTRACT	9
12B - Depilatories	ACHILLEA MILLEFOLIUM EXTRACT	1
12C - Face and Neck (exc shave)	ACHILLEA MILLEFOLIUM EXTRACT	17
12D - Body and Hand (exc shave)	ACHILLEA MILLEFOLIUM EXTRACT	12
12F - Moisturizing	ACHILLEA MILLEFOLIUM EXTRACT	19
12G - Night	ACHILLEA MILLEFOLIUM EXTRACT	4
12H - Paste Masks (mud packs)	ACHILLEA MILLEFOLIUM EXTRACT	1
12I - Skin Fresheners	ACHILLEA MILLEFOLIUM EXTRACT	6
12J - Other Skin Care Preps	ACHILLEA MILLEFOLIUM EXTRACT	7
13B - Indoor Tanning Preparations	ACHILLEA MILLEFOLIUM EXTRACT	2
		135

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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: December 4, 2012

SUBJECT: Comments on the Draft Report on *Achillea millefolium* -Derived Ingredients Prepared for the December 10-11, 2012 CIR Expert Panel Meeting

Key Issues

As no search strategy is included in this Panel book, it is not clear if CIR staff completed additional literature searches for the *Achillea millefolium*-derived ingredients.

Please consider the botanical template provided by the CIR SSC when completing CIR reviews of plant-derived ingredients. This report should also include some basic information about the plant, e.g, what type of plant it is, what does it look like, where does it grow, and the report should include some information on historic uses of this plant. Please see the reference books in Carol Eisenmann's office for this information. If this information was in the original CIR report, it should be mentioned in the summary of the original safety assessment.

p.3, 6 - The UV absorbance value given in the report is wrong. The data memo correctly describes the UV absorbance as "a peak around 190 nm and small shoulders at 270 nm and 320 nm". Please indicate that is the absorbance for a 1% aqueous dilution of the water extract of *Achillea millefolium* described in reference 2. Since the CIR Expert Panel requested information on UV absorption, it should also be mentioned in the Summary.

Additional Comments

Memo - The date on the memo (June 11, 2012) is incorrect.

Memo, History, p.3 - "ISO subjects" needs to be corrected to "150 subjects"

p.3 - The summary of the Original Safety Assessment should include information that is useful to the current assessment. As the listed functions have changed restating that Achillea Millefolium Extract "functions as a biological additive" is not necessary.

p.3 - The analysis of the aqueous extract that is used as a cosmetic ingredient should be described more completely. It would be helpful to state that a phytochemical profile was completed. This analysis is important for what they did not find, e.g., alkaloids (important plant toxicants) in addition to what they found. Please indicate that the luteolin level was only a few ppm. Please correct the spelling of "L-alamini"

p.4 - Please correct the spelling of "zanthan"

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p.4, 6, 12, Table 3 - The new concentration of use information (2012 survey) provided on October 31, 2012 (found in revised wave 2) needs to be added to the report and provided to the CIR Expert Panel.

p.4 - The statement "No new toxicokinetics data were submitted." implies that CIR staff did not look for new data. If CIR staff looked for information, the statement should be changed to "No new toxicokinetics data were identified."

p.5 - Please name the other plants that were included in the multi-herb mixture (reference 11). Although the study may have used the phrase "catalytic concentration of AST", "serum activity" would be more appropriate.

p.5 - The following sentence is not complete: "The rats were killed and necropsied after 90 days, in particular the testes, epididymis, prostate and seminal vesicle (including coagulating glands)."

p.6 - If available, please include the type of extract used in reference 19.

p.6 - In the description of the LLNA, please include the solvent (dimethylformamide) used.

p.6 - The type of extract used in the products tested in HRIPTs was not stated. It is not correct to state that these products contained the aqueous extract described. Please note that the product tested in reference 22 was an indoor tanning product; therefore, the hyperpigmentation observed is not surprising.

p.7 - In the Summary, please include the route of exposure and the gestation days of exposure in the description of the developmental toxicity study. The HRIPT of the indoor tanning product (0.00045% Achillea Millefolium Extract) still needs to be added to the Summary.

p.8-11, Table 2 - Table 2 would be more useful if it was sorted by plant part, then alphabetically by component.

p.12, Table 4 - Please define "na"