Safety Assessment of Chamomilla Recutita-Derived Ingredients as Used in Cosmetics

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

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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Memorandum

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

At the September 9-10, 2013 CIR Expert Panel meeting, the Panel concluded that chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower powder, chamomilla recutita (matricaria) flower water, and chamomilla recutita (matricaria) flower oil are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing. The Panel also concluded that the available data are insufficient for determining that chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower/leaf extract, chamomilla recutita (matricaria) flower/leaf/stem extract, chamomilla recutita (matricaria) flower/leaf/stem water, chamomilla recutita (matricaria) leaf extract, and chamomilla recutita (matricaria) oil are safe under the intended conditions of use in cosmetics. The issuance of a tentative report with these conclusions was approved.

Included in this package for your review is the Draft Final Report, the CIR report history, Literature search strategy, Ingredient Data profile, 2013 FDA VCRP data, Minutes from the September 2013 Expert Panel Meeting, Comments from the Council, and Unpublished data received from the Council. The following unpublished data/comments were received, and relevant information is underlined in the draft final report:

(1) Comments from the Council (pcpc1 data file)
(2) Use concentration data from a Council survey – previously reviewed (data1 pdf file),
(3) HRIPT data summary on towelettes containining 0.01% chamomilla recutita (matricaria) extract (data2 pdf), and
(4) HRIPT data summary on a hair gel styling mist containing 0.00006% chamomilla recutita (matricaria) flower/leaf extract (data 2pdf)

As noted above, human skin irritation and sensitization data on products containing chamomilla recutita (matricaria) extract and chamomilla recutita (matricaria) flower/leaf extract, and comments from the Council and BASF were received. All comments have been addressed. According to one of the comments, the discussion should state that the ingredients considered safe are "safe when formulated to be non-sensitizing," as opposed to simply "safe as used," because:

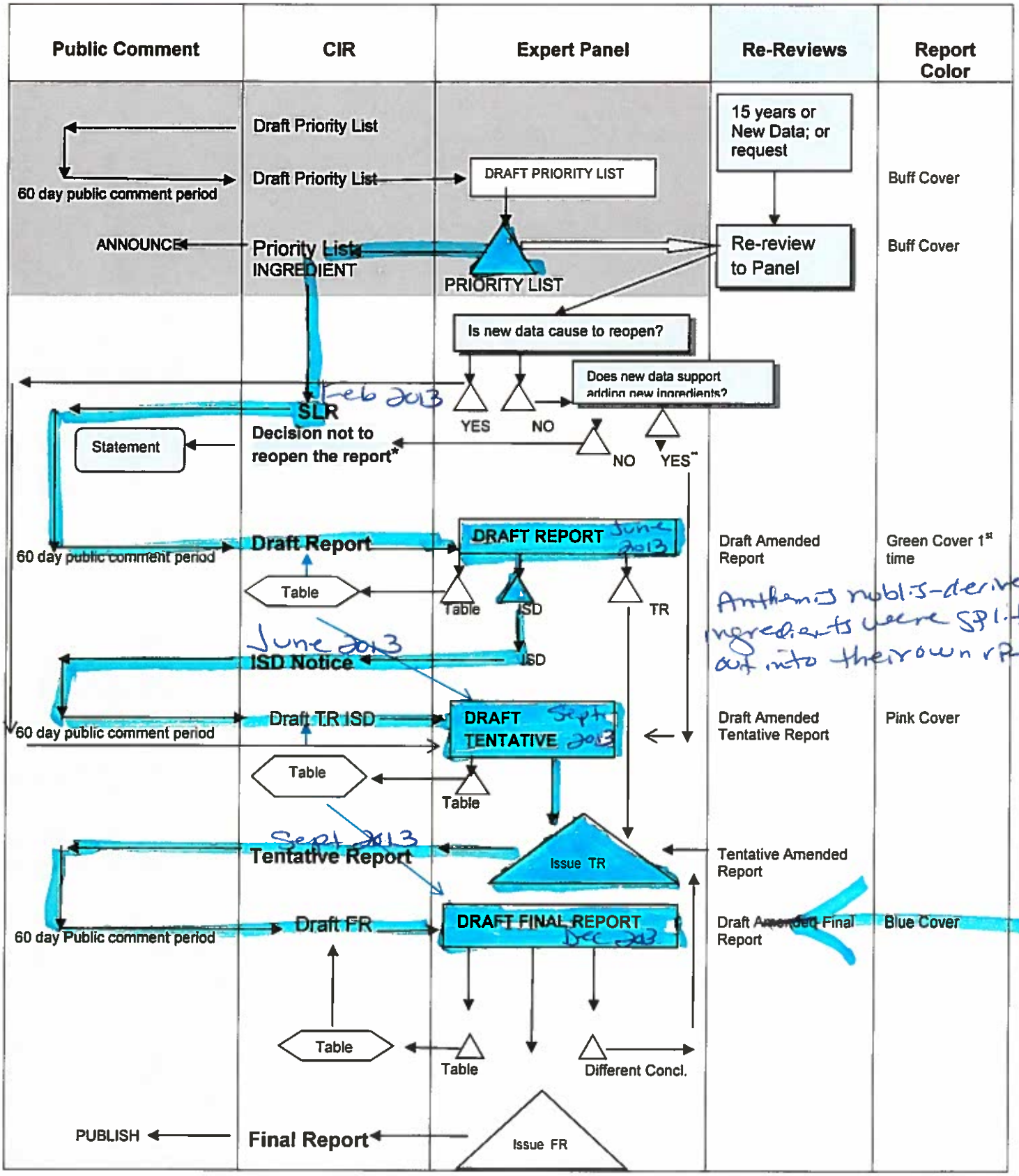
- The composition, including concentrations of plant constituents that have the potential to be sensitizing (e.g., sesquiterpene lactones), can be quite variable in the ingredients, depending on the growth conditions of the plant and the extraction methods used to produce the ingredient.
- The available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

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

After considering the new HRIPT data summaries along with other the available data, the Panel needs to determine whether a final report with the conclusions stated in the first paragraph should be issued at this Panel meeting.

SAFETY ASSESSMENT FLOW CHART

Chamomilla Recutita — Dec 2013



CIR History of:

Chamomile Ingredients

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

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

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

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

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

The Panel also determined that the available data are insufficient for evaluating the safety of the *Chamomilla recutita*-derived ingredients in cosmetic products and that the the following data are needed: (1) Skin irritation and sensitization data on chamomilla recutita (matricaria) flower extract at a use concentration of 10%. This insufficient data announcement became publicly available on June 14, 2013.

The Panel also agreed that data on bisabolol and azulene, both components of chamomilla recutita (matricaria) flower oil, from CIR final safety assessments on these ingredients might be useful in assessing the safety of chamomilla recutita (matricaria) flower oil, and that data on bisabolol should be incorporated into this safety assessment. However, it was agreed that azulene (insufficient data conclusion) should be mentioned in the discussion. Additionally, because one reported constituent, β-farnesene, is an insecticide, and toxicity has been reported for other components, namely linalool and quercetin, associated with *Chamomilla recutita*, the chamomile safety assessment should focus on these constituents. The Panel noted that the pesticides and heavy metals content should be below levels of toxicologic concern.

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

The following data were received after public availability of the insufficient data announcement: (1) Human skin irritation study on a cuticle softener containing 0.3% chamomilla recutita (matricaria) flower extract; (2) Study on the assessment of plants/herbs/herb extracts and their components for use in animal production; (3) Skin sensitization study on a shave balm containing 0.2% chamomilla recutita (matricaria) flower extract; and (4) Updated use concentration data received from the Personal Care Products Council.

The Panel agreed that the HRIPT data on products containing chamomilla recutita (matricaria) flower extract can be used to evaluate the safety of chamomilla recutita (matricaria) flower-derived ingredients over the range of use concentrations reported. For chamomilla recutita (matricaria) ingredients derived from the whole plant, stem, or

leaf, the Panel determined that, in the absence of chemical characterization data, the available data are insufficient for evaluating the safety of these ingredients.

The Panel also agreed that the discussion section of the safety assessment should be expanded to include any concerns relating to the toxicity of chamomilla recutita (matricaria) plant components (e.g., linalool, linalool acetate, farnesene, azulene, terpenes, and terpenoids). This decision was based on concern over potential additive effects of toxic components that may result from the presence of various botanical ingredients in a single product. Furthermore, the Panel noted that plant components of toxicological concern should not exceed any limitations that may have been established by the International Fragrance Association (IFRA). The Panel also stressed that products should be formulated to minimize the presence of pesticide and heavy metal impurities that could result from the presence of chamomilla recutita-derived ingredients.

The CIR Expert Panel concluded that chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower powder, chamomilla recutita (matricaria) flower water, and chamomilla recutita (matricaria) flower oil are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing. The Panel also concluded that the available data are insufficient for determining that chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower/leaf extract, chamomilla recutita (matricaria) flower/leaf/stem extract, chamomilla recutita (matricaria) flower/leaf/stem water, chamomilla recutita (matricaria) leaf extract, and chamomilla recutita (matricaria) oil are safe under the intended conditions of use in cosmetics. The issuance of a tentative report with these conclusions was approved.

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

The following unpublished data were received and have been added to the draft final report: (1) HRIPT on towelettes containing 0.01% chamomilla recutita (matricaria) extract and (2) HRIPT on a hair gel styling mist containing chamomilla recutita (matricaria) flower/leaf extract. Comments from the Council were also received and have been addressed.

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

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

SciFinder Searches

Search Terms

Chamomilla Recutita (Matricaria) Extract
Chamomilla Recutita (Matricaria) Flower
Chamomilla Recutita (Matricaria) Flower Extract
Chamomilla Recutita (Matricaria) Leaf Extract
Chamomilla Recutita (Matricaria) Flower/Leaf Extract
Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Extract
Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Water
Chamomilla Recutita (Matricaria) Flower Oil
Chamomilla Recutita (Matricaria) Flower Powder
Chamomilla Recutita (Matricaria) Flower Water
Chamomilla Recutita (Matricaria) Oil
Chamomilla recutita
Matricaria recutita
Chamomile

Search Updates

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

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

Chamomilla Recutita-Derived Ingredients

DR. BELSITO: So chamomile, by which we mean matricaria recutita, not the Roman chamomile. I guess the first comment that -- well, just to tell you where we are with this. I can't find it in my report. But basically we looked at this in June and it was lumped with anthemis nobilis, and we said wait a minute. These are two different plants, and we need to separate them out and look at them separately. So that's what we did. For the chamomilla recutita, we asked for sensitization at 10 percent and composition of ingredients other than the oil and sensitization and irritation data at the highest level of use. So we've gotten some new unpublished skin irritation and sensitization data. We've updated the use concentration data. We also said, wait a minute. This chamomilla recutita has a lot of bisabolol in it, and let's look at our safety report on that. So that's where we are here.

I guess my first comment on this report is first of all, kamillosan is referenced in both this report and in the anthemis nobilis report. In the anthemis nobilis report, it's said to contain 10.5 percent anthemis nobilis. And then it starts showing up in this report. So I don't think it's both. So we need to clarify it. I mean my reading of the anthemis nobilis report suggests that kamillosan is probably anthemis nobilis; however, having said that, my understanding of the alternative medical use for "chamomile," namely chamomile tea and all of these topical and nutritional supplements that are available in Europe, are actually chamomilla recutita; that when people talk about chamomile for botanical drug use, that's the species they're referring to. Having said that, I agree when we're -- if we're going to put data in where we're not sure, where it just says "an extract of chamomile" or "a chamomile tea was applied to tinctures to the eyes of reproducing conjunctivitis," either it shouldn't go in either report or it may be should go in both reports and say we're just not sure whether this is matricaria or chamomilla recutita or it's anthemis nobilis. But kamillosan definitely has to be one or the other, and we should be able to see that from the manufacturer.

DR. SNYDER: I agree. I had the same issue with regard to the studies in which we don't know which species was used in the testing. So it either has to go in both reports or it has to be deleted from both reports.

DR. BELSITO: Right now it's in both reports pretty much, and that may be okay because by and large they sort of add to support safety of one or the other. But I also think maybe when we're putting them in, somehow there should be a subheading that says "Chamomile Species Unknown" or something so we separate it out and it's a weak component of that part of the document, if we're going to keep it in.

MR. JOHNSON: Dr. Belsito, what particular study are you referring to with the kamillosan?

DR. BELSITO: Just put "find kamillosan." You'll find it in both the anthemis nobilis documents where at one point -- I mean when we get to the anthemis nobilis, you'll see it, but it says that kamillosan (10.5 percent). I can look it up right now actually. Let me just close out of here and go to anthemis nobilis. Kamillosan is with two "ls," right? So on document 25, not the page number but the document, but 25 of the.pdf, the second paragraph. On anthemis nobilis it says "kamillosan ointment (containing extracts and oil of anthemis nobilis 10.5 percent) to treat cracked nipples." So that's in the anthemis nobilis report. And then in the chamomile report, again you have -- well, I thought I saw kamillosan here.

MR. JOHNSON: Actually it's right before the use section, the paragraph immediately above that.

DR. BELSITO: Oh, I just misspelled it and that's why I didn't find it. Yeah, so just above it says "kamillosan, an alcoholic extract of chamomile flowers that contains 100 milligrams of chamomilla recutita." I mean maybe it contains both, but I think we need to verify that. It seems to me to be strange that it would be 10.5 percent anthemis nobilis and 150 milligrams of chamomilla recutita. Maybe it is, I don't know, but it was just strange that it appeared in both reports.

And then under Non-Cosmetic Use you talk about "Kamillobad and mouth sprays, Kamillosan M spray, containing chamomile extracts." So I think you need to get the

MSDSs or whatever for those products and check them again and make sure that they're in the proper report. It comes up in case reports also in kamillosan.

I think, again, my understanding is that the alternative medical uses for chamomile are all matricaria or chamomilla recutita, not anthemis nobilis, but I may be wrong.

DR. SNYDER: So going back to chamomilla recutita, we're still insufficient there.

DR. BELSITO: Okay, let me go back through the whole thing. Go ahead, Paul, while I go back through that document.

DR. SNYDER: Well, we had previously gone -- in June we had gone insufficient for skin irritation and sensitization with the flower extract at 10 percent, and we received it at.3 and.2 -- irritation at.3 and sensitization at.2. And then we did get another -- on the second Wave we got an eye lotion at.4 percent with flower extract on 100 individuals. So we're still --

DR. LIEBLER: So my question is was the 10 percent real? That's so high.

MR. JOHNSON: No.

DR. SNYDER: It's at 0.5.

DR. ANSELL: It's been corrected.

DR. LIEBLER: Oh, okay, I didn't see that anywhere.

MR. JOHNSON: Yeah, it's 0.5.

DR. SNYDER: Is the highest use now?

MR. JOHNSON: Yes.

DR. ANSELL: The new maximum is 0.5 flower extract in lipstick.

DR. BELSITO: Well, I thought, though, it was -- well, first of all, again, in the introduction, we need to list what we're reviewing. It says "ingredients as used (German chamomile)," "information relevant to verify 11 chamomile ingredients as used in cosmetics." I think we need to list the ingredients right up front that we're discussing because it's not in the title. And it's like you start the document, you really don't know what the heck you're going to be looking at.

DR. SNYDER: This one has the missing abstract.

DR. BELSITO: Yeah, it's missing an abstract as well, but I mean that's because it's really the first time we're looking at it when an abstract hasn't been generated. But I think as a matter of just boilerplate, except when it's 5 million products like the PEG-PPG document where you can just reference Table 1 or some table in the document, I think what we're reviewing when it's only five or six or seven ingredients should be listed up front in the discussion -- I mean in the introduction.

I also think that it remains insufficient, but not for sensitization and irritation. I think we have all the information on the flower ingredients, and we have no information on the plant and stem and really whole extract, and they're not really used in cosmetics. If you look at what's used, probably because the plant and the stem of chamomile are not used in cosmetics. It's the flowers that are used. But I don't think that we can rule on the safety of the plant stem because when you look, we have no composition data and there's maybe one or two studies that just say "chamomilla recutita extract," which I would suspect is the flower extract, but we don't know what the heck it's an extract of.

So I would say that all of the flower ingredients, which are most of them, and I think pretty much all of them that are reported to be in use are safe. But anything from the stem and the leaf is insufficient, at least at this time, for what is the chemical composition of a matricaria recutita stem and leaf.

DR. LIEBLER: So what's really missing is the organics.

DR. BELSITO: Yeah.

DR. LIEBLER: If you look at Table 5, you've got very spotty coverage of the organics. You've got the apigenin under chamomilla recutita flower extract and then nothing until you get to caffeic acid whereas you've got pretty extensive data on the flower oil.

DR. SNYDER: What about the azulene issue also, Don?

DR. BELSITO: I think that is going to be addressed by the botanical boilerplate. And I think, again, it's present in low amounts and the concentrations used are low. It's.5 maximum leave-on, is that correct?

DR. SNYDER: .4, yeah.

DR. BELSITO: .4.

DR. LIEBLER: So, Don, now that the maximum use concentration is down to a half a percent, you're okay with the irritation and sensitization data that we have in hand? We're not quite that high, but we're close?

DR. BELSITO: Yeah, I mean I think that what you're seeing here are -- it gets very confusing because people -- a lot of the case reports are people who are sensitive to compositae, which chamomilla recutita is a member of that genus of families. So they patch-test positive to compositae mix. Then they bring them back and they are patching them to various species of the compositae plant, and so you're seeing positive reactions there.

Again, in Europe these are used as alternative medicines, if that's the correct word. So you see a lot of products like kamillosan, which are containing higher levels of this ingredient than you would find in a cosmetic product. And they're being put on damaged skin, which is why people are using them, and then you're seeing some sensitization come out. But I think in the animal studies and the naïve studies, I think we're fine.

DR. LIEBLER: Okay.

DR. BELSITO: Is there one particular study or is it just the bulk of case reports?

DR. LIEBLER: No, no. I wanted to get your impression of this because until just a few minutes ago, I thought well, we're nowhere close to 10 percent. We're still insufficient on irritation and sensitization. Now I think we're close, and I wanted to get your reaction to it.

DR. SNYDER: So where are we on the use concentration because the report now says -- I mean I'm reading here and now it says "any concentrations up to 1.2 percent of the flower." So where are we getting this.5 percent number that was --

DR. ANSELL: From our -- no, it didn't get into the report, but Carol's reporting now the new maximum is 0.5 flower extraction in lipstick products. The report is not correct when it states the maximum use concentration is 1.2 percent of the flower. The 1.2 percent should be 0.5 percent. And in Wave 2 and HRIPT it's.4 percent.

DR. SNYDER: Yeah, that's the one I referred to.

DR. BELSITO: So in the use --

DR. SNYDER: The Cosmetic Use section.

DR. BELSITO: So it's the flower extract -- no, it's the flower or --

DR. SNYDER: This says "the flower."

DR. BELSITO: Right.

DR. SNYDER: In the report.

DR. BELSITO: It says, "Hair Non-Coloring 1.2."

DR. ANSELL: And that should be.5.

DR. BELSITO: And that should be.5. And then lipstick?

DR. ANSELL: Similarly,.5.

DR. BELSITO: For the flower? We don't have a lipstick use.

DR. ANSELL: Flower extract.

DR. BELSITO: Flower extract. Incidental ingestion, that is.5. I think the.4 -- so the highest reported use is going to be.5. There's a.61 for dermal contact for the extract. But, again, the extract has a total of six reported uses. Everything else is flower, flower extract, flower/leaf extract, flower oil, flower water. The flower/leaf extract is probably going to be the biggest issue because there's 349 uses. But, again, we don't know what's in the leaf. If you look, the flower is very well defined. For the chemical composition you've got the extract, flower oil, and flower. And if you scroll down the extract there's not a lot there. Caffeic acid, apigenin, apigenin-7-glucoside --

DR. LIEBLER: Yeah, it's very spotty.

DR. BELSITO: It's extremely spotty. Obviously, there's a lot more in there that we don't know. So I don't know how we can say because the composition of the flower and the composition of the rest of the plant is more than likely I think very different in this case.

DR. LIEBLER: Well, we just don't know.

DR. BELSITO: Right.

DR. LIEBLER: I mean we just don't know, so I think as part of our due

diligence to ask for the data.

DR. BELSITO: So this was the first time we're seeing the report, so I would say the flower ingredients -- the flower oil, the flower extract, everything that is derived from the flower -- is safe as used. And anything derived from the full plant -- the leaf, the stem -- is insufficient at this point for chemical composition.

So, Dan -- in your draft discussion, Wilbur, in the last sentence, I said "The Panel agreed that, given the current use concentrations to the ingredients derived from chamomilla recutita flowers, these components" not "should," but "would be present at levels that are below the threshold of toxicological concern. The safety of ingredients derived from c-recutita leaf and stem are insufficient for chemical composition." Paul?

DR. SNYDER: So this issue was also brought up by the Council. I think we're using the threshold of toxicological concern a little too loosely. I think that is a very defined threshold. I can of think of many instances -- I understand what we're trying to say, but I think we're using it inappropriately. So I think we have to be cautious about that.

DR. ANSELL: And that is our concern as well, that TTC as it's used, capital T-T-C, is a very defined process. What we really mean in these cases is not the toxicologic concern, but we're not concerned at the levels they're present. And so conceptually what we find, we just don't like that specific terminology. Just turning it to TCT would be okay.

DR. BELSITO: Toxicologic concern threshold?

DR. ANSELL: No, we're just not --

DR. LIEBLER: No, that would be. So I think the suggestion after I read the memo from Council and I basically agree with the point is that by throwing the term "threshold of toxicologic concern," we're using that as a shorthand for a more specific statement about our conclusion. So I agree that in cases where we can say "below the levels likely to cause sensitization," "below the levels likely to cause irritation," et cetera, so that we could be a little bit more specific in our language rather than just laying down the TTC card every time.

DR. BELSITO: So are you making an editorial change someplace, Dan?

DR. LIEBLER: Well, "The Panel concluded that these components are not present at levels of concern." We're saying the same thing. We're just using --

DR. BELSITO: What page are you on?

DR. LIEBLER: Under the draft discussion.

DR. GILL: Let me clarify something. I think I heard Linda say "below the levels of toxicologic concern." Is that getting back into the language the Council had and the Panel is uncomfortable with, or should we stick to something more along the lines of what Dan just mentioned, the low levels that could cause concern?

DR. LORETZ: I mean our specific concern was that those were --

DR. GILL: So we sort of steer away from "threshold."

DR. LORETZ: Right, right.

DR. GILL: Because I think below the levels of toxicologic concern include --

DR. BELSITO: So just below "any" level of toxicologic concern or "the" levels? I mean what is -- because there are a number of toxicologic endpoints. I guess what conveys best is for each and any toxicologic endpoint that you would be concerned about because in some cases we're talking about genotox and in other cases we're talking about sensitization that are below --

DR. SNYDER: So "The Panel concluded these components are present at levels that are below --

DR. BELSITO: "Would be present at levels below --

DR. GILL: Or "not present at levels of toxicologic concern."

DR. LIEBLER: I think the problem with this sentence is that this is a draft discussion. These are sort of bullet points that would be included. This isn't the actual, probably the actual language we will have in the discussion when we review the document next time.

So let me just make a point. You've got compounds lumped in here that may produce sensitization, others that have insecticidal activity, and some maybe genotoxic or carcinogenetic. So these are different endpoints. And I think rather than just lump them together and say "below the threshold of toxicological concern," we perhaps deal with each of the concerns and rephrase as "below the levels likely to produce any risk of genotoxicity," "below the levels

likely to produce sensitization," et cetera. So when they develop the discussion, you refer to the compounds of interest with respect to the endpoints that we're concerned about.

So I think the Council's point is in a draft discussion like this and not end up as more final language. But this would be inappropriate to have this whole laundry list of compounds and different effects and then just say "below the levels of toxicological concern" for all of them.

Jay, am I reading your message right?

DR. ANSELL: Well, that's it. It's like the Xerox people. It's okay to make a photocopy, just don't call it a Xerox. The language we agreed to in the last report was not of concern. I think that would work here.

DR. SNYDER: I agree. I don't understand what you're saying, Dan, but I think then it would become a huge discussion that would have to be updated.

DR. LIEBLER: Well, it doesn't have to be.

DR. SNYDER: To go through all the genotox, every little thing. We're just saying that we see the components of these ingredients, and then we just concluded "these components are not at levels of toxicologic concern in cosmetics."

DR. ANSELL: Right. "At these levels they are not of concern."

DR. SNYDER: "In cosmetics." Always "in cosmetics."

DR. BELSITO: Well, I think that as with the issues that we were discussing about having frameworks for abstracts and a boilerplate, we'll get to that when we discuss the botanical ingredients.

DR. ANSELL: We can come back to this.

DR. BELSITO: Unfortunately, I don't think that that is until the end of our session today. So I think we can just highlight the draft discussion and say it will have to be worded according to whatever boilerplate we come up on.

DR. LIEBLER: Right. I think trying to wordsmith this now at this point is a waste of time.

DR. BELSITO: So we'll go to the boilerplate for botanicals, but do we all agree that the flower ingredients are safe, but anything from the plant -- the stem, the leaf -- is unsafe until we have composition?

DR. SNYDER: I just want to go back to -- Wilbur has separated out very clearly what we had data for and what was used, and I'd like to go back to that because --

DR. BELSITO: You're talking about the little roadmap?

DR. SNYDER: Yeah, this here.

DR. BELSITO: If you look at basically the uses, the only one that has got a large number of uses is flower/stem or leaf, I forget which, and that's Table 6. You've got six reported uses for what's just called the extract and then you have mostly flower. The only other one is what's listed as a flower/leaf and that's a huge number, 349. I mean I suppose we could finesse that because the highest use is.02, and we know what's in the flower. But if we finesse that, then -- I suppose we could argue that we're not finessing the extract because it's up to.61 on mucous membranes. But I think -- this is really the first time we're seeing the document. I would say the flower ingredients are safe, and for the stem and leaf and the whole extract we need available composition data.

MR. JOHNSON: But Dr. Belsito, this isn't actually the first time because the last time the anthemis nobilis and chamomilla recutita ingredients were in one report. So we separated --

DR. BELSITO: No, I understand, but it's the first time we're seeing the report as chamomilla recutita.

MR. JOHNSON: Yes.

DR. BELSITO: So my understanding is this is almost like it's the first time we're seeing it. Is that not correct? I mean there was no decision made -- I guess we did issue some insufficiencies last time --

DR. ANSELL: Which were addressed.

DR. BELSITO: Yeah, so I have no clue how you consider this document that we're seeing. But I think if this is going out as -- it will go out as an insufficient whether it's a pink, a green, a final, I don't care.

DR. LIEBLER: So the insufficiency -- if the insufficiencies were for irritation, sensitization, concentration of use, and for composition, we may be okay on irritation, sensitization, and concentration of use. But we're definitely not okay on composition.

DR. BELSITO: Yes.

DR. LIEBLER: So we're still insufficient on that key point.

DR. BELSITO: Yeah, unless you would like something of that.6 for the extract because we have.4 on the lipstick right now.

DR. LIEBLER: Right, and we have -- Jay just indicated.5, but I don't know what that was for. He said that that was the latest information.

DR. BELSITO: .5 is the Hair Non-Coloring.

DR. LIEBLER: Hair and Non-Coloring, okay.

DR. BELSITO: So it reduced the highest use concentration down to now.61 for the extract and.5 for the flower ingredients.

DR. LIEBLER: So are we still short of sufficient on sensitization?

DR. BELSITO: We have an HRIPT on 104 patients at.4 percent. And I think that, given the fairly widespread use of botanical products particularly in Europe that are actually marketed as over-the-counter drugs, if that word is appropriate to the European market and the limited number of reports that we're seeing and the literature, I think it's okay.

DR. LIEBLER: So you think we're close enough.

DR. BELSITO: Well, if you want to be hardnosed, we could ask for --

DR. LIEBLER: No, no. This is why I asked the question, because I defer to your judgment on this. If you feel that that's close enough and you have a better sense of whether reports are in the literature on adverse reactions to these as used as over-the-counter drugs, that would change my thinking. But if we're not in an area where we really have some concern, then I'm fine with what we have there. So as far as I'm concerned, the insufficiency boils down now to composition.

DR. BELSITO: Right.

DR. ANSELL: So we provided a study on the assessment of plant herbs or extracts and their components.

DR. GILL: This was in Wave 2 data?

DR. ANSELL: Yeah.

DR. BELSITO: Where was this? It was in Wave 2?

DR. SNYDER: In Wave 2 all I had was irritation and sensitization data.

DR. BELSITO: Yeah, that's all I had, too.

DR. SNYDER: I didn't have any composition data in Wave 2.

DR. BELSITO: The only composition --

MR. JOHNSON: Wave 2 is the --

DR. BELSITO: Was just the bisabolol.

MR. JOHNSON: It's in Data 2.

DR. ANSELL: Where is that in the --

MR. JOHNSON: Data 2, subsequent to the plants and herbs.

DR. ANSELL: How do I relate that to a page number?

DR. BELSITO: We're in Wave 2?

MR. JOHNSON: No, actually it was the.pdf that accompanied the safety assessment.

DR. BELSITO: What page?

MR. JOHNSON: It was identified as Data 2.pdf file.

DR. BELSITO: What page of the entire document?

MR. JOHNSON: It would be on page 69.

DR. GILL: Of the report.

DR. BELSITO: No, we don't have page numbers in the report.

DR. LIEBLER: It's on.pdf page 69.

DR. ANSELL: It's an assessment of plants, herbs, plant/herb extracts and their natural synthetic -- description of the plants, systemics, plant parts and products, ingredients and constituents.

DR. BELSITO: There are some nice pictures.

DR. LIEBLER: I'm not seeing the data.

DR. BELSITO: Yeah, I don't see anything.

DR. LIEBLER: I'm seeing descriptions of the types of compounds that are present, but not amounts. Now, there's a picture on.pdf 74 of the bisabolol family compounds. The closest we have is a description from the essential oil, which is not where our insufficiency lies. And there's four bullet points: Up to 15 percent chamazulene and precursor matricin and up to 50 percent bisabolols and bisabolol oxides. That's for the oil. So we're still short --

DR. ANSELL: On these --

DR. LIEBLER: Right, for the leaf and flower.

DR. ANSELL: Right, therapeutic relevant compounds like the tributyltins are absent in the root.

DR. LIEBLER: I mean it's a literature review. It doesn't have the information that would go into Table 5, I guess it is. So that's what we need.

DR. BELSITO: Plus on page 72 of the.pdf, it sort of justifies what we're asking for. It says "The roots are used for pharmaceuticals of the anthroposophical therapy. The essential oils differ considerably from the aerial part." So we already have information that things in this plant differ. And we don't have a --

DR. SNYDER: It even goes on further.

DR. BELSITO: Yeah, it's just part of the essential oils. We just don't know the actual percentages.

DR. LIEBLER: So this just doesn't suffice. I mean it's useful appendix material, but it doesn't address our need.

DR. BELSITO: Well, I think it's nice because it hits us with okay, here are the issues, the coumarins, et cetera. And then it goes on to talk about the quality controls for chamomile flowers in preparations, which gets back to my point. I honestly think that this is another case where probably everything in cosmetics more or less is coming from the flower. But when you read the literature and the way people label things, it's the flower and the stem because there are little bits of stem that haven't gotten off of the flower so we label it both ways. But in order to rule -- I mean that's just a guess just like I think the literature is ambiguous on exactly what it is.

DR. LIEBLER: And the question of what's actually in these? You can imagine a -- remember that "kitchen confidential?" You can imagine a "botanical confidential." Yeah, yeah, we actually grind up stems, and we put them in our cheap botanicals.

DR. BELSITO: Okay, anything else here?

DR. LIEBLER: Yeah, I do have a couple of other issues on this report beyond the composition. So this is actually related to the composition, but on the.pdf --

DR. BELSITO: Can Paul just interrupt?

DR. SNYDER: It looks like it says here "The composition of the essential oil in roots differs from that in flowers."

DR. LIEBLER: Right. It says that right in the.pdf that we were just looking at.

DR. BELSITO: Right, okay. Where are you, Dan?

DR. LIEBLER: .pdf page 28. This is back to the report under Provocative Testing. So there's a series of studies here -- a couple of them are pretty large studies -- and it looks like the extracts that were used in these studies were specially prepared for these studies by methods that look like they're somewhat different from those described in our report for the commercially available products.

And I'm not saying that there's a problem with this, but I think we need to note it maybe eventually in our discussion. For example, the second paragraph under Provocative Testing starts "The frequency of allergic reactions to a compositae plant mixture." It describes the preparation of ether extracts. Now, up earlier in the document the methods for preparing these -- steam distillation or maceration in oil -- are described and ether extract is different. And if you took a fresh product or a fresh plant and prepared an ether extract, you'll probably get the maximum concentration of any potentially bioactive organics. And this extract could actually have somewhat different properties and perhaps even produce greater responses than you might get from a commercially prepared extract.

So I'm referring to these in my notes as sort of homebrew extracts that were

prepared for these studies, and there are a few of them that I've noted. There's one that I noted on.pdf page 28, the study on.pdf page 29, second paragraph under Chamomilla Recutita, the "allergenicity of chamomilla recutita." There's another; this one is "defatted with acetone and macerated in phosphate buffered saline." Then there's another one that was an issue of extract in petrolatum and another one of the extraction solvent. For each, the extract was not stated.

So the problem with these studies is that in some cases they produce what looks like a significant number of positive reactions to the extracts, but you have no way of being able to relate the data back to the type of extract that is commercially provided to producers of cosmetic products.

So I'm not saying that these data aren't useful or can't be evaluated, but we need to have some way to put an asterisk on them that's basically in the discussion. "The Panel noted that extracts prepared for some of the studies were prepared by methods that appear to be outside the standard procedures for preparing the commercially used ingredients."

DR. BELSITO: Well, I mean the provocative tests are all patch tests, so they're not industry tests. These are dermatologists in Europe patch-testing people with Finn Chambers.

The ether extracts were all probably produced by a guy by the name of Hausen in Germany who's since passed away. He was really interested in botanical dermatology and provided a lot of us, including myself, with these ether extracts of various plants that he had prepared in his lab. And that's probably what they were. The conjunctival testing I don't know about, but I would suspect that all of the other patch-test data that you're seeing from Europe on these patients are probably Hausen's ether extracts.

But I think it's worth making a note, but again this is not like it's big-time safety testing. This is diagnostic testing to rule out allergic reactions to chamomile in patients suspected of having allergic reactions or in some cases of compositae-sensitive patients to see if they would also react to chamomilla recutita.

So this type of stuff is nice. I think it should be in the report. And if you start seeing thousands of cases of positive patch-tests to an ingredient, as you will see more than likely. We see them coming up -- when we see this huge blip on reactivity, I think it's meaningful. But in this case you're really not seeing this type of overwhelming number of patients coming up positive to chamomile, including some compositae-sensitive patients, which I think is interesting.

DR. LIEBLER: Okay, so anyway I made my point.

DR. BELSITO: I mean we can make the point, "ether extract (which is not a typical cosmetic method of manufacturing this ingredient)" or something.

DR. ANSELL: Well, I think your point is much more interesting as it relates to the whole test. Not only is it a nontypical preparation, it's on nontypical people.

DR. BELSITO: Right.

DR. ANSELL: So perhaps that can be carried into the discussion.

DR. LIEBLER: Right. Well, I'm not saying that we don't use the data. I'm simply saying that we note in the discussion that the types of -- in addition to the variety, plant to plant variety for the botanicals, you have this added variety in some of the test materials that were used in some of the studies that we cited. And that's all, but it needs to be noted.

DR. ANSELL: Well, and the patients, the subjects, may not be typical either.

DR. BELSITO: If you're concerned, I think that any dermatologist reading this when they see provocative testing is going to know that this is a select group of patients. These aren't normal individuals coming in for HRIPTs to assess whether a specific chemical can induce sensitization at a certain level. I mean if you want -- because otherwise you're going to have to say it every time you talk about the next group of tests. If you want in all documents to create a boilerplate for provocative testing --

DR. LIEBLER: No, no, I'm not going there. This is a case that may occur with other botanicals, but it certainly doesn't apply to all provocative testing. It would not require a boilerplate.

DR. BELSITO: Well, I mean actually it does because you never know whether that material that was used is actually cosmetic-grade material. These can be made up by the investigator. A lot of them are commercially available from companies. Presumably they're buying cosmetic grade. But you're not going to know that, I can guarantee you, from the reports in the literature necessarily unless you go back and they say they purchased it from Chemotechnique

in Malmö, Sweden. And you go back to Chemotechnique and you check their MSDS sheet and you look at -- maybe it'll say cosmetic grade or whatever.

DR. ANSELL: I agree with Dan's point. I think it's a very interesting one. But I also think Dan's reaction to 56 of the patients who tested positive, suggesting a high allergenicity potential, is perhaps not the right conclusion either. So I just wanted to add that not only is the test material atypical, but the subjects themselves. Maybe we need something about provocative testing.

DR. BELSITO: That's what I was saying. I mean if you're concerned that this could be misinterpreted, the issue came up when we were looking at -- I don't remember if it was gallites or what -- in a lipstick and they took patients who had cheilitis. So this is a patient population where you're looking for something in a lipstick and they saw a very high percentage of patients patch-testing positive to whatever ingredient we were looking at. That's the same thing here.

So if you want to create some type of boilerplate to alert people that when we're talking about provocative tests, "provocative tests refer to patch-tests and other testing techniques that are done in patients suspected of having an allergic reaction to this ingredient or potentially allergic reactions to this ingredient and are not representative of the sensitization capacity of these ingredients in the normal population; furthermore, it's not clear that the ingredient used for patch-testing is the same as commercial-grade cosmetic material." And just create that as a boilerplate before all provocative testing.

DR. LIEBLER: So I don't think we need to make the boilerplate queue any longer. We have more boilerplate candidate language than what the staff will ever get around to drafting for us. And this is probably -- this could be addressed in the discussion because we're going to have to have a paragraph in the discussion that acknowledges the variety of the range of ingredient compositions that we're dealing with here -- between the oil and the flower and the stem leaf. And once we do have data to discuss that, we'll say the Panel had to consider that. We also had to consider that the preparation methods differed between industry, and in addition some of the preparations used and some of the testing described in the literature also may further differ from those for commercial products. And we don't need to say anything more, just simply that we were aware of that, that we took that into consideration.

Then there's the whole other issue of whether people in provocative testing are atypical. It sounds like that's well-known to people who are familiar with that sort of literature and doesn't need to be beaten to death. So I think that sort of takes care of itself.

I actually have a couple of other issues I wanted to get on to, if I may. These are the sections on the anticarcinogenicity. I'm not really sure that -- so this is on.pdf page 35. I'm not really sure that these sections are relevant. The toxicity to the cell lines associated with cancer -- so basically this isn't in vivo studies where they were able to inhibit skin carcinogenicity like we'll see with the rosemary. But instead these are atoxicity to tumor cell lines. And you can beat tumor cell lines to death with chemicals in vitro. That doesn't mean that's a true anticancer effect or an anticarcinogenicity effect. So I don't think this is, based on the data we're showing here, it's not necessarily cancer specific or really relevant to in vivo activities.

DR. BELSITO: So would you get rid of the entire anticarcinogenicity section?

DR. LIEBLER: Yes.

DR. SNYDER: We had this discussion last time, and the other team -- we had a lot more in there, remember? We had a lot more other data on those types of issues. And they relinquished, I think, all but this data. They were kind of adamant that this data had some biological --

DR. LIEBLER: So we could have -- we could consider the in vivo model, which is in the third paragraph, to remain. But the first two are basically cell line studies; that you're killing tumor cell lines with these compounds. I don't think that has any particular in vivo relevance. So the first two paragraphs of that anticarcinogenicity section could go.

DR. BELSITO: So you would continue -- you would keep the cytotoxic activity?

DR. LIEBLER: Yeah, you could keep that because at least it's an in vivo model.

DR. BELSITO: Well, if we do keep the first two paragraphs, tomorrow I think that it's sort of redundant going in the first paragraph to say "against the following human cancer

cell lines, human prostate cancer cells." Just say "against the following human prostate cancer cells derived from," but I will --

DR. LIEBLER: Another thing you could do if the other team really wants to keep that in is that you could decrease it substantially because it's much ado about probably nothing.

MR. JOHNSON: So, that study on the flower oil, would that be deleted as well?

DR. BELSITO: The first two paragraphs, Wilbur, is what Dan's suggesting.

MR. JOHNSON: Yeah, I'm talking about -- yes.

DR. BELSITO: The cytotoxic activity? Is that what you're asking about?

DR. LIEBLER: The third paragraph?

MR. JOHNSON: Under the oil subheading, there's another anticancer activity study. Since we were dealing with that section, I didn't know whether or not you were also referring to the data on the oil in terms of deleting it.

DR. LIEBLER: Yeah, right, the flower oil. I mean it's the same issue.

MR. JOHNSON: Okay.

DR. LIEBLER: It's basically these cells being beaten with these compounds.

So I also had some more concerns under Biological Activity,.pdf page 36, the paragraph under Anti- Inflammatory Activity, chamomilla recutita, the effect of chamomilla --

DR. SNYDER: That's another one they wanted to keep.

DR. LIEBLER: Well, I think there's poor justification for it. I remember reading in the transcript of our discussion, they were interested in maintaining the stuff on wound healing, and I don't think it's necessary.

DR. SNYDER: And, Dan, and the anti-inflammatory.

DR. LIEBLER: So I think this is of dubious relevance, basically its effects on neutrophils in vitro, and concentrations are much higher than would be in vivo biologically relevant.

DR. BELSITO: So delete it or shorten it.

DR. LIEBLER: Right. And I had the same on.pdf under Pharmacologic Activity, the GABA-like activities.

I think that's also irrelevant, as is the Antioxidant Activity. The Antioxidant Activity paragraph right under it is about the reaction with DPPH, which is -- you can buy this radical in a jar from Sigma. It's the most stable radical in the world, and you can buy it in a jar and lots of things react with it and it doesn't make anything biological. So that paragraph can go. So, again, this is the middle of 37.

DR. BELSITO: So both paragraphs deleted or shortened. We'll see if the other team is okay.

DR. LIEBLER: Okay, that's it.

DR. BELSITO: Paul?

DR. SNYDER: So I want to go back and ask Dan -- so in looking at the boilerplate for the botanicals I think there's lots of issues to discuss, but what it came down to me was the real issue is the same issue that we're presented with here. What is the composition of the starting material and what were the extraction methods or methods used to derive the ingredients that are used in cosmetics? And so if you go to the Methods of Manufacture section in this document, we don't say anything about --

DR. BELSITO: Page?

DR. SNYDER: I have a Word document, so I --

MR. JOHNSON: Page 20.

DR. SNYDER: So I think in these botanicals what we're obligated to do is talk about really the materials and methods, what are the components and the composition of those components, and then what are the methods used to make the extractions or derive the ingredients that are used then in cosmetics?

And so I think we need to have those expanded upon in a little bit more detail because throughout this report -- I just went through it while you guys were having that discussion and highlighted -- we have aqueous solvent, ether solvent. We have extraction. We have I think four or five different extraction methods used. And so I see now that in the animal studies, we're doing an aqueous extract as opposed to a solvent extract that was used for the cosmetic --

DR. LIEBLER: So there are two issues, Paul. These are good points you bring up. There are two issues, though, that we tend to confuse. One is how the commercially supplied ingredient is extracted from the plants.

DR. SNYDER: Right.

DR. LIEBLER: And that's provided briefly under Method of Manufacture. And if we had any more complete information that would be welcome, but at least we do have information here.

And then there's the issue of how that ingredient that was originally extracted by steam distillation, let's say, how that was then presented to the test system or the people or the patch or the animals. Was that put in petrolatum? Was that put in an aqueous suspension? Was that put in whatever? And that's going to be study-to-study specific whereas the method by which the extract was produced in the first place is a separate issue.

DR. SNYDER: Okay.

DR. LIEBLER: So it's two different things.

DR. SNYDER: Thanks for covering it. So the animal testing that was done was an extract in an aqueous solution.

DR. LIEBLER: Right.

DR. SNYDER: Would that be significantly different from one that was in a solvent or in a different -- do you know what I'm saying? Because that could change the exposure.

DR. LIEBLER: Only to the extent that if the aqueous mixture didn't fully dissolve all its stuff. It might have been that that's the form that the product was available to them in. A lot of times these decisions are sort of practical decisions based on how you receive the product.

DR. SNYDER: So I guess the point I was trying to make was should we have some language in our report that says exactly what you said, that the issue of the extraction method is irrelevant to exposures or irrelevant to toxicity?

DR. LIEBLER: Oh, it's not irrelevant because it determines what the mixture contains after it's taken out of the plant. Then the next step is the presentation of that mixture, depending on the vehicle used in a particular study or the composition of the product. And in both steps there's a lot of variation, I guess. That's the problem. And I think we need to capture that in our discussion and ultimately in our boilerplate.

DR. BELSITO: Anything else, Paul?

DR. SNYDER: No, I'm fine.

MR. JOHNSON: Dr. Belsito, just one comment. In Wave 2, some of the structural components of chamomilla recutita were provided. And I would just like to know whether or not those structures should be included in the report because at the last meeting you had mentioned including some of the structural components, the structures for those in the report. They're in Wave 2.

DR. LIEBLER: I saw them. I think they're fine to put into the report.

MR. JOHNSON: Okay.

DR. LIEBLER: Because you're basically showing some of the major organic components.

DR. BELSITO: Anything more on chamomilla recutita?

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

Chamomile Ingredients

So, let me see, chamomile, it's a tentative report. So, kind of context, this is the second time we've seen the report, although now what we have is Chamomilla Recutita -- how do you say that? German Chamomile split from Roman. And so, in this case, we have the Recutita -- is that how you say it?

DR. HILL: Latin, or would it be --

DR. MARKS: Any rate, we have, in June, we gave an insufficient notice, we wanted skin irritation sensitization data for the flower extract, the use concentration at 10 percent. And then, in the -- I have, in my notes, the new use concentration of the flower extract is 0.5 percent, that's page 49 --

MS. EISENMANN: Yes, that's correct.

DR. MARKS: Previously, it was 10 percent. So is this insufficient data notice incorrect, that we really don't need it for 10 percent?

MS. EISENMANN: There was, when I started going back and asking for high concentration, you know, they say we made a mistake, it's really slow. What they end up doing is giving me the concentration of the whole extract, and not just the part that's the plant, so they might be using a 10 percent of a trade name material that contains an extract.

DR. MARKS: Okay.

MS. EISENMANN: So frequently, these get revised down when they report that high.

DR. MARKS: So, the new use concentration is really 0.5 percent of the flower extract?

MS. EISENMANN: Correct. And I was able to find our IPT was in Wave 2 with 0.4 percent.

DR. MARKS: Yes. So my question is, is that going to be enough to -- it's very close, obviously. How many parts per million does that work out to be, the difference between -- what is 0.1 percent in parts per million, is that like 100, or what? Did you do the math on that, I didn't.

MR. HELDRETH: 1000.

DR. MARKS: 1000 ppm. So now the question is, certainly, if we were dealing with, like, methylisothiazolone, methylchloroisothiazolinone, a thousand ppm would be really significant. Is it with this extract with components of it which would be quite diluted. So, for me, the issue was do we issue a tentative report limiting it to 0.4 percent, which is the HRIPT, or do we just issue a safe, since it's so close to the 0.5? I could go either way. I don't think there's, even though it's a thousand ppm, I don't think it's going to make that much difference with a botanical extract.

DR. BERGFELD: You can put it in discussion.

DR. MARKS: Yeah, okay. So --

MR. HELDRETH: There is one concentration that's higher for the Chamomile Recutita extract that is not plant part specific, it's 0.61, just to say.

DR. MARKS: Thank you. Which, you're on page, let me see, page 49?

MR. HELDRETH: Correct.

DR. MARKS: And let me take a look -- where are you looking, Bart, on that, because somehow I've got --

MR. HELDRETH: It's on --

DR. MARKS: It's probably --

MR. HELDRETH: Table 6.

DR. MARKS: It's --

MR. HELDRETH: 0.61 for dermal contact --

DR. MARKS: Oh, yes, I guess it's because it was just six uses, I tended to focus on the 966 uses of the flower extract, 0.5. So, again, I don't think, now we're talking about 2000 ppm, probably doesn't -- now, it is being used in baby products, I just wanted to, on that same page, 49, you see 26 baby products at a very low concentration, 0.0097, but I just wanted to be

sure we had noted that as a team.

DR. BRESLAWEC: Yes, and that's a rinse-off.

DR. MARKS: Yeah, a rinse-off. Let me see, inhalation, there's some inhalation, so we can put that boilerplate. Discussion, okay, any other needs? I think we can move forward with a safe, then, to me, unless Ron, Ron or Tom, you'd have any other -- and I wanted to bring up azelene also, which is found on page 39 in the discussion.

DR. HILL: My comment, I guess it indirectly addresses that, which is that we have no chronic tox data on most of these, and only oral on the flower and flower extract chronic tox. So the whole thing, I still don't have a problem with the conclusion, but I think the discussion needs to be very clear, and we're getting there the way it is now, that the whole thing rests on the fact that the concentrations, in general, of use or low, the leave on concentrations of use are quite low, and that's what provides with plenty margin of safety. I haven't stated that in a way that, I wouldn't want it captured directly that way, but that's the jist of it, the assessment of safety rests on the fact that overall use concentrations are quite low, leave on concentrations are even lower.

DR. BRESLAWEC: Dr. Marks, Dr. Hill, I would just like to elaborate that this follows the approach that the panel seems to have adopted for botanicals, not because there's so little, but because, initially, you're looking at products that are used in foods and are often grass. And as a result, you don't need to concern yourself with systemic toxicity unless you have dermal penetration, and so you're focusing more on sensitization and irritation --

DR. HILL: And, again --

DR. BRESLAWEC: As opposed to just de facto because they're used as very low --

DR. HILL: And, again, I say I'm not in full agreement with that for the reasons I stated earlier in that, just because something's grass doesn't mean it's perfectly safe when you wear it on your skin. It's just that, in this particular case, we've got low concentrations particularly, and notably so in the leave on, and so things like azulene, which are raised, why it might be a problem if the concentrations in the final product were a whole lot higher. But it would have to be a whole lot higher before we'd even begin to talk about it, so that's what I'm hoping that we will somehow capture. Otherwise, somebody says, well, gee, there's this stuff and that stuff and that stuff in there, isn't this a problem. And I think it needs to be very clear it would be a problem if we had these things being used at very high concentrations. But the fact that we are giving our assessment safe as used in cosmetic ingredients, we need to be sure that somebody who reads this knows that it rests on the art, the current art based on what we see in those tables. And that's important, very important.

DR. MARKS: Any other comments? So that's just a discussant point.

DR. SLAGA: What is the conclusion, safe?

DR. MARKS: Safe.

DR. SLAGA: No concentration limit?

DR. MARKS: I don't think so.

DR. SLAGA: We don't need to set concentration limits because --

DR. MARKS: No, no, we're talking about sensitization.

DR. SLAGA: No, the sensitization data is good up to 0.4.

DR. MARKS: 0.4.

DR. SLAGA: So anything I would say --

DR. MARKS: Limit.

DR. SLAGA: -- say that, safe as used up to 0.4 percent, because there are some uses for leave ons above that.

DR. MARKS: Tom, that's fine. If you could tell, Ron I was wavering as to whether to set a limit or not. You're being, holding, being pure, which I like.

DR. BERGFELD: May I ask a question?

DR. MARKS: Yes.

DR. BERGFELD: If it were a higher concentration, you're worried about sensitization?

DR. MARKS: Well, we don't have data that support --

DR. BERGFELD: I know, I was asking what --

DR. SHANK: That would be --

DR. BERGFELD: That would be your primary irritation and sensitization, or more sensitization?

DR. SLAGA: Sensitization.

DR. BERGFELD: Then you could put in your discussion what you did earlier that it should be compounded to be (inaudible) formula.

DR. SHANK: I just think we're tending to go to this limitation when formulated to not. First, it was, would be irritating, and that seemed to be okay, now irritation is quite different -- I'm preaching to the choir, here -- irritation and sensitization, which is two different things, and --

DR. BERGFELD: But there is a threshold of sensitization.

DR. SHANK: Okay.

DR. BERGFELD: I'm just --

DR. SHANK: If the dermatologists are fine with saying --

DR. BERGFELD: Well, they were fine before --

DR. MARKS: Well --

DR. SHANK: One case, only one case.

DR. BERGFELD: Well, I was reminded there was one other case.

DR. SHANK: Just one, yeah.

DR. BERGFELD: Two, now.

DR. SHANK: Two now.

DR. MARKS: Now, I'm fine with setting a limit, I don't think that's -- because we know it's definitely safe, using the HRIPT in Wave 2 up to 0.4 percent, and that's, as I mentioned in the beginning, I was struggling, wavering whether or not, since now, Bart, you have it up to 0.6 percent, I was looking at the flower extract at 0.5 percent. Let's set it to 0.4 percent. This is going to go out as a tentative report, industry has one at 0.6 or 0.5, then we can put safe as used.

DR. SHANK: Well, Table 6 lists the flower at 1.2 percent in leave on.

MS. EISENMANN: That's a mistake, though.

DR. SHANK: Okay. It's kind of hard, then, to --

MS. EISENMANN: Well, if you look --

DR. SHANK: So what are the real numbers, then?

MS. EISENMANN: Well, it's 0.5 there, too, if I remember --

DR. SHANK: There?

MS. EISENMANN: Correct. Yes, if you look at the Table that came from me, it's 0.5 there.

DR. SHANK: 0.5.

DR. BRESLAWEC: This is in a permanent wave product?

MS. EISENMANN: Uh-huh.

DR. MARKS: Safe up to 0.4 percent. And, let me see, I think I'm the one, and that's what I'll make a motion tomorrow, and we'll see where it goes with the Belsito team. Halyna, yes?

DR. BRESLAWEC: Yes. Again with the search strategy. It would be perhaps useful to search for some of the components, especially as it relates to the toxicokinetics, the flavins, the epogenic and luteolin.

MS. EISENMANN: I was just concerned about the statements in the pharmacokinetics section that it says the data were not found in the published literature, and I did a quick look on chamomile and kinetics and found three references. I mean, this is a highly used ingredient, there's going to be a lot of, I think, German data on the components under kinetics. And I'm not sure it necessarily needs to be in here, but the statement that says there's no data just doesn't seem appropriate. There's got to be a different way to state that there may be data on the components, but we didn't look for it, or -- I don't know how you want to state it, but just saying there's no data I don't think is the right -- and I'm not saying you necessarily need to put all the data in there, but the way it is written, to me, was troubling.

DR. MARKS: So you'll communicate that with Monice to Wilbur. Perhaps -- well, first of all, I think, as with the previous botanical, doing individual searches, although we don't have Wilbur here to directly comment that, apparently, a number of those individual

components came up. But I think that's to be heeded in the future as to when there are important components, that should be part of the search strategy, and mentioned when it's under the search strategy. Ron Hill?

DR. HILL: And then Bart. But we had this discussion, I think, the last time or the time before, and I've made note of it in several of these reports. I mean, the concept of toxicokinetics with these botanical extracts is not even an appropriate concept. So, I mean, if you know what components you ought to be looking for, that would be one thing. So I react exactly the same way you do to that in the sense of toxicokinetics, N/A, because that's what I'd kind of like to see. I mean, I don't know if we just not have that section in there or we deal with it in some other manner, but if you want to talk kinetics, then you have to talk about particular components, particular compounds, and that will be different for each one of those compounds based on their biohandleing. So --

DR. MARKS: So let's get back on page 39 in the draft discussion, the second -- no, the third sentence is azulene has been identified as a component. The panel previously concluded there's insufficient to support the safety of azulene for use in cosmetic products, then it says the panel agreed that the component should be present at levels that are below the threshold of toxicologic concern. To me, there's a contradiction there, if you said there's insufficient data on azulene, and then you say the levels are below the toxicological concern. How can you say that if you have insufficient data? Bart?

MR. HELDRETH: I think it's, maybe it's useful to say that, okay, there's azulene out there and it has a certain toxicity in certain situations, but I think we're failing to get to the point of there's not complete chemical characterization of these ingredients. And if we don't know what concentration azulene is in each of these ingredients, what do we really know about how that's going to be effective at all. So maybe there's data on azulene, but we don't have data on how much azulene is in each one of these ingredients. And I think that's what Wilbur was going towards when he said there's no data, because nobody's given us characterization data on these ingredients, and it's not in the literature that we've seen.

DR. MARKS: So, Rons, Tom, how would you -- to me, if I read this discussion as it is right now, I'm a little bit concerned. Halyna?

DR. BRESLAWEC: Look at Table 5.

DR. MARKS: And what page is that?

DR. BRESLAWEC: Jeez, I don't know.

DR. HILL: 32, 31.

DR. MARKS: No, Tables would be after 39.

DR. HILL: I'm on, sorry, I've got the advance report, that's why.

SPEAKER: Page 25?

DR. MARKS: 45.

DR. BRESLAWEC: In the flower oil, there is data, there's characterization.

DR. MARKS: Oh, yes, 0.4 percent, am I reading that correctly, in the flower oil? Carol, you have a look like you want to say something. Nonverbally, you're communicating to me, that isn't captured in this mic.

MS. EISENMANN: Yes, for at least the oils and for chamomile there are probably plenty of data. I mean, there's a lot of botanicals where there are not data, but for the oil of this one, I think there's probably enough data.

DR. SHANK: I think we have to keep in mind that these are, the plant and the oil are grass food ingredients, so the concern is the skin, not systemic toxicity. So we need skin data, and we have some.

DR. MARKS: Okay. So, again, Ron Shank, you feel we can move forward with a safe?

DR. SHANK: Yeah, I say safe up to 0.4 percent.

DR. MARKS: Yes, right, that's based on --

DR. SHANK: Based on the skin sensitization.

DR. MARKS: Right.

DR. BERGFELD: 0.4 or 4?

DR. MARKS: 0.4 percent.

DR. SHANK: Now, in your experience, clinical experience, is there much

difference between 0.5 percent and 0.4 percent? Is there that kind of a cut off?

DR. MARKS: Well, that's why I asked it be transposed to parts per million, because I always -- and when you talk, it depends on the chemical, a thousand parts per million is really a lot for Formaldehyde or MCIMI. So, in this botanical, is there a difference? I don't know. I'm perfectly happy presenting it, as you suggest, Ron Shank, setting the limit at 0.1 percent, and then we'll see where the Belsito -- 0.4 percent, I mean -- and see what the Belsito team has to say. And we can have that discussion tomorrow. I was, I could go either way, to tell you the truth, because chamomile hasn't come up in my clinical experience as a big sensitizer, and it's in lots of botanicals now. Lots, what was it, the use was like 700, or something? It was a lot. So I'll propose that limit tomorrow. I think the important thing is, we're moving forward with a tentative report safe, and then the discussion, perhaps, will revolve around the we set a limit of 0.4 percent, which is the HRIPT results in Wave 2. Monice?

MS. FIUME: I just want to ask for clarification so I can report back to Wilbur. The whole azulene started because of wording in the discussion? Do you have any suggestions for him on the wording of that first paragraph of the discussion? Because that's, I think, what started it.

DR. MARKS: So, again, that's page 39 in the PDF.

DR. HILL: I think you follow with a sentence that says, well, now we're setting a limit, but in the arts of use, the concentrations are low. I mean, 0.4 percent would be low. If you then look at the percentage of azulene that's in the, what you're putting in there, so it would be whatever modest percentage of it is azulene of the 0.4 percent you're putting in the product, so you just say the concentrations of use are low. Azulene would be kept well below the threshold of any toxicological concern. That's true of any of the ingredients in there that have potential toxicological issues.

DR. MARKS: Yeah.

DR. HILL: If you were proposing to uses at 40 percent, we might look again at if it's 40 percent and we smear it over our entire body, what would be the potential for systemic tox. But that's not the case here, and that's my point. And that, regardless of grass, because, I mean, the PDR for herbals says don't use it if you're pregnant, so there's something. This is one, right?

MS. WEINTRAUB: No, that's rosemary.

DR. HILL: Okay. Sorry. But this is the one with bazabalol, right? And so we have reduced numbers of fetuses, and so forth. I mean, it isn't written in here, but potentially, we have the same concern.

DR. MARKS: Well, I think the last sentence of that first paragraph is fine, the components are present below the threshold of toxicologic concern. For me, the contradiction was you have a component which you previously said there was insufficient data that support the safety. How, then, can you say it's below the toxicologic concern? Ron Shank, did you have that, or is that just me, looking at the way this paragraph was constructed? To me, there was a contradiction.

DR. SHANK: I don't see a contradiction.

DR. MARKS: Okay.

DR. SHANK: I've always been tentative about saying everything's fine, so long as there's no toxicological concern. That, to me, is a dodge. In the context of this particular paragraph, it's okay, but --

DR. MARKS: Okay. So you didn't like the last sentence, particularly?

DR. SHANK: Not particularly.

DR. MARKS: So how would you rephrase that, or would you leave that sentence out? I'll let you think about it, and you can give Wilbur feedback.

DR. SHANK: Well, a possible alternative would be to delete that sentence and just say the levels of these toxic components in cosmetic ingredients is sufficiently low to be not of toxicological concern.

DR. MARKS: Okay.

DR. SHANK: It's a little bit different.

DR. MARKS: Right. I think that's what you said, Tom.

DR. SLAGA: It's in the extract and not the pure compound. The pure

compounds are a concern, but not (inaudible).

DR. HILL: If it's there, it's there. I mean, we can suggest that one compound might be antagonizing the effects of the other, because we were about to come back to azulene. Do we not have some information that tells us if this much gets into the system, we have a problem, and if it's below that, it's fine? We have no toxicology on azulene? Because then we do have a problem, we're missing something.

DR. MARKS: Well, we're referring back to that, our previous conclusion of insufficient -- but I think the way you state it, Ron, and you implied, Tom, is the way to go with that paragraph, that last sentence. So, Monice, if you would give that feedback for Wilbur, and we're going to see this again, obviously, this is a tentative report, and the counsel can weigh in, also, on this. Okay. Any other comments? Tomorrow I'm going to move that a tentative report be issued with a conclusion of safe up to 0.4 percent for the Chamomilla Recutita, or however that's pronounced -- who had Latin?

DR. BERGFELD: I did, but it was too many years ago. (Laughter)

DR. MARKS: I hesitate to use the common German chamomile, but I may resort to that tomorrow, just so there's a Latin linguist in the audience. Unfortunately, Belsito is going to be coming after, I'll ask him. Okay. So safe up to 0.4 percent, and we'll massage the discussion, we'll see the next rendition in the tentative report.

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

Chamomile Ingredients

DR. MARKS: So this is the second time we've seen this report. However, now the German chamomile has been split out from the Roman chamomile nobilis. And so, this, the chamomilla recutita, the German chamomile, we felt we could move onto a tentative report with a "safe up to 0.4 percent," based on an HRIPT in wave two that showed the 0.4 percent as "safe."

Its use concentration is up to 0.5 percent flower extract and 0.61 percent in the extract. But we decided to limit it to the 0.4 percent. Even though there are small differences, it turns out to be 1,000 to 2,000 parts per million difference.

So again, move "safe up to 0.4 percent" in the chamomilla recutita.

DR. BERGFELD: And you're putting that in the conclusion, the restriction?

DR. MARKS: Yes.

DR. BERGFELD: Don?

DR. BELSITO: Well, we had -- we thought that the flower ingredients were okay. We're a little concerned that we had no information really about the composition of the stem and the leaf. And there was some information that at least the composition of the root was significantly different from other parts of the plant.

So we thought that the components that were prepared from the chamomilla recutita flower were safe as used, and the others were, at this point, insufficient for composition of the plant and the leaf.

We also wanted clarification of exactly what chamilosin was because it appeared in both reports, and in the anthemis report, it said that chamilosin was 10.5 percent anthemis nobilis. And if, in fact, it's anthemis nobilis, then the information on chamilosin, unless it also happens to contain chamomilla recutita, would need to be removed from this report.

And the last issue is the data that we got on chamomile teas and extracts where it wasn't clear which chamomile was being used. It's my understanding that chamomile tea is from chamomile from chamomilla recutita, and that the homeopathic uses of chamomile when referred to as chamomile are also chamomilla recutita, but that's just my understanding. I don't think there's any clear definition unless we can get it from that PDR that was referenced in other botanical that would tell us. Chamilosin I actually think is chamomilla recutita and not anthemis nobilis, but that needs to be clarified.

But having said all that, the flower ingredients we're okay with. The other components of the plant were not, "insufficient for composition."

DR. MARKS: So, Don, you didn't feel the difference in concentrations between the HRIPT and what it's being used with would be -- raise any concern for sensitivity?

DR. BELSITO: Of the flower ingredients?

DR. MARKS: Yeah, the flower extract and the extract.

DR. BELSITO: No. I mean, we had an HRIPT a.4 percent.

DR. MARKS: Right.

DR. BELSITO: And I thought that was fine. But we don't know what's in the other ingredients.

DR. MARKS: But we have a use of 0.5 percent. So you didn't think that difference between --

DR. BELSITO: I didn't think it was a huge difference. We did discuss -- some of my teammates were concerned about, you know, the number of case reports here. But it was pointed out that those were special populations who are known to be allergic to compositae plants, that this is a member of the compositae. They share a lot of the same allergens. And so, you really weren't looking at any kind of data from the population in general, that these were very select populations, which raised the discussion as to whether, you know, just for people who aren't dermatologists and may not understand when they see data under the heading of "provocative testing," if we somehow can maybe asterisk it and say, you know, provocative testing is testing on people with skin disease who are thought to be allergic and are not representative of incidence rates in the general population. That may one way of handling it.

But, no, I thought, you know, the difference between.4 and.5 for these,

particularly given the level of, you know, the turpenes of concern didn't bother me.

DR. MARKS: Okay. Composition? So you want an "insufficient data for composition of" --

DR. BELSITO: "Sufficient" for all the extracts of the flower, but "insufficient" for the whole plant and the leaf.

DR. BERGFELD: I see part of Marks' team wagging their heads.

DR. BELSITO: We have --

DR. BERGFELD: Is that agreeable?

DR. MARKS: Yeah.

DR. SHANK: Basically --

DR. MARKS: Yes. I'll second that motion, Don.

DR. BERGFELD: That was a motion?

DR. BELSITO: Yes.

DR. BERGFELD: Because we had another motion. All right, so we have a second motion. Halyna?

DR. BRESLAWEC: I would ask the Panel to discuss whether they believe that "formulating to be non- sensitizing" would be a conclusion that they would consider, especially since this is a similar. This is the same category, the compositae family, as the achillea, for which a "formulated to be non-sensitizing" conclusion is reached.

DR. BELSITO: A very important point, and I would agree. Yes.

DR. BERGFELD: So you're applying that to what?

DR. BELSITO: Again, I think for all the botanicals in which we're looking at sensitizing components that are below the levels of concern, we should have obviously the botanical discussion, pointing out the specific components that could be of concern when stacked on other botanicals and reinforce that in the conclusion by saying, "when formulated to be non-sensitizing." Yes, I would agree.

DR. BERGFELD: So what you've actually said, you're going to expand your discussion to include that -- expand the discussion, but put into your conclusion, the statement should be "formulated to be non-sensitizing." Okay.

DR. BELSITO: Correct.

DR. BERGFELD: Okay. So we have a --

DR. SHANK: Can I just ask a question? When we say "when formulated to be non-sensitizing," what is that saying to the formulator? Do they have to test their formulas and demonstrate that it's non-sensitizing? Irritation is an easy test, but sensitization is much more involved. So what are we saying to the formulator specifically?

DR. BELSITO: I think what we're saying to them is we're also pointing out the specific, you know, ingredients components of the botanical products that would be of concern. And usually those are fragrance ingredients that are in the botanicals. So, for instance, something like the chamomilla recutita has linalool, which is a known fragrance sensitizer. It has linalool acetate.

So we would be going through, and there are usually, again, going to be terpenes, terpenoids, and listing those of concern. And so, what we're telling the manufacturer is if you're combining this with another botanical that also has high levels of linalool, then you need to go back and you need to really then go to RIFM and look at the data that RIFM has set in terms of limits of use of these fragrance ingredients in fragranced products. Those limits exist for most of the things we're going to be concerned about. And then, you'd better not be stacking linalool above a level that would be restricted by IFRA.

So the International Fragrance Research Association sets limits on fragrance ingredients that are sensitizers. And the limits are actually set using a QRA approach. And as you've seen, as we will get to idyl propyl and butyl carbonate, where the Europeans have also put a lower limit on an underarm deodorant. Underarm deodorants typically have lower limits because they're braided skin. If you shave your underarms, they're occluded. They're more absorptive.

So what we're telling manufacturers is, these are the components of concern. If it's pulegone, we know it's toxic levels. You'd better keep your levels less than that. If it's a sensitizer, almost all of them are going to be fragrance ingredients. They can go to IFRA and look

at the IFRA dossiers and see where those cutoffs have been set. So that's what we're telling them.

DR. BERGFELD: Jim?

DR. MARKS: Don, I wanted you to clear up in the last meeting, not this one, you had asked for absorption. Was that still necessary?

DR. BELSITO: No, I didn't think it was necessary.

DR. MARKS: Okay, good.

MR. JOHNSON: I have a question to ask?

DR. BERGFELD: Okay, Wilbur?

MR. JOHNSON: Yes. Dr. Belsito, for the discussion, you want that expanded to specifically mention those components that are of concern relating to their sensitization potential.

DR. BELSITO: You know, it's unfortunate that we're doing botanicals before we've looked at how we're going to approach botanical boilerplates. But, yes, I think in general, when we are doing these botanical products, we have to point out those components of a botanical that we're concerned about.

And, you know, in this case, there's farnesene, there's linalool, and linalool acetate, azulene. And just point out, you know, what we're concerned about with these individual chemicals, whether it's a toxic endpoint or carcinogenic endpoint, a sensitizer endpoint. And, you know, say, yo', in these specific products, we're not seeing an issue if they were used singly at the levels we're told they're used. But we're concerned that these components could be in another botanical that could be stacked into a product and could exceed these levels. So that's what we're going to say. And all of that will need to be I the discussion.

Now, not to skip ahead too much, but we sort of thought, well, you can do boilerplates for pesticides. You can do boilerplates for aflatoxin. You can do an introductory boilerplate for botanical in general, but it's very difficult to create a schema that is going to address all the botanicals. So really, when you're creating a discussion, you've got some guidelines, but it's going to be case by case depending on the botanical.

Like the phytosterols, I don't think we need a botanical discussion. There's nothing really in them of concern. With others where you get things like pulegone, thujone, and, in particular, a lot of them you're going to get, you know, these "fragrance sensitizers," you know, we'll need to point those out, you know, just as examples of what the Panel is concerned about.

DR. MARKS: Okay.

DR. BERGFELD: Looking at any other discussion? Now, we have a motion that has been placed and it's been seconded. And would you restate that motion after all this discussion?

DR. BELSITO: Yes, that the flower -- those components of the chamomilla recutita that are derived from the flower are safe as used when formulated to be non- sensitizing. Those components that are derived from other parts of the plant are insufficient, and the insufficiency is composition of those parts.

DR. BERGFELD: Thank you. I'd like to call for the question then. All those in favor of this conclusion? Thank you. Unanimous.

Safety Assessment of Chamomilla Recutita-Derived Ingredients as Used in Cosmetics

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The 2013 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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ABSTRACT: The *Chamomilla recutita*-derived ingredients function mostly as fragrance ingredients and skin conditioning agents in cosmetic products. These ingredients are used at concentrations up to 0.5% (chamomilla recutita (matricaria) flower) in cosmetic products. Because formulations may contain more than one botanical ingredient, caution was urged to avoid reaching levels of toxicity for constituents. The Expert Panel concluded that the *Chamomilla recutita* flower-derived ingredients are safe in the present practices of use and concentration in cosmetics, when formulated to be non-sensitizing. However, the Panel determined that the available data are insufficient to make a determination that ingredients derived from chamomilla recutita leaf and stem, and the whole plant are safe under the intended conditions of use in cosmetics and that chemical composition data on these ingredients are needed.

INTRODUCTION

This report presents information relevant to evaluating the safety of the following 11 chamomile (German chamomile [*Chamomilla recutita* (*matricaria*)]) ingredients as used in cosmetics: chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower powder, chamomilla recutita (matricaria) flower water, chamomilla recutita (matricaria) flower oil, chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower/leaf extract, chamomilla recutita (matricaria) flower/leaf/stem extract, chamomilla recutita (matricaria) flower/leaf/stem water, chamomilla recutita (matricaria) leaf extract, and chamomilla recutita (matricaria) oil. These ingredients function mostly as fragrance ingredients and skin conditioning agents in cosmetic products. In addition to being a skin conditioning agent, chamomilla recutita (matricaria) flower/leaf/stem extract also functions as a flavoring agent and an oral care agent. Chamomilla recutita (matricaria) leaf/stem extract functions as a cosmetic biocide only. It should be noted that chamomilla recutita (matricaria) flower oil is also known as German chamomile oil, a term which is used frequently in the published literature.[1]

Azulene has been identified as a component of chamomilla recutita (matricaria) flower oil. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) has concluded that the available data are insufficient to support the safety of azulene (not to be confused with guaiazulene) for use in cosmetic products.[2] Because chamomilla recutita (matricaria) flower oil may contain (-)-α-bisabolol at concentrations as high as 41.45%, safety test data from the 1999 CIR final report on bisabolol are included in Table 1 for the Panel's review.[3] The Panel concluded, in 1999, that bisabolol is safe as used in cosmetic products; reported use concentrations ranged from 0.001% to 1%.

CHEMISTRY

The plant source of the ingredients reviewed in this safety assessment is *Matricaria chamomilla* L. [Asteraceae]. Compositae family is the previous or historical name for the Asteraceae family. *Chamomilla recutita* and *Matricaria recutita* are synonyms for *Matricaria chamomilla*.[4] The definitions of 11 chamomile ingredients presented in this safety assessment are included in Table 2. The structural formulas for constituents of chamomilla recutita (matricaria) flower oil and chamomilla recutita (matricaria) flower extract are included in Figure 1.

Physical and Chemical Properties

Chemical and physical properties of chamomilla recutita (matricaria) flower oil are included in Table 3. Information on the other 10 ingredients was not found, nor was unpublished information provided.

Method of Manufacture

Chamomilla Recutita (Matricaria) Flower Oil

Chamomilla recutita (matricaria) flower oil is produced via steam distillation of chamomile (*Chamomilla recutita*) flowers.[5,6] According to another publication, chamomilla recutita (matricaria) flower oil is prepared by steam distillation of the flowers and stalks of *Chamomilla recutita* (*Matricaria*).[7] Whether the difference in source material influences the composition of the cosmetic ingredient is unknown.

Chamomilla Recutita (Matricaria) Flower Extract

One of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract has the INCI name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract (see Table 4). This

trade name mixture is manufactured by prolonged maceration of flowers in a mixture of mineral oil and apricot kernel oil.[8] Another trade name mixture associated with chamomilla recutita (matricaria) flower extract has the INCI name, propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract (see Table 4). This trade name mixture is manufactured by hydroglycolic extraction.[9]

Composition/Impurities

Composition data (contents of the mixture, not the plant-derived ingredient) on various trade name mixtures containing *Chamomilla recutita (Matricaria)* ingredients are summarized in Table 4.[10]

Data on the composition (contents of the plant-derived ingredient) of chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower oil, and chamomilla recutita (matricaria) flower are included in Table 5. Additional information relating to composition is included below.

Chamomilla Recutita (Matricaria)

The chamomile species *Chamomilla recutita* may be classified into 4 different chemotypes, depending on the main constituent of the essential oil:[11] bisabolol, bisabolol oxide A, bisabolol oxide B, and bisabolone oxide A. A characteristic constituent of chamomile flowers is the essential oil, which contains bisabolol, matricine, or its artifact (chamazulene), *trans* -farnesene, and *cis*- as well as trans-*en*-*in*-dicycloether as typical components. Other than the coumarins herniarin and umbelliferone, flavonoids are the main hydrophilic constituents of the flower. Pectin-like polysaccharides with a main chain of α-1→4-linked polygalacturonic acid and a highly branched polysaccharide with β-1→4-linked xylose are also present.

The occurrence of formaldehyde in intact *Chamomilla recutita* (*Matricaria*) plants was evaluated. Wild *Chamomilla recutita* (*Matricaria*) and 2 varieties of this plant, BK-2 and *Degumil*, grown in Hungary were studied.[12] The BK-2 and *Degumil* varieties were grown in central Hungary, whereas, the wild type was grown in southern Hungary. Formaldehyde (HCHO) in dimedone adduct form (formaldemethone) was identified and quantified using automatic overpressured layer chromatography (OPLC). Plant samples were frozen, powdered, and treated with a 0.2% solution of dimedone in methanol. Each plant part (root, shoot, or inflorescence) suspension was then centrifuged and the supernatant was used for OPLC. The inflorescence (≈ 6.5 µg HCHO/g) and root (≈ 7 µg HCHO/g) samples of the intact, soil-grown *Degumil* variety contained the greatest quantity of HCHO, followed by the shoots and inflorescence of the cultivated BK-2 and *Degumil* varieties. The wild type contained similar amounts of HCHO in its inflorescence (≈ 5µg HCHO/g) and shoots (5µg HCHO/g). The amount of HCHO bound by the dimedone reagent increased as the concentration of dimedone increased, until a maximum was reached.

Influence of Plant Line

A study was performed to characterizethe individual variability of components in 10 selected lines (U2, U5, U7, U10, U14, S7, S10, S17, S22, and S24) that originate from the chamomile (*Chamomilla recutita*) plant population.[13] Seedlings were planted in Poland in October of 2000 and flower heads were harvested during the following year. For the 10 chamomile lines investigated, the essential oil content ranged from 0.25 to 0.55%. Of the 60 components of essential oil detected using gas chromatography, 19 were identified. The major components were: bisabolol oxide B (24.08% to 33.75%), bisabolol oxide A (5.75% to 10.92%), chamazulene (30.42%), farnesene (3.89% to 5.90%), spathulenol (3% to 4.90%), and spiroether (12.63% to 19.95%). Polyacetylene – spiroether is the component of chamomile essential oil that has anti-inflammatory activity. Concentration ranges for 2 other sesquiterpenes (minor components) were α-bisabolone oxide (2.53% to 7.52%) and α-bisabolol (0.12% to 0.73%). The monoterpenes sabinene, limonene, and cineol were present in small amounts, and only traces of α-pinene, *p*-cymene, and γ-terpinene were detected.

Influence of Country of Origin

A study identified the following impurities in dry chamomile (*Chamomilla recutita*) grown in Croatia: lead and cadmium heavy metals, and the herbicides linuron, fluazifop-p-butyl, and cycloxydim.[14] Cadmium and all 3 herbicide residues in dried samples of industrially grown dry chamomile were found to be above the suggested and accepted tolerance values. The source of this information is an abstract of a study in Croatian.

Influence of Drying Process

In the post-harvest processing of *Chamomilla recutita*, drying is an important process for preserving plant material, because it inhibits enzymatic degradation and limits microbial growth.[15] The phenolic content of *Chamomilla recutita* consists of the flavonoids, flavone glycosides (e.g., apigenin 7-glucoside) and flavonols (e.g., quercetin glycosides and luteolin glucosides). The effect of drying on the total phenol content of aqueous chamomile extracts has been reported. Freshly extracted chamomile flowers had a higher content of phenols (19.7 ± 0.5 mg/g dry weight (dw)) compared to any of the dried samples, except for those that were freeze-dried ($p \leq 0.05$). There was no significant difference between the total phenol content in samples that were freeze-dried, air-dried, or oven-dried at 40ºC. However, a major decrease in the phenol concentration of chamomile flowers oven-dried at 80ºC (13 ± 1 mg/g dw; $p \leq 0.05$) was noted. Data showing the effect of drying on content of the flavonoid apigenin 7-glucoside were also presented. Extracts produced from fresh chamomile had an apigenin 7-glucoside content of 3.0 ± 0.4 mg/g dw, which was significantly higher than amounts reported for any of the dried samples ($p \leq 0.05$). There was no significant difference in the apigenin 7-glucoside content among the chamomile flowers that were freeze-dried, air-dried, or oven-dried at 40ºC (2.0 ± 0.4 mg/g dw). The greatest decrease in apigenin7-glucoside content (1.0 ± 0.3 mg/g dw) was observed in samples oven-dried at 80ºC.[15]

Chamomilla Recutita (Matricaria) Flower

Chamomilla recutita (matricaria) flowers contain a volatile oil (0.24 to 2.0%) that is blue in color.[16] The two key components (-)-alpha-bisabolol and chamazulene account for 50 to 65% of the total volatile oil content. Other components of the oil are as follows: (-)-alpha-bisabolol oxide A and B, (-)-alpha bisabolone oxide A, spiroethers (cis- and trans- en-yn-dicycloether, sesquiterpenes (anthecotulid), cadinene, farnesene, furfural, spathulenol, and proazulene (matricarin and matricine). Chamazulene is formed from matricine during steam distillation of the oil.

Chamomilla Recutita (Matricaria) Flower Oil

Chamomilla recutita (matricaria) flower oil contains anti-inflammatory and spasmolytic sesquiterpene lactones such as α-bisabolol, blue chamazulene (weaker anti-inflammatory effect), farnesene, polyenes, and several flavonoids.[17] *Chamomilla recutita* imported from Argentina may contain larger amounts of the strongly allergenic sesquiterpene lactone anthecotulide, and, additionally, may be contaminated with the morphologically similar dog fennel (*Anthemis cotula*), which contains up to 7.3% anthecotulide. However, *Chamomilla recutita* of European origin contains only traces of anthecotuliode. According to a more recent publication, anthecotulide was not detectable in 34 chamomile (*Matricaria recutita*) preparations.[18] These 34 chamomile preparations included preparations that were on sale in German public pharmacies, a number of herbal infusions from pharmacies and supermarkets, and some consumer products (e.g., shampoos) containing chamomile extracts.

The essential oil production of cultivated (BK-2, *Degumil*) and wild chamomile populations of 4 typical chamomile-rich regions of Hungary was studied.[19] The Hungarian BK-2 contained more chamazulene in its essential oil than the German *Degumil* type, which is cultivated mainly for α-bisabolol content. Both components have important anti-inflammatory activities. Wild populations can be easily distinguished from cultivated ones, based on their high content of bisaboloides. This is true particularly for the flower of Szabadkigyós wild type, for which the average content of biologically active (-)-α-bisabolol was 48%.

Chamomilla Recutita (Matricaria) Flower Oil
and Chamomilla Recutita (Matricaria) Flower Extract

Kamillosan® (an alcoholic extract of chamomile [*Chamomilla* (matricaria) *recutita*] flowers that contains 150 mg of chamomilla recutita (matricaria) flower oil), the hydroalcoholic extract (42% ethanol) of *Chamomilla recutita* (matricaria) flowers, and pure chamomilla recutita (matricaria) oil (plant part source not stated) were analyzed (using HPLC) to identify the coumarin derivatives umbelliferone and herniarin. Kamillosan® contained 41.8 µg umbelliferone/ml and 93.1 µg herniarin/ml, and the hydroalcoholic extract of *Chamomilla recutita* (matricaria) flowers contained 36.0 µg umbelliferone/ml and 114.0 µg herniarin/ml. Pure chamomilla recutita (matricaria) oil contained 540 µg herniarin/ml.[20] Information on Kamillosan® content is presented because it is tested in some of the studies included in this safety assessment. It should be noted that, according to the following statement, Kamillosan® may contain Roman chamomile (also known as *Chamaemelum nobile* or *Anthemis nobilis*) or German chamomile (also known as *Matricaria recutita* or *Chamomilla recutita*):[21] "In Europe, medicinal preparations are made containing either Roman chamomile (*Chamaemelum nobile*) or German chamomile (*Matricaria recutita*), both members of the Compositae (Asteraceae) family. On the continent, an ointment marketed under the name Kamillosan® contains German chamomile, while a product with the same name marketed in Britain contains Roman chamomile."

USE

Cosmetic

Chamomile ingredients (*Chamomilla recutita* (matricaria)) function mostly as fragrance ingredients and skin conditioning agents in cosmetic products.[1] Chamomilla recutita (matricaria) flower/leaf/stem extract, however, also functions as a flavoring agent and oral care agent.

Information on uses of these ingredients as a function of product type was supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2013.[22] The most frequently used ingredient (use in almost 1000 products) was chamomilla recutita (matricaria) flower extract. The Personal Care Products Council (Council) conducted a survey of ingredient use concentrations in 2013, indicating use at concentrations up to 0.5% (chamomilla recutita (matricaria) flower) in lipstick.[23]

As shown in Table 6, both VCRP uses and use concentration data were provided for the following 5 ingredients:

- chamomilla recutita (matricaria) extract
- chamomilla recutita (matricaria) flower
- chamomilla recutita (matricaria) flower extract
- chamomilla recutita (matricaria) flower/leaf extract
- chamomilla recutita (matricaria) flower oil

VCRP frequency of use data, but no use concentration data, were available for:

- chamomilla recutita (matricaria) flower water and
- chamomilla recutita (matricaria) oil

Use concentration data, but no VCRP data, were available for:

- chamomilla recutita (matricaria) flower powder

Neither VCRP data nor use concentration data were available for:

- chamomilla recutita (matricaria) flower/leaf/stem extract
- chamomilla recutita (matricaria) flower/leaf/stem water
- chamomilla recutita (matricaria) leaf extract

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

The following ingredients are used in products that are sprayed (highest maximum use concentration = 0.01% chamomilla recutita (matricaria) flower extract in hairspray): chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower/leaf extract, and chamomilla recutita (matricaria) flower oil. Additionally, the following 2 ingredients are used in face powders (highest maximum use concentration = 0.002% chamomilla recutita (matricaria) flower/leaf extract]): chamomilla recutita (matricaria) extract and chamomilla recutita (matricaria) flower/leaf extract. Because these ingredients are used in aerosol/pump hair sprays (i.e., chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower/leaf extract, and chamomilla recutita (matricaria) flower oil) or powders (chamomilla recutita (matricaria) extract and chamomilla recutita (matricaria) flower/leaf extract), they could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[24,25,26,27] 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.[24,25]

Non-Cosmetic

Chamomilla Recutita

The chamomile species used in medicine is *Chamomilla recutita,* and hydroalcoholic extracts of chamomile flowers are often used in ointments or creams (e.g., Kamilosan^{R}). Additionally, bath additives (e.g. Kamillobad^{R}) and mouth sprays (e.g., Kamillosan M Spray) containing chamomile extracts as the active ingredient are offered for topical and oral treatment.[11] The use of chamomile in aroma therapy for the treatment of patients with dementia has also been reported.[28] Regarding use in pharmaceurtical products, it should be noted that Matricaria (*Chamomilla recutita*) flowers, Matricaria oil (from flowers), and Matricaria liquid extract are listed in the British Pharmacopoeia.[29]

Chamomilla recutita (matricaria) (German chamomile) is listed among the spices and other natural seasonings and flavorings that are generally recognized as safe (GRAS) for their intended use in food for human consumption.[30] It is also listed among the spices and other natural seasonings and flavorings that are GRAS for their intended use in animal drugs, feeds, and related products.[31]

Chamomilla recutita (matricaria) flowers are listed among the essential oils, oleoresins (solvent-free), and natural extractives (including distillates) that are GRAS for their intended use in food for human consumption.[32] They are also listed among the essential oils, oleoresins (solvent-free), and natural extractives (including distillates) that are GRAS for their intended use in animal drugs, feeds, and related products.[33]

FDA has determined that the available data are inadequate for establishing general recognition of safety and effectiveness of chamomile flowers as used in digestive aid drug products.[34]

The fragrant flowering heads of both German chamomile (*Chamomilla recutita*) and Roman chamomile (*Anthemis nobilis*) are collected and dried for use as teas and extracts.[35] Additionally, 2 ointments marketed under the name Kamillosan® are available in Europe, one containing German chamomile (also known as *Matricaria recutita* or *Chamomilla recutita*) and, the other, containing Roman chamomile (also known as *Chamaemelum nobile* or *Anthemis nobilis*).[21]

TOXICOKINETICS

Data on the absorption, distribution, metabolism, and excretion of the *Chamomilla recutita*-derived cosmetic ingredients reviewed in this safety assessment were not found in the published literature, nor were unpublished data provided. However, because (-)-α-bisabolol, a constituent of chamomilla recutita (matricaria) flower oil, may be present at concentrations as high as 41.45%, the data presented in Table 1 relating to absorption and systemic exposure to bisabolol may be considered, including data addressing skin penetration, skin penetration enhancement, and repeated dose oral and dermal toxicity. In addition to these data, a summary of *in vitro* data on the transfer of volatile oil components is included below.

Chamomilla recutita (matricaria) oil was tested *in vitro* to identify the components of this volatile oil that are able to pass through membranes under different conditions.[36] The aromatic components of chamomilla recutita (matricaria) oil examined were the following terpene derivatives: chamazulene, (-)-α-bisabolol, α-farnesene, β-farnesene, and matricin. A membrane diffusion model (cellophane membrane) was used, and the buffer solution (pH 1.1) used to represent the stomach was: 1 N HCl (94 g), NACl (0.35 g), and glycocol (0.5 g) in water (1,000 ml). The following buffer solution (pH = 7.5) was used to represent the plasma: Na_2HPO_3 (20.5 g) and KH_2PO_4 (2.8 g) in water (1,000 ml). Using this membrane diffusion model, the transfer of chamomilla recutita (matricaria) oil from aqueous volatile oil to pH = 1.1 (stomach), and then from buffer pH = 1.1 to buffer pH = 7.5 (plasma) was studied. The results indicated that the transfer of chamomilla recutita (matricaria) oil to the acidic moiety was faster than its transfer from buffer pH =1.1 to buffer pH = 7.5. This transfer was described as steady. In the case of transfer from aqueous solution to buffer pH = 1.1, 36.4% of the initial amount of volatile oil passed through the membrane, while this value was found to be 13.7% in the case of transfer from buffer pH =1.1 to buffer pH = 7.5. The transfer of some chamomilla recutita (matricaria) oil components was more favorable to buffer pH = 1.1 than from pH = 1.1 to pH = 7.5, and most of the components, except for chamazulene, passed through the membranes. The authors noted that though *in vitro* investigations do not always simulate processes in the human body, the membrane diffusion model used may offer some valuable information on the behavior of chamomilla recutita (matricaria) oil under different conditions.

TOXICOLOGY

Acute Toxicity

Oral

Chamomilla Recutita (Matricaria) Flower Extract

The acute oral toxicity of a lyophilized water extract of *Chamomilla recutita* (matricaria) flowers was evaluated using 2 groups of 12 female mice of the Swiss-NOS strain. The 2 groups received a single oral dose of 720 and 1440 mg/kg, respectively, and were observed for 24 h post-dosing. None of the animals died, and there was no evidence of acute toxicity.

Chamomilla Recutita (Matricaria) Flower Oil

The acute oral toxicity of chamomilla recutita (matricaria) flower oil (dose = 5 g/kg) was evaluated using 10 rats (strain not stated).[37] Dosing was followed by a 14-day observation period. None of the animals died, and an LD_{50} of > 5 g/kg was reported. Consistent with these findings, acute oral LD_{50} values of 8,560 mg/kg and 10,000 mg/kg in rats have also been reported for chamomilla recutita (matricaria) flower oil, but details relating to the test protocol and study results were not included.[38]

Chamomilla Recutita (Matricaria) Flower Oil

In an acute toxicity study, doses of chamomilla recutita (matricaria) flower oil (10, 100, 1000, 1600, 2900, 4300, and 5600 mg/kg) were administered orally to groups of male NIH mice (number per group not stated).[39] The extract of the essential oil (extraction solvent not stated) was obtained through a vapor distillation process, from the flowers of *Matricaria chamomilla*. The observation period was not stated. None of the animals died. This study was performed prior to the antigenotoxicity study summarized in the Genotoxicity section of this report.

Dermal

Chamomilla Recutita (Matricaria) Flower Oil

The acute dermal toxicity of chamomilla recutita (matricaria) flower oil (dose = 5 g/kg) was evaluated using 6 rabbits (strain not stated).[37] None of the animals died during the 14-day observation period, and an LD_{50} of > 5 g/kg was reported. The skin reactions observed are reported in the section on Skin Irritation.

Repeated Dose Toxicity

Animal

Chamomilla Recutita (Matricaria) Flower Extract

Prior to dosing, the blended flower powder of *Chamomilla recutita* (matricaria) was suspended in deionized water and kept in a water bath at 40˚C for 24 h. The mixture was filtered first with fine muslin cloth, and then with filter paper. The clear filtrate was dried in a water bath at 40˚C, and the clear paste obtained was used in the study. Sprague-Dawley rats of either sex (number not stated; males or females only not specified) received doses (1, 2, 4, and 8 g/kg body weight) of chamomilla recutita (matricaria) flower extract (aqueous extract), dissolved in water, for 14 days.[40] Additional details regarding the dosing procedure were not included. Neither signs of toxicity nor mortalities were observed at doses up to 4 g/kg body weight. Information relating to effects of the 8 g/kg dose was not included. All of the animals remained physically active.

Data on repeated dose toxicity were presented in a study on the effect of chamomile tea on the activity of hepatic phase I and phase II metabolizing enzymes from the rat.[41] Chamomile tea is made from the dried flower heads of *Chamomilla recutita* (matricaria). Five female Wistar rats (8 to 9 weeks old) had free access to Chamomile tea solution (2% w/v in water), whereas the control group had access to water. After 4 weeks of treatment, the animals were killed. Ingestion of the tea solution had no significant influence on body weight, and there were no signs of gross pathology of internal organs. Liver weight /body weight ratios of treated rats were not significantly different from control values.

Human

Chamomilla Recutita (Matricaria) Flower

Fourteen healthy volunteers (7 males, 7 females) were given 200 ml of chamomile tea (from *Chamomilla recutita* [matricaria] flowers) daily for 2 weeks. None of the subjects reported adverse effects after ingestion of the tea.[42] An analysis of urine samples collected before dosing, during the dosing period, and after dosing indicated that depletion of creatinine and the elevation of hippurate and glycine were strongly associated with chamomile tea intake.

Ocular Irritation

Chamomilla Recutita (Matricaria) Flower Oil

The hen's egg test – chorioallantoic membrane (HET-CAM assay) was used to determine the irritation potential of chamomilla recutita (matricaria) flower oil.[43] HET-CAM assays were performed with 6 replicates and repeated 3 times. The oil was applied to the CAM of fresh, fertile eggs that had been incubated for 72 h. Undiluted chamomilla recutita (matricaria) flower oil was not irritating to the hen's egg chorioallantoic membrane.

Chamomilla Recutita (Matricaria) Flower Extract

One of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract has the INCI name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract (see Table 4). It is also known as vegetol matricaire 4140 huileux, contains 1 to 4.9% chamomilla recutita (matricaria) extract, and mineral oil and prunus armeniaca (apricot) kernel oil are the extraction solvents. The ocular irritation potential of this trade name mixture was evaluated using 6 male albino New Zealand white rabbits.[44] The mixture (0.1 ml) was instilled into the conjunctival sac of the right eye in each rabbit, and eyes were not rinsed. Reactions were scored at 1 h post-instillation and then at 1, 2, 4, and 7 days post-instillation. The trade name mixture was classified as a non-irritant in this study.

Another trade name mixture associated with chamomilla recutita (matricaria) flower extract has the INCI name, propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract (see Table 4 for composition). It is also known as vegetol matricaire mcf 793 hydro, contains 5 to 9.9% chamomilla recutita (matricaria) flower extract, and propylene glycol and water are the extraction solvents. The ocular irritation potential of this trade name mixture (diluted to 15% with sterile water; 0.1 ml instilled) was evaluated using 6 New Zealand rabbits.[45] Reactions were scored at 24 h, 48 h, and 72 h post-instillation. The trade name mixture (diluted to 15% and) was classified as a non-irritant.

The ocular irritation potential of a trade name mixture associated with chamomilla recutita (matricaria) flower extract (INCI name = propylene glycol (and) water, salvia officinalis (sage) leaf extract, and chamomilla recutita (matricaria) flower extract) was evaluated using 6 male albino New Zealand white rabbits.[46] The trade name mixture is also known as vegetol sp gr 051 hydro (extraction solvents = propylene glycol and water) and contains 0.1 to 0.9% chamomilla recutita (matricaria) flower extract. It was tested according to the protocol stated at the beginning of this section. Based on the results in this study, this trade name mixture was classified as a non-irritant.

Skin Irritation

Chamomilla Recutita (Matricaria) Flower Oil

In the acute dermal toxicity study on chamomilla recutita (matricaria) flower oil involving 6 rabbits (strain not stated), summarized earlier, the following skin reactions were observed after dosing (time period not stated) with 5 g/kg: slight redness (2 rabbits), moderate redness (4 rabbits), slight edema (2 rabbits), and moderate edema (4 rabbits).[37]

Undiluted chamomilla recutita (matricaria) flower oil was applied to the backs of hairless mice (number and strain not stated). Details relating to the test procedure were not included. The oil was classified as non-irritating.[7] In another experiment, chamomilla recutita (matricaria) flower oil was applied (under occlusion) to intact or abraded skin of rabbits (number and strain not stated) for 24 h. The oil was classified as moderately irritating.

Chamomilla Recutita (Matricaria) Flower Extract

One of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract has the INCI name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract (see Table 4 for

composition). It is also known as vegetol matricaire 4140 huileux, contains 1 to 4.9% chamomilla recutita (matricaria) extract, and mineral oil and prunus armeniaca (apricot) kernel oil are the extraction solvents. The skin irritation potential of this trade name mixture was evaluated using 6 male albino New Zealand white rabbits.[44] A 14 cm x 14 cm area on the right flank was clipped free of hair and scarified. Skin of the left flank remained intact. The mixture was applied to the test sites (scarified and intact sites) at a rate of 0.5 ml^2 per area. The test site was then covered with a 2 cm x 2cm gauze pad, secured with another adhesive patch, for 23 h. Reactions were scored at 24 h and 72 h after patch application. The trade name mixture was classified as a non-irritant.

Another trade name mixture associated with chamomilla recutita (matricaria) flower extract has the INCI name, propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract (see Table 4 for composition). It is also known as vegetol matricaire mcf 793 hydro, contains 5 to 9.9% chamomilla recutita (matricaria) flower extract, and propylene glycol and water are the extraction solvents. The skin irritation potential of this trade name mixture (undiluted) was evaluated in the Draize test using 6 New Zealand rabbits, according to a procedure similar to that in the preceding study. The mixture was classified as a non-irritant.[45]

The skin irritation potential of a trade name mixture associated with chamomilla recutita (matricaria) flower extract (INCI name = propylene glycol (and) water, salvia officinalis (sage) leaf extract, and chamomilla recutita (matricaria) flower extract) was evaluated using 6 male albino New Zealand white rabbits.[46] The trade name mixture is also known as vegetol sp gr 051 hydro (extraction solvents = propylene glycol and water) and contains 0.1 to 0.9% chamomilla recutita (matricaria) flower extract. The test procedure is stated at the beginning of this section. The mixture was classified as a non-irritant.

Human

Predictive Testing

Chamomilla Recutita (Matricaria) Flower Oil

The skin irritation potential of chamomilla recutita (matricaria) flower oil (4% in petrolatum) was evaluated in a 48-h closed patch test involving human subjects (number not stated). Skin irritation was not observed.[7]

Predictive/Provocative Testing

Chamomilla Recutita (Matricaria) Flower Extract

The skin irritation potential of a cuticle softener containing 0.3% chamomilla recutita (matricaria) flower extract was evaluated in an epicutaneous patch test using 50 subjects (19 to 63 years old; sex distribution non-standardized) who were classified as follows: 29 normal, healthy subjects, 3 with eczema, 1 with an allergy, and 17 with sensitive skin.[47] Chamomilla recutita (matricaria) flower extract was prepared by supercritical fluid extraction with carbon dioxide, and consists of the following components: 8-15% essential oil with 10-25% bisabolol and 5-35% bisabolol oxides, 0.8-2.5% matricine (analyzed as chamazulene), cis- and trans-en-in dicycloether, spartulenol, herniarine, waxes, and non-volatile components. The undiluted product was applied to the back (test area dimensions not stated) for 48 h using Haye's Test chambers (square test chambers). Sodium dodecyl sulfate (1% in water) and water served as positive and negative controls, respectively. Reactions were scored 30 minutes after patch removal and at 72 h post-application. The product did not induce skin irritation in any of the subjects tested. The positive control caused skin irritation in 15 subjects, and there were no reactions to the negative control. The product was classified as harmless relative to its skin irritation potential.

Skin Irritation and Sensitization

Animal

Chamomilla Recutita (Matricaria) Extract

The cross reactivity of carabron (sesquiterpene lactone isolated from *Arnica longifolia*) with chamomilla recutita (matricaria) extract was evaluated using 5 female albino guinea pigs of the Pirbright white strain.[48] The chamomilla recutita (matricaria) extract tested was a *Chamomilla recutita* (Matricaria) whole plant ether extract. A 10% acetone solution of carabron (0.05 ml) was applied daily (weekends excluded) to a 2 cm^2 area of the clipped and shaved flanks; slight erythema developed on day 9. Neither the application of patches nor the test substance application period was mentioned in this study. Applications were continued for up to a period of 4 weeks and were discontinued when a strong inflammatory reaction (+++) was observed. The challenge phase was initiated 2 weeks after the end of the induction phase. Four different concentrations

of carabron (0.3%, 1%, 3%, and 10%) were applied to the opposite flank. Challenge reactions (slight spotty erythema, down to the 0.3% dilution) were observed in all animals. The animals were also challenged with 10% chamomilla recutita (matricaria) extract, and there were no sensitization reactions in any of the 5 guinea pigs previously sensitized to carabron.

Human

Predictive Testing

Chamomilla Recutita (Matricaria) Flower Extract

A human repeated insult patch test on a shave balm containing 0.2% chamomilla recutita (matricaria) flower extract was performed using 105 subjects (males and females; mean age = 47).[49] Initially, each subject received nine 24 h induction applications of the test substance (0.2 ml; test area dimensions not stated), using occlusive patches. The induction phase was followed by a 10- to 15-day non-treatment period. A 24 h occlusive patch containing the test substance (0.2 ml) was applied to each subject during the challenge phase. Adverse events were not reported during the study, and the authors concluded that there was no evidence that the product induced skin sensitization.

The skin sensitization potential of an eye lotion containing 0.4% chamomilla recutita (matricaria) flower extract was evaluated in an HRIPT using 107 healthy subjects (males and females; between 18 and 70 years old).[50] A semiocclusive patch containing the test substance (volume and application area not stated) was applied to the upper back, between the scapulae, for 24 h on Mondays, Wednesdays, and Fridays. This procedure was repeated for a total of 9 induction applications (same test site). Reactions were scored 24 h after patch removal on Tuesdays and Thursdays, and 48 h after patch removal on Saturdays. Following a 2-week, non-treatment period, a challenge patch was applied for 24 h to a previously untreated site on the back. Reactions were scored at the time of patch removal and at 48 h and 72 h. Dermal reactions were not observed at any time during the study. The authors concluded that the eye lotion did not exhibit a clinically significant potential for eliciting dermal irritation or sensitization.

Chamomilla Recutita (Matricaria) Extract

The skin irritation and sensitization potential of facial cleansing and makeup remover towelettes containing 0.01% chamomilla recutita (matricaria) extract was evaluated in an HRIPT involving 50 subjects (ages not stated).[51] The product was tested, under occlusive conditions, as a mixture of the wipe fabric and the material with which the wipe was impregnated. Patches were applied to the back (same site, area dimensions not stated) for a total of 9, 24 h induction applications. Following a 2-week non-treatment period, challenge patches were applied for 24 h to the same sites used for induction. Reactions were scored at 24 h, 48 h, and 72 h post-application. The product did not cause skin irritation or allergic contact dermatitis in any of the subjects tested.

Chamomilla Recutita (Matricaria) Flower/Leaf Extract

A hair gel styling mist containing 0.00006% chamomilla recutita (matricaria) flower/leaf extract was evaluated for skin irritation and sensitization potential using 103 subjects (ages not stated).[52] The HRIPT procedure was the same as in the preceding study, except that semiocclusive patches were used and challenge sites were scored at 24 h and 72 h post-application. The volume applied and dimensions of the test aerea were not stated. The product did not cause skin irritation or allergic contact dermatitis in any of the subjects tested.

Chamomilla Recutita (Matricaria) Flower Oil

The skin sensitization potential of chamomilla recutita (matricaria) flower oil was evaluated in the maximization test using 25 healthy volunteers (21 to 42 years old).[53] The test material (4% in petrolatum) was applied, under occlusion, to the volar forearm of each subject for a total of 5 alternate-day 48-h periods. The test site was pre-treated with 5% sodium lauryl sulfate (24-h application, under occlusion) prior to application of the test material. A 10-day non-treatment period was observed after the induction phase. Challenge patches were then applied, under occlusion, to new test sites for 48 h. The application of challenge patches was preceded by a 1-h application of 10% aqueous sodium lauryl sulfate (under occlusion). Reactions were scored at the time of challenge patch removal and 24 h later. There was no evidence of contact sensitization in any of the subjects tested.

Provocative Testing

Chamomilla Recutita (Matricaria)
Chamomilla Recutita (Matricaria) Extract

The skin sensitization potential of chamomilla recutita (matricaria) extract (ether extract) was studied using 24 patients (men and women; age range: 23 to 82 years) with Compositae allergy.[54] The plant extract (1%) was applied to the back of each patient using Finn chambers on Scanpor®. Patch test reactions were scored at 2, 3, or 4 days, and, frequently, on days 5 to 7, according to the International Contact Dermatitis Research Group (ICDRG) grading scale. An additional group of 5 patients was also patch tested with the plant extract (2.5% in petrolatum). Of the 24 patients, 18 (i.e. 75%) had positive reactions to 1% chamomilla recutita (matricaria) ether extract. Most of the reactions were ++ (9 patients) and 2 patients had a +++ reaction. Additionally, 7 patients had a + reaction and 3 patients had a doubtful (?+) reaction. Of the 5 patients, 4 had positive reactions (scores not stated) to 2.5% chamomilla recutita (matricaria) ether extract. The 5 patients were also involved in a standard photopatch test, and the results are included in the section on Phototoxicity.

The frequency of allergic reactions to a Compositae plant mixture containing chamomilla recutita (matricaria) extract (ether extract) was evaluated using 3,851 patients (ages not stated) patch tested between 1985 and 1990.[55] Other components of the plant mixture included: Ether extracts of arnica, feverfew, tansy, and yarrow. Eighty-four patients (ages not stated) were patch-tested with chamomilla recutita extract (ether extract; test concentration = 2.5%) during the same period. The ether extract was prepared by cutting the fresh plant material (all above-ground parts) into 20 cm long pieces and extracting them with diethyl ether. Patches (Finn chambers on Scanpor) were secured to the back of each subject, using self-adhesive tape, for 24 h. Reactions were scored according to International Contact Dermatitis Research Group (ICDRG) recommendations. Positive reactions (at least ++) to the Compositae plant mixture were observed in 118 patients (3.1% of 3,851 patients tested). Of the 85 patients tested, there were 48 (56.5% of patients tested) positive reactions to chamomilla recutita extract.

Another study to investigate the frequency of *Compositae* (*Asteraceae,* daisy family) sensitivity was performed.[56] Thirty adult patients (24 females, 6 males; mean age = 34.7 years) with "extrinsic" atopic dermatitis were patch tested with *Chamomilla recutita* (matricaria, 2.5% in petrolatum), sesquiterpene lactone mix (SL mix, 01% in petrolatum), and *Compositae* mix (C mix, 6% in petrolatum). The C mix contained the following ingredients: arnica (*Arnica Montana*) extract, chamomile (*Chamomilla recutita*) extract, tansy (*Tanacetum vulgare*) extract, feverfew (*Tanacetum parthenium*) extract, and yarrow (*Achillea millefolium*) extract. Patch testing was performed using Finn chambers on Scanpor® and Curatest®. Reactions were scored on days 2 and 3, and, where possible, on days 5 through 8 according to a grading scale (- to +++) recommended by the International Contact Dermatitis Research Group (ICDRG). A total of 9 patients reacted to SL mix and/or C mix. Of these 9, 5 had positive reactions to *Chamomilla recutita* (matricaria). All of the patients sensitive to *Chamomilla recutita* (matricaria) were C mix positive.

Danish gardeners and greenhouse workers (19, ages not stated) with Compositae-related symptoms were patch tested with 2.5% *Chamomilla recutita* (matricaria) in petrolatum.[57] The test protocol was not included in this study. Positive reactions were observed in 11 of the 19 patients tested (58% sensitization rate).

From 1991 to 2009, selected patients with known or suspected Compositae allergy were patch tested. Of the 36 patients (ages not stated) patch tested with ether extracts of *Chamomilla recutita* (matricaria), 30 (or 94%) had positive patch test reactions.[58] The majority of these reactions (90%) were strongly positive (++ or +++ reactions); the relevance was most frequently recorded as unknown.

Chamomilla Recutita (Matricaria) Extract and Tea

A conjunctival provocation test was performed on 7 hay fever patients who had experienced conjunctivitis after ocular rinsing with *Chamomilla recutita* (matricaria) tea (from flower heads).[59] *Chamomilla recutita* (matricaria) tea extract (tea extracted in phosphate-buffered saline) was evaluated in the provocation test. Initially, one drop of the tea extract (1:1,000,000 wt/vol) was instilled into the conjunctival sac. If a reaction was not observed within 20 minutes, the next concentrations (progressively increased by ten-fold) were instilled into the conjunctival sac of the other eye. The conjunctivitis initially experienced after ocular rinsing with the tea was reproduced via conjunctival provocation. Two of the patients had a positive conjunctival response to very dilute solutions of the extract (1:100,000 wt/vol and 1:1,000,000 wt/vol, respectively). Three and two patients had positive responses to 1:1000 w/v and 1:100 w/v, respectively. Additionally, all 7 patients had positive skin prick tests to the tea extract. Only 2 of the 100 control hay fever patients had a positive conjunctival reaction to the tea extract, suggesting to the authors that these were not irritant reactions. It was concluded that ocular rinsing with *Chamomilla recutita* (matricaria) tea can induce allergic conjunctivitis.

The allergenicity of chamomilla recutita (matricaria) extract was evaluated using 9 patients (7 women, 2 men; mean age = 36 years).[60] These patients had a history of systemic allergic reactions after ingestion of honey and/or after drinking *Chamomilla recutita* (matricaria) tea (from flower heads). To produce the plant extract, *Matricaria chamomilla* was defatted with acetone and macerated in phosphate buffered saline. The mixture was then stirred, centrifuged, and filtered. The extract (3.5 mg/ml) was applied to the volar surface of the forearm and a prick test was performed. Skin sites were examined after 15 minutes, and a positive reaction was defined as a wheal with a diameter > 3 mm. Twenty subjects (10 atopic, 10 nonatopic) served as controls. A positive reaction to chamomilla recutita (matricaria) extract was observed in all 9 patients. Results were negative in the 20 control subjects. A CAP inhibition assay (i.e., inhibition of binding of specific IgE to Andujar honey) was also performed. Precipitation of food allergy reactions is well known in some patients with pollinosis when they consume natural food, such as honey or chamomile tea. The Pharmacia CAP system (fluorometric assay) used is a system for titration of total and specific IgE. Pooled serum was obtained by mixing equal parts of serum from 5 of the 9 patients with the soluble extract of *Chamomilla recutita* (matricaria) pollen (358 µg protein/ml). Duplicate 100-µl aliquots of serial two-fold dilutions (in phosphate buffered saline [PBS]) of the competing fluid-phase antigen were incubated (2-h incubation period) with an equal volume of serum from the serum pool. Fluorometric assay was performed at the end of the incubation period. Percent inhibition for each dilution was calculated, and the concentration of the extract that caused 50% inhibition of IgE binding to Andujar honey (C_{50}) was determined. A C_{50} of 45.72 µg/ml was reported for chamomilla recutita (matricaria) extract.

In the same study, the 9 patients were subjected to a conjunctival challenge with *Chamomilla recutita* (matricaria) tea (from flower heads). One drop of phosphate buffered saline (PBS, negative control) was placed in the conjunctival sac. If a reaction was not observed, the tea (1 drop per dilution, every 15 minutes) was instilled as a series of 10-fold dilutions in PBS. The initial dilution instilled was $1:10^5$ (w/v). A positive reaction was defined by congestion of the conjunctival mucosa and itching of the eye. The same 20 subjects (10 atopic, 10 nonatopic) served as controls. A positive reaction to *Chamomilla recutita* (matricaria) tea was observed in all 9 patients, only at low-level dilutions (1/10 or 1/100). Results were negative in the 20 control subjects.[60]

Chamomilla Recutita (Matricaria) Extract

The skin sensitization potential of chamomilla recutita (matricaria) extract was evaluated using 76 patients, all sensitive to 6% *Compositae* mix (contains chamomilla recutita (matricaria) extract) in petrolatum.[61] The extraction solvent for each extract was not stated. Chamomilla recutita (matricaria) extract (2.5% in petrolatum) was applied to the back for 2 days using Finn chambers on Scanpor® tape. Reactions were scored on days 3 to 5, and possibly, on day 7 according to ICDRG criteria. Of the 76 patients, 49 had positive reactions to the extract. In a subsequent test (same procedure), 52 of the 76 patients had positive reactions to the extract.

Chamomilla Recutita (Matricaria)
Chamomilla Recutita (Matricaria) Flower Extract

A skin sensitization study was performed using 35 patients (26 women, 9 men; mean age = 59) sensitive to sesquiterpene lactones mix and 22 control patients (17 women, 5 men; mean age = 52) who were not sensitive to sesquiterpene lactones mix.[62] All patients were patch tested with the following: chamomilla recutita (matricaria) flower extract (1, 3, 10, 32, and 100% aqueous extract) and chamomilla recutita (matricaria) (2.5% w/w in petrolatum). Chamomilla recutita (matricaria) flower extract was actually an aqueous extract of *Chamomilla recutita* tea (from dried flower heads). Each test substance concentration (15 µl) was applied to the back using a Finn chamber (8 mm diameter) on Scanpor® tape. Chambers were removed after 2 days. Reactions were scored according to ICDRG recommendations on days 3 and 7. The numbers of patients with positive reactions to chamomilla recutita (matricaria) flower extract were as follows: 100% aqueous (30 patients; + to +++ reactions), 32% aqueous (27 patients; + to +++ reactions), 10% aqueous (21 patients; + to +++ reactions), 3% aqueous (14 patients; + to +++ reactions), and 1% aqueous (9 patients; + to +++ reactions). The number of patients with +++ reactions decreased with decreasing aqueous flower extract concentration. Of the 35 patients patch tested with *Chamomilla recutita* (matricaria) (2.5% w/w in petrolatum), 22 had positive reactions (+ to +++). The following 2 of 22 control patients (not sensitive to sesquiterpene lactones mix) had positive reactions to chamomilla recutita (matricaria) flower extract: subject 1 (++ reaction to 100% aqueous and subject 2 (++ [100% aqueous], + [32% aqueous], ++ [10% aqueous], + [3% aqueous], and + [1% aqueous].

Chamomilla Recutita (Matricaria) Flower Extract

The sensitization potential of wild chamomilla recutita (matricaria) flower extract (extraction solvent not stated) in 129 patients sensitive to Compositae mix was evaluated.[63] Patches (Finn chambers on Scanpor) containing 2.5% chamomilla recutita (matricaria) flower extract in petrolatum remained in place for 2 days. Reactions were scored on days 2 to 4, and,

whenever possible, on days 5 to 8 according to ICDRG recommendations. Of the 129 patients, 83 (64%) had positive reactions to the test material. When 74 chrysanthemum-positive patients were patch-tested with wild chamomilla recutita (matricaria) flower extract (2.5% in petrolatum), 58 (78%) had positive reactions.

The skin sensitization potential of aqueous extracts of *Chamomilla recutita* (matricaria) tea (from flower heads) was evaluated using 20 patients (13 women, 7 men; mean age = 56 years) with known contact allergy to sesquiterpene lactone mix (containing altolactone, costunolide, and dehydrocostuslactone).[64] Aqueous extracts (1%, 10%, and 100%) of 2 different kinds of *Chamomilla recutita* (matricaria) tea (identified as I and II) were tested. Each solution (15 µl) was applied to the back, using a Finn chamber on Scanpor tape, for 48 h. Reactions were scored on days 3 and 7 according to ICDRG recommendations. For 9 of the 20 patients, reactions were also scored on day 10. The following positive reactions to *Chamomilla recutita* (matricaria) tea I were reported: 1% aqueous (2 reactions, + and ++), 10% aqueous (4 reactions, + to ++), and100% aqueous (11 reactions, ++ predominated). The following positive reactions to *Chamomilla recutita* (matricaria) tea II were reported: 1% aqueous (1 reaction, ++), 10% aqueous (10 reactions, + to +++; mostly ++), and 100% aqueous (11 reactions, + to +++; mostly ++).

Chamomilla Recutita (Matricaria) Extract
Chamomilla Recutita (Matricaria) Flower Oil

Up to 14 adult patients who had previously tested positive (at least a 2+ reaction) to ether extracts of *Chamomilla recutita* (2.5% in petrolatum) and/or *Arnica montana* (0.5% in petrolatum) were patch tested with the following: *Chamomilla recutita* (2.5% in petrolatum) and chamomilla recutita flower oil (1% and 4% in petrolatum).[65] A patch (Finn chambers on Scanpor® tape) containing either of the test materials was applied to the back for 2 days. Reactions were scored on day 3, and, possibly, day 7 according to ICDRG recommendations. Of the 10 patients patch tested with *Chamomilla recutita* (2.5% in petrolatum), 9 had positive reactions (+ to +++) and 1 had a doubtful positive follicular reaction. Only 2 of 14 patients had reactions to chamomilla recutita flower oil (doubtful positive reaction to 4 % [1 patient]; ++ reaction to 4% and 1% [1 patient]).

Chamomilla Recutita (Matricaria) Flower Oil

The skin sensitization potential of chamomilla recutita (matricaria) flower oil (2% in yellow, soft paraffin) was evaluated using 74 patients (ages not stated), all negative to balsam of Peru.[66] Of the 74 patients, 3 were positive to chamomilla recutita (matricaria) flower oil. Though negative to balsam of Peru, these 3 patients were also positive to 1 or more of the 3 other balsams (colophony, turpentine, and wood tars: *oleum betule* and *oleum fagi*). Details relating to the test procedure were not stated.

Of 200 patients patch tested with chamomilla recutita (matricaria) flower oil in Poland, 2 positive reactions were reported.[67] Details relating to the patch test procedure were not included.

Eighty-six patients with positive reactions to a perfume mixture containing the following ingredients were tested with chamomilla recutita (matricaria) flower oil:[68] eugenol, isoeugenol, cinnamic aldehyde, geraniol, cinnamic alcohol, oakmoss absolute, hydroxycitronellal, and amyl cinnamic alcohol. Neither the test concentration of chamomilla recutita (matricaria) flower oil nor details relating to the test protocol were included. Two (or 3.4%) of the 86 patients were sensitive to the oil.

Case Reports

Chamomile/Chamomile Extract

Rapid onset of a transient rash, burning, stinging, and itching at the application sites were reported for a 24-year-old woman who had applied a cosmetic skin mask formulation to her face.[69] Components of the skin mask were as follows: whole egg, lecithin, allantoin, aloe gel, melissa extract, and chamomile extract (extraction solvent not stated). The genus and species of the chamomile extract were not stated. Open testing (i.e., without prick, scratch, or chamber) with 1% chamomile extract (in physiologic saline) produced an extensive wheal and flare reaction on intact forearm skin. Open test results were negative for the saline control and 1% chamomile extract in 10 control subjects. The authors concluded that the patient appeared to have developed immunologic contact urticaria.

A 20-year-old woman complained of a short-lasting cough and rhinitis after inhaling fragrance from a chamomile-scented toilet paper.[70] The genus and species of the chamomile were not stated. Chamomile allergenicity was evaluated in a

prick test and radioallergosorbent test (RAST). Results for the prick test (wheal mean diameter = 12 mm) and RAST (Pharmacia ImmunoCAP system (CAP system): 12.9 KU/l (v.n. < 0.35) were positive. Results were also positive when the chamomile-scented toilet paper was evaluated in a prick-by-prick test (mean diameter of wheal = 9 mm (toilet paper) and 5 mm (histamine). Two atopic subjects and 2 healthy subjects served as controls for the prick-by-prick test, and results were negative for the chamomile-scented tissue.

Chamomilla Recutita (Matricaria) Flower

Occupational dermatitis of the hands was observed in a 27-year old florist, and patch test results revealed positive reactions to the petals and leaves of *Matricaria recutita* (*also Chamomilla recutita*).[71] Details relating to the patch test procedure were not included.

Delayed-type contact dermatitis of the face was observed in a 62-year-old female who worked in a flower stall 1 day per week.[72] The patient presented with a relapsing dermatitis of the face for 1 year. Relapse of dermatitis was observed within 24 h of working a single afternoon in the shop. Patch test results indicated positive reactions to the flowers, petals, and stems of *Matricaria recutita*. Details relating to the patch test procedure were not included.

A 54-year-old female cosmetician complained of sneezing, coughing (with occasional dyspnea), orbital pruritus, dacryorrhea, and rhinitis.[73] Her work involved the preparation and application of herbal beauty masks containing 24% chamomile flower (*Matricaria chamomilla*). Dermatitis of both hands, with intermittent vesiculation, was observed. Open patch testing (immediate reactions read after 30 and 60 minutes) revealed a positive reaction to chamomile flower. The diameter of the wheal was ≈1 cm. A positive prick test reaction (++) to chamomile pollen was also reported. A provocation test was performed using acoustic rhinometry, and the duration of exposure to chamomile flower was 3 minutes. Sneezing, dyspnea, and nasal chonchae swelling and hyperemia were reported. The decrease in volume of the nasal cavities was 3x that of the normal volume. Results of the provocation test were classified as strongly positive.

A 22-year-old female with facial eczema had been a frequent drinker of steaming-hot chamomile tea over the past year.[74] At times, the facial eczema was accompanied by lip swelling. Patch testing revealed a + D2/++ D4 reaction to 2.5% *Chamomilla recutita* in petrolatum. During follow-up at 4 months, the patient reported that she no longer drank chamomile tea and that there had been no further relapses of the eczema. It should be noted that the fragrant flowering heads of both German chamomile (*Chamomilla recutita*) and Roman chamomile (*Anthemis nobilis*) are collected and dried for use as teas and extracts.[35]

A 41-year-old atopic woman with hand eczema reported that she had not used chamomile tea externally, but had used the tea when treating her dog's inflamed eyes.[58] When patch tested, a +? follicular reaction to *Chamomilla recutita* (2.5% in petrolatum) was reported. In a subsequent identical patch test one month later, a ++ reaction was reported.

Chamomilla Recutita (Matricaria) Flower Extract

An 8-year old boy with hay fever and bronchial asthma had a severe anaphylactic reaction after ingestion of a *Matricaria chamomilla*-tea (from flower heads) infusion for the first time.[75] At 2 weeks after the reaction occurred, the patient was subjected to a skin prick test, beginning with a 1:100,000 wt/vol concentration of *Matricaria chamomilla* tea extract (tea extracted in phosphate-buffered saline). Skin test sites were read after 15 minutes, and a wheal of at least 3 mm x 3 mm was considered a positive reaction. Ten patients with hay fever and 10 normal subjects served as controls. Testing at a concentration of 1:100 wt/vol elicited a 4 mm by 6 mm wheal. None of the control subjects reacted to the tea extract. The enzyme-linked immunosorbent assay (ELISA) was used to test the 8-year-old patient's serum for specific IgE antibodies to antigens contained in the tea extract. IgE activity toward the tea extract was noted; however, this was not true for serum samples from 22 healthy subjects or from 5 patients with hay fever.

Acute eczema on the forearms and hands was observed in a 50-year old metalworker after using a product for cleaning metallic items.[76] The patient had no personal or family history of atopy, but had psoriasis. Treatment of the eczema involved washing and applying compresses (over 2-month period) with *Chamomilla recutita* (matricaria) tea (from flower heads). Patch tests were performed using Finn chambers; neither the area of application nor test concentration was stated. The following reactions were reported: Treatment with *Chamomilla recutita* (matricaria) tea resulted in a + reaction on day 2 and a ++ reaction on day 4. Negative results were reported for 5 control subjects tested with the tea.

A healthy, 35-year-old pregnant woman was given an enema containing glycerol and Kamillosan® (oily extract of *Chamomilla recutita* (matricaria) flowers).[77] The extraction solvent was not stated. Urticaria, larynx edema, tachycardia, and

hypotension followed, indicative of an anaphylactic reaction. In the skin prick test, Kamillosan® induced a 5 x 5 mm wheal reaction.

Eyelid angioedema was observed in a 23-year-old female after applying compresses of chamomile tea (obtained from the dried flower heads of *Chamomilla recutita*).[78] She had a history of seasonal rhinitis, conjunctivitis, and exercise-induced asthma. Prick test results were positive (++) for chamomilla recutita (matricaria) flower extract (extraction solvent not stated), and the level of IgE antibody was expressed as 3.37 kUA/l. In a subsequent oral challenge test performed with diluted chamomile tea, generalized pruritus of the face was the only symptom observed. The patient was diagnosed as having immune-mediated contact urticaria.

Work-related rhinoconjunctivitis and asthma were diagnosed in a 43-year-old man 11 years after he began working at a tea-packing plant.[79] The plant processed black tea (*Camellia sinensis*) as well as various herbal teas, including tea from chamomile flowers (*Chamomilla recutita*), lime (*Tilia cordata*), and dog rose. His symptoms occurred when chamomile tea was packaged. Furthermore, he became symptom-free when the production of herbal teas was transferred to another factory. A skin prick test with chamomile extract at a concentration of 10 mg/ml elicited a 6-mm wheal response. Prick test results were negative for black tea and lime tea extracts.

Phototoxicity

Chamomilla Recutita (Matricaria) Extract

Five patients were initially patch tested (Finn chambers on Scanpor® tape) with 2.5% chamomilla recutita (matricaria) ether extract, and the results were positive in 4 patients. The 5 patients were also evaluated in a standard photopatch test. The first reading (day 1) was followed by UV-irradiation and a second reading at day 3. Additional details regarding the test procedure were not included. Photoaggravation (score not provided) was observed in one of the 5 patients.[54]

Chamomilla Recutita (Matricaria) Flower Oil

Chamomilla (matricaria) flower oil (non-viscous, tested as received) was evaluated for phototoxicity using 12 Skh:hairless-1mice and 2 miniature swine.[80] The light source was a 6-kW long-arc xenon high pressure burner (UVA and UVB proportions approximated those found in mid-latitude summer sun spectrum) or a bank of 4 fluorescent F40BL black light lamps (UVA region, centered over 350 nm). A single application of the oil (20 µl) was made to an area of the back that was approximately 2 cm^2. Six mice and 1 swine were then exposed to one of the light sources, and, the remaining 6 mice and 1 swine, to the other light source at 30 minutes post-application of the oil. The duration of exposure to the fluorescent blacklight source was 1 h (integrated UVA intensity = 3 W/m^2), and, 40 minutes (intensity of weighted erythemal energy = 0.1667 W/m^2), to the xenon lamp. If application of the oil elicited a response from skin exposure to the blacklight lamp or elicited more than a barely perceptible response to the xenon lamp, the oil was considered phototoxic. The area of skin treated with the oil, but not irradiated, served as the control for primary irritant reactions. One group of control mice was treated with 8-methoxypsoralen (8-MOP, 0.01% in methanol), and another group was treated with an appropriate vehicle only. Exposure to the xenon lamp caused barely perceptible erythema in animals pretreated with vehicle only or with chamomilla (matricaria) flower oil. Parallel results were obtained using the blacklight lamp. 8-MOP was phototoxic.

Suppression of Sensory Irritation

Chamomilla Recutita (Matricaria) Flower Oil

Chamomilla recutita (matricaria) flower oil (German chamomile oil, bisabololoxide A type) was evaluated for its effect on capsaicin-induced sensory irritation in mice.[81] The intradermal injection of capsaicin into the mouse paw resulted in dose-dependent, paw-licking behavior due to sensory irritation. Co-administration of the oil suppressed this behavior in a dose dependent-manner over the 1% to 5% concentration range. The source of this information is an abstract of a Japanese study.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Chamomile

An epidemiology study examined the use of herbal products by pregnant women in Italy and pregnancy outcome.[82] The number of subjects (mostly between 31 and 40 years old) interviewed was 392. Of the 392 subjects, 109 reported having taken one or more herbal products during pregnancy; the remaining 283 were classified as non-users. The most frequently used herb was chamomile (48; 44% of the 109 subjects), followed by licorice (15; 13.8% of the 109 subjects). For the 37 regular users of chamomile and 14 regular users of licorice, there was a higher frequency of threatening miscarriages (21.6% and 35.7%, respectively) and preterm labors (21.6% and 16.7%, respectively) when compared to non-users. Whether or not the frequency of threatening miscarriages in users of chamomile versus non-users was statistically significant was not stated. An unspecified cardiac malformation (thought to have been related to Down's syndrome) and an enlarged kidney were diagnosed in 2 neonates, following regular maternal consumption of chamomile. Regarding pregnancy outcome in the study population, no statistically significant differences were evident between users and non-users, except for a higher incidence of newborns small for gestational age (11.9% vs. 5.3%; $p = 0.039$). However, after further analysis of the data, it was noted that a possible influence of regular intake of 2 herbs (chamomile and licorice, taken from the beginning of pregnancy) on threatening miscarriages and preterm labors of low birth weight infants could be hypothesized.

GENOTOXICITY

Chamomilla Recutita (Matricaria) Flower Oil

The genotoxicity of chamomile recutita (matricaria) flower oil was evaluated using 5 groups of five male NIH mice. Three groups of mice received oral doses of 10, 100, and 1000 mg/kg, respectively.[39] The extract of the essential oil (extraction solvent not stated) was obtained through a vapor distillation process, from the flowers of *Matricaria chamomilla*. The negative control group was dosed orally with corn oil and the positive control group was dosed intraperitoneally (i.p.) with an aqueous solution of methyl methanesulfonate (25 mg/kg). Following injection with an aqueous suspension of 5-bromodeoxyuridine (BrdU) and then colchicine, the mice were killed and bone marrow cell suspensions prepared for microscopic examination. At each dose, the incidence of sister chromatid exchanges was comparable to that noted in bone marrow cells from control animals (i.e., not more than 1.1). A high incidence of SCE's was observed after dosing with MMS, and the difference between this incidence and that for animals dosed with corn oil was statistically significant ($p < 0.05$). Additionally, when compared to control values, chamomile recutita (matricaria) flower oil produced a non-significant cytotoxic effect. The results for an acute oral toxicity preliminary test on the crude oil are included in that section of this report.

Chamomilla Recutita (Matricaria) Flower Extract

One of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract has the INCI name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract (see Table 4 for composition). It is also known as vegetol matricaire 4140 huileux, contains 1 to 4.9% chamomilla recutita (matricaria) flower extract, and mineral oil and prunus armeniaca (apricot) kernel oil are the extraction solvents. The genotoxicity of this mixture (in DMSO) was evaluated in the Ames test using the following bacterial strains with and without metabolic activation: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2 *uvrA* pKM101.[83] The mixture was tested at doses up to 5,000 µg/plate. DMSO served as the negative (vehicle) control, and the following positive controls were used: 2-nitrofluorene, sodium azide, 9-aminoacridine, methyl methanesulfonate, and 2-aminoanthracene. Neither signs of toxicity or a precipate were observed over the range of doses tested. When compared to the negative control, the statistically significant increases in the number of revertants observed in strain TA100 without activation or in strain WP2 *uvrA* pKM101 with activation were slight, but there was no dose-relationship associated with these findings. Therefore, these changes were considered biologically insignificant. The authors concluded that the trade name mixture did not induce any biologically relevant increase in the number or revertants in any of the strains, with or without metabolic activation.

Antigenotoxicity

Chamomilla Recutita (Matricaria) Flower Oil

Chamomile recutita (flower) oil-induced inhibition of genotoxicity produced by daunorubicin (DAU, mutagen) and the genotoxicity of the oil were evaluated using the following groups of 5 male NIH mice:[84] control group administered corn oil orally (0.1 ml), positive control group treated with corn oil (0.1 ml) and DAU administered by intramuscular injection (10 mg/kg), a group administered chamomile recutita (flower) oil (500 mg/kg), and 3 groups treated with DAU and chamomile recutita (flower) oil (5, 50, and 500 mg/kg), respectively. Specifically, the effect of the 3 doses of essential oil on the rate of sister chromatid exchange (SCE) induced by DAU in spermatogonia was studied. Chamomile recutita (flower) oil was not genotoxic. However, dosing with this essential oil resulted in inhibition of SCE induced by DAU, and % inhibition was as follows at administered doses of the oil: 5 mg/kg (47.5% inhibition), 50 mg/kg (61.9% inhibition), and 500 mg/kg (93.5% inhibition).

Chamomilla Recutita (Matricaria) Flower Oil

Antigenotoxicity studies were performed using groups of 5 male NIH mice. The extract of the essential oil (extraction solvent not stated) obtained through a vapor distillation process from the flowers of *Matricaria chamomilla* was evaluated. When compared to mice dosed with corn oil**,** sister chromatid exchanges induced by daunorubicin were decreased in mice pre-treated with crude chamomile recutita (matricaria) flower oil at doses ranging from 5 to 500 mg/kg.[39] Administration of the crude oil to daunorubicin-treated mice caused a statistically significant, dose-dependent reduction in the genotoxic damage (SCE's). The antigenotoxic response corresponded to 25.7, 63.1, and 75.5% at doses of 5, 50, and 500 mg/kg, respectively. Similarly, a statistically significant, dose-dependent decrease in genotoxicity (SCE's) was observed in MMS-treated mice after dosing with the crude oil. The 3 doses of crude oil tested (250, 500, and 1000 mg/kg) induced 24.8, 45.8, and 60.6% inhibition of genotoxicity, respectively.

Chamomilla Recutita (Matricaria) Tea Extract

Modification of the *in vitro* activity of heterocyclic aromatic amines [HAA, in DMSO] with the hot water extract of *Chamomilla recutita* (matricaria) tea was studied in the Ames plate incorporation test, with and without metabolic activation, using *Salmonella typhimurium* strain TA98.[85] Initially, measured volumes of the tea extract (usually 1, 5, 10, 50, and 100 µl) were plated in triplicate to establish a dose-response curve. DMSO served as the negative control, and there were 3 sets of positive controls, 2-amino-3- methylimidazo[4,5-*f*]quinolone (IQ), 2-amino-3,4-dimethylimidazo[4,5-*f*]quinolone (MeIQ), and B[*a*]P. Test results were expressed as the induced number of revertants by subtracting the number of spontaneous revertants (20-38 revertants/plate) from the total number obtained on each plate. A sample was considered mutagenic if it produced a dose-related increase in the number of revertants, when compared to the control, and if the number of revertants was at least 2.5 times greater than the spontaneous level. *Chamomilla recutita* (matricaria) tea (from flower heads) extract alone was not mutagenic.

HAAs were tested in combination with 2 doses of the tea extract, 10 and 50 mg tea leaves/plate (i.e., 10 and 50 milligram equivalents [mgEQ]). All tests were performed in triplicate. At both doses, *Chamomilla recutita* (matricaria) tea extract caused mild inhibition of the mutagenicity of IQ-type HAA (tested up to 0.5 ng/plate), but caused potentiation of the mutagenicity of 2-amino-3,7,8-trimethylimidazo[4,5-f]quinoxaline (7,8-DiMeIQx, tested at 5 ng/plate) and 4,7,8-TriMeIQx (tested at 10 ng/plate).[85]

CARCINOGENICITY

Carcinogenicity studies on the chamomile ingredients reviewed in this safety assessment were not found in the published literature, nor were unpublished studies provided.

Anticarcinogenicity

Chamomilla Recutita (Matricaria) Flower Extract

The cytotoxic activity of the following chamomilla recutita (matricaria) flower extracts against Yoshida ascites sarcoma was evaluated using Wistar Glaxo albino rats: 4.27% chamomilla recutita (matricaria) flower (petroleum ether

extract), 10.04% chamomilla recutita (matricaria) flower (ethanol extract), and 13.73% chamomilla recutita (matricaria) flower (distilled water extract).[86] The following procedure was followed prior to determining these 3 extract yields. Following filtration, the aqueous solutions were lyophilized or the organic solvents were removed in vacuo. The crude total extracts were then dissolved in phosphate buffer solution (pH 7.2) and sterilized by filtration. Ascites sarcoma cells were transplanted by i.p. injection into the rats. At 7 to 8 days post-injection, ascitic fluid was drawn from each animal, centrifuged, and the sediment was resuspended in the original volume with phosphate buffer solution. The tumor cells were then washed and resuspended in the same buffer solution to obtain a final concentration of 15×10^5/ml. Cytotoxicity was evaluated using the dye test. Equal volumes (0.2 ml) of serially diluted extracts (50 to 6.25 mg/ml) and of cell suspensions were mixed and incubated for 60 minutes. Trypan blue solution was then added to the mixture, and the differential count of stained and unstained cells was performed. Cytotoxicity was expressed as the LD_{50}. All 3 extracts were classified as exhibiting a poor cytotoxic effect ($LD_{50} > 10$ mg/ml).

Chamomilla Recutita (Matricaria) Flower Oil

The anticancer activity of chamomilla recutita (matricaria) flower oil against human leukemia HL-60 and NB4 cells was evaluated *in vitro* at concentrations up to 200 ppm.[87] The cells used were from human promyelocytic cell lines, and the oil was evaluated at concentrations of 25, 50, 75, 100, and 200 ppm in cells cultured for 24 h. Untreated cells served as controls. At the highest test concentration, the percentage of dead cells was 78.4% for HL-60 cells and 86.03% for NB4 cells.

BIOLOGICAL ACTIVITY

Immunomodulatory Activity

Chamomilla Recutita (Matricaria) Extract

The immunomodulatory activity of chamomilla recutita (matricaria) extract (extracted with methanol/water 50%) was studied using groups of 6 Balb/c mice.[88] The plant was grown in Egypt. Each of 6 animals was dosed i.p. with the extract (20 mg/dose/animal) for 5 consecutive days. Six untreated mice served as controls, and received the solvent (not stated) used to dissolve the extract. Blood samples were collected from the retro-orbital plexus. Dosing with the extract enhanced the total white blood cells count (up to 1.2×10^4 cells/mm^3). Bone marrow cellularity was also increased significantly ($P < 0.01$), and the same was true for spleen weight ($P < 0.01$). When 2 groups of mice were immunosuppressed with cyclophosphamide (200 mg/kg body weight), it was found that pretreatment of one of the groups with the extract restored the resistance of these mice against lethal fungal infection with the predominantly granulocyte-dependent *Candida albicans*. The results of this study confirmed the immunomodulatory activity of chamomilla recutita (matricaria) extract.

Chamomilla Recutita (Matricaria) Flower Oil

In another study, the efficacy of chamomilla recutita (matricaria) flower oil in alleviating atopic dermatitis-like immune alterations was evaluated using the following 4 groups of 10 BALB/c mice (7 weeks old):[89] normal group (saline applied throughout atopic dermatitis induction stage and oil treatment period), control group (saline applied following induction of atopic dermatitis), vehicle group (jojoba oil applied), and experimental group (3% chamomilla recutita (matricaria) flower oil applied after atopic dermatitis induction). Initially, the mice were sensitized twice per week with 1% 2,4-dinitrochlorobenzene (DNCB,100 µL), applied to dorsal skin (8 cm^2). During the following week, the animals were challenged twice with 0.2% DNCB (100 µL) for atopic dermatitis induction. Next, 3% chamomilla recutita (matricaria) flower oil (70 µL) was applied daily (6 times per week) for 4 weeks. Control mice were treated with saline or jojoba oil. Blood samples were collected following the second DNCB challenge and at 2 and 4 weeks after application of the oil.

When compared to the jojoba oil or saline control groups, the application of chamomilla recutita (matricaria) flower oil resulted in significant reduction ($p < 0.05$) of serum IgE levels at the end of the 4-week application period. When compared to 2 weeks of application (1.80 mg/mL reduction), 4 weeks of oil application caused a 31% (13.75 mg/mL) reduction in the serum IgG1 level. Additionally, when compared to the saline control group (37.43 ng/mL serum histamine level) or jojoba oil control group (30.60 ng/mL serum histamine level or 40% lower) at 2 weeks, application of the oil resulted in a significantly lower (18.45 ng/mL or 51% lower, $p < 0.05$) serum histamine level. The frequency of scratching following application of the oil was significantly lower when compared to either control group. The immunoregulatory potential of chamomilla recutita (matricaria) oil for alleviating atopic dermatitis through influencing of T helper 2 lymphocyte activation was demonstrated in this study.[89]

Wound Healing Activity

Chamomilla Recutita (Matricaria) Flower Extract

The wound healing activity of chamomilla recutita (matricaria) flower extract was evaluated using 2 groups of 6 Sprague-Dawley rats. [40] One group of rats received chamomilla recutita (matricaria) flower extract (aqueous extract) in drinking water at a dose of 120 mg/kg/day. The wound closure rate was assessed by tracing the wound on days 1, 5, 10, and 15 post-wounding. Epithelialization was said to have occurred when the eschar fell off without leaving a residual raw wound. Control rats were maintained on plain drinking water. Healing was assessed by the rate of wound contraction, period of epithelialization, wound-breaking strength, granulation tissue weight, and hydroxyproline content. When compared to controls on day 15, test animals had a greater reduction in wound area (61% - test; 48% - controls), faster epithelialization, and a statistically significantly higher wound-breaking strength ($p < 0.002$). Wet and dry granulation tissue weight and hydroxyproline content were also significantly higher in test animals. It was concluded that chamomilla recutita (matricaria) flower extract facilitated wound healing.

SUMMARY

The safety of German chamomile (*Chamomilla recutita* (*matricaria*)) ingredients is reviewed in this assessment. These ingredients function mostly as fragrance ingredients and skin conditioning agents in cosmetic products. The VCRP and Council survey data combined indicate that the following 8 chamomile ingredients have been used in cosmetic products: chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower/leaf extract, chamomilla recutita (matricaria) flower oil, chamomilla recutita (matricaria) flower powder, chamomilla recutita (matricaria) flower water, and chamomilla recutita (matricaria) oil. Of the ingredients reviewed in this safety assessment, the highest use concentration has been reported as 0.5% for chamomilla recutita (matricaria) flower.

Chamomilla recutita (matricaria) flower oil is produced by the steam distillation of chamomile (*Chamomilla recutita*) flowers. One of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract [INCI name: mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract] is manufactured by prolonged maceration in a mixture of mineral oil and apricot kernel oil. Another trade name mixture associated with chamomilla recutita (matricaria) flower extract [INCI name: propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract] is manufactured by hydroglycolic extraction.

Sesquiterpenes, sesquiterpene alcohols (α-bisabolol, major component), and paraffin hydrocarbons are among the components of chamomilla recutita (matricaria) flower oil.

A UV spectral analysis has indicated an absorption maximum of 285 nm for chamomilla recutita (matricaria) flower oil. Additionally, a logP value of 5.29 has been reported for this ingredient.

The following ingredients did not induce acute toxicity when administered orally to mice or rats: chamomilla recutita (matricaria) flower (1,440 mg/kg), chamomilla recutita (matricaria) flower oil (5,000 mg/kg), and chamomilla recutita (matricaria) flower oil (5,600 mg/kg). The same was true for chamomilla recutita (matricaria) oil (5,000 mg/kg) when administered dermally to rabbits. Chamomile recutita (matricaria) flowers (in the form of herbal tea) did not induce oral toxicity when consumed repeatedly by rats or humans. Chamomilla recutita (matricaria) flower extract also did not induce oral toxicity in rats when administered repeatedly.

The antimicrobial activity of chamomilla recutita (matricaria) flower oil has been demonstrated using various bacterial and fungal strains.

Seven hay fever patients experienced conjunctivitis after ocular rinsing with *Chamomilla recutita* (matricaria) tea (from flowers). The results of a provocation test involving the tea extract confirmed that the tea induced allergic conjunctivitis. Chamomilla recutita (matricaria) flower oil was not irritating to the hen's egg chorioallantoic membrane in the HET-CAM *in vitro* assay for assessing ocular irritation potential. The following trade name mixtures associated with chamomilla recutita (matricaria) flower extract were evaluated for ocular irritation in rabbits: mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract, propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract, and propylene glycol (and) water salvia officinalis (sage) leaf extract chamomilla recutita (matricaria flower extract). Each was classified as a non-irritant.

Skin irritation was observed in an acute dermal toxicity study on chamomilla recutita (matricaria) flower oil involving rabbits. Undiluted Chamomilla recutita (matricaria) flower oil was classified as non-irritating to the skin of hairless mice, and moderately irritating to the skin of rabbits. The following trade name mixtures associated with chamomilla recutita (matricaria) flower extract were evaluated for skin irritation in rabbits: mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract, propylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract, and propylene glycol (and) water salvia officinalis (sage) leaf extract chamomilla recutita (matricaria flower extract). Each was classified as a non-irritant.

Cross-reactivity of 10% chamomilla recutita (matricaria) extract with carabron (a sesquiterpene lactone) was not demonstrated in a guinea pig skin sensitization study.

In a single application, epicutaeous patch test involving 29 normal subjects and 21 patients (17 with sensitive skin; 3 with eczema; 1 with allergy), results for a cuticle softener containing 0.3% chamomilla recutita (matricaria) flower extract were negative for skin irritation. In human predictive patch tests, chamomilla recutita (matricaria) flower oil (4%) was neither a skin irritant in subjects tested nor a skin sensitizer in a maximization test involving 25 subjects. Other predictive HRIPT results for a shave balm containing 0.2% chamomilla recutita (matricaria) flower extract (105 subjects), an eye lotion containing 0.4% chamomilla recutita (matricaria) flower extract (107 subjects), a facial cleansing and makeup remover towelettes containing 0.01% chamomilla recutita (matricaria) extract, and a hair gel styling mist containing 0.00006% chamomilla recutita (matricaria) flower/leaf extract were negative for skin irritation and sensitization.

In provocative tests, skin sensitization was observed in 18 of 24 patients patch tested with 1% chamomilla recutita (matricaria) ether extract and in 4 of 5 patients and 48 of 85 patients patch tested with 2.5% chamomilla recutita (matricaria) ether extract in petrolatum. Five of 9 patients with positive patch test reactions to sesquiterpene lactone mix also had an allergic reaction to 2.5% *Chamomilla recutita* (matricaria) [plant part(s) not specified] in petrolatum. Skin sensitization was also observed in 19 gardeners and greenhouse workers with compositae-related symptoms who were patch tested with 2.5% *Chamomilla recutita* (matricaria) in petrolatum. Of 36 patients patch tested with ether extracts of *Chamomilla recutita* (matricaria), 30 had positive patch test reactions, most of which were ++ or +++. Similarly, of the 35 patients patch tested with 2.5% *Chamomilla recutita* (matricaria) in petrolatum, 22 had sensitization reactions (+ to +++). The number of patients (group of 35, sesquiterpene lactones mix sensitive) with positive reactions to chamomilla recutita (matricaria) flower aqueous extract decreased with decreasing test concentrations (100% [30 patients] to 1% [9 patients]). Of 129 patients (sensitive to compositae mix) patch-tested with 2.5% chamomilla recutita (matricaria) flower extract, 83 had sensitization reactions. In the prick test, chamomilla recutita (matricaria) extract (applied to forearm, 3.5 mg/ml) induced wheal formation in all 9 patients.

Provocative testing also yielded patch test reactions to chamomilla recutita flower oil, a doubtful positive reaction in 1 of 14 patients (4% concentration) and a ++ reaction to 4% and 1% in a second patient. Patch testing also resulted in a low incidence of skin sensitization to chamomilla recutita (matricaria) flower oil in 3 of 74 patients (2% in yellow soft paraffin), 2 of 200 patients, and 2 of 86 patients. The 86 patients were also sensitive to a perfume mixture. Positive reactions to chamomilla recutita (matricaria) flower extract and *Chamomilla recutita* plant parts (petals, leaves, flowers, and stems) were also observed in case reports.

Barely perceptible erythema was observed in hairless mice and miniature swine treated with chamomilla recutita (matricaria) flower oil in a photoxicity study, and these results were classified as negative. Photoaggravation was observed in 1 of 5 patients tested with 2.5% chamomilla recutita (matricaria) ether extract in a standard photopatch test.

For 37 regular users of chamomile (herbal product, genus and species not stated), both the frequency of threatening miscarriages and the frequency preterm labors were 21.6% higher when compared to non-users (group of 283); many of the subjects also consumed licorice.

The incidence of sister chromatid exchanges in bone marrow cells from mice dosed orally with chamomilla recutita (matricaria) flower extract was comparable to that observed in in bone marrow cells from control mice. The genotoxicity of one of the trade name mixtures associated with chamomilla recutita (matricaria) flower extract [mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) extract] was evaluated using the following bacterial strains: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2 *uvrA* pKM101. Results were negative both with and without metabolic activation. The antigenotoxic activity of chamomilla recutita (matricaria) flower oil and chamomilla recutita (matricaria) flower oil t was also demonstrated *in vitro*.

Carcinogenicity data on chamomile ingredients were not found in the published literature. Chamomilla recutita (matricaria) flower extract and chamomilla recutita flower oil caused a significant decrease in cell viability in human cancer cell lines.

Various biological effects of chamomile ingredients (*Chamomilla recutita (matricaria)*, such as immunomodulatory activity and wound healing activity, have been identified in the published literature.

DISCUSSION

As botanical ingredients, derived from natural plant sources, are complex mixtures, the Panel expressed concern that multiple botanical ingredients may each contribute to the final concentration of a single constituent. Azulene has been identified as a component of chamomilla recutita (matricaria) flower oil, and the Panel previously concluded that the available data are insufficient to support the safety of azulene for use in cosmetic products. The Panel also expressed concern over components of chamomilla recutita (matricaria) flower extract (i.e., quercetin, and quercetin-3-glucoside (isoquercitrin)) that may be genotoxic/carcinogenic, and components of chamomilla recutita (matricaria) flower oil (i.e., β-farnesene, linalool, and linalool acetate) that may be sensitizers (linalool and linalool acetate) and have insecticidal activity (β-farnesene). The Panel concluded that these components are not at levels of toxicologic concern in cosmetics, but also noted that, given the presence of *Chamomilla recutita*-derived ingredients in fragrances, plant consituents of toxicologic concern should not exceed any limitations that may have been established by the International Fragrance Association (IFRA). Thus, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects. The Panel also expressed concern about pesticide residues and heavy metals that may be present in *Chamomilla recutita*-derived ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities in the ingredient before blending into cosmetic formulations.

The Panel was concerned that cosmetics containing these ingredients be formulated to be non-sensitizing because the levels of potentially sensitizing constituents in the ingredients (e.g., sesquiterpene lactones), can be quite variable (depending on plant growth conditions, extraction methods, and other factors), and the data available from sensitization tests may not represent the complete spectrum of concentrations of such constituents in the ingredients as used in cosmetic products. In addition, the Panel was concerned that the concentrations of potentially sensitizing constituents should not exceed levels of concern in formulations containing ingredients from multiple plant species that each can contribute such constituents to the overall formulations.

In response to the Panel's request for skin irritation and sensitization data on chamomilla recutita (matricaria) flower extract, human repeated insult patch test (HRIPT) data on products containing 0.2%, 0.3%, and 0.4% chamomilla recutita (matricaria) flower extract were received. The 3 studies yielded negative results, and were considered sufficient, together with other skin sensitization data in the safety assessment, for evaluating the skin irritation and sensitization potential of all 5 *Chamomilla recutita* (matricaria) flower-derived ingredients in cosmetics. Current use concentration data received from the Personal Care Products Council indicate that *Chamomilla recutita* (matricaria) flower-derived ingredients are being used in leave-on products at concentrations up to 0.5% (chamomilla recutita (matricaria) flower extract), and the Panel agreed that the HRIPT data on products containing chamomilla recutita (matricaria) flower extract can be used to evaluate the safety of *Chamomilla recutita* (matricaria) flower-derived ingredients over the range of use concentrations reported. The Panel also considered that FDA has listed *Chamomilla recutita* flowers as generally recognized as safe (GRAS) for their intended use in food for human consumption. However, the Panel determined that the available data are insufficient for determining that ingredients derived from *Chamomilla recutita* leaf, and stem, or the whole plant are safe for use in cosmetics and that chemical composition data on these ingredients are needed.

Provocative patch testing involves patients with diseased skin. The Panel discussed the relevance of positive provocative test results for chamomilla recutita (matricaria) extract (ether extracts) at concentrations up to 2.5%, considering that the method of preparation of these extracts is dissimilar to those used to produce commercial *Chamomilla recutita*-derived ingredients. The commercial ingredients are produced by steam distillation or using multiple extraction solvents, such as oils, propylene glycol, water, and carbon dioxide, whereas, the ether extracts of freshly cut plants would probably contain the maximally concentrated organic constituents. Therefore, the content of the ether extracts prepared specifically for the tests performed may deviate from the content of the commercially-supplied ingredients.

Because chamomilla recutita (matricaria) flower oil may contain (-)-α-bisabolol at concentrations as high as 41.45%, safety test data from the CIR final report on bisabolol are included in Table 1 of this safety assessment. The Panel concluded

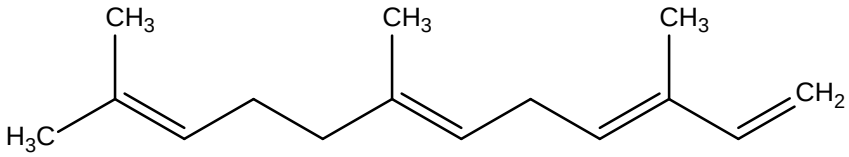
that bisabolol is safe as used in cosmetic formulations; reported use concentrations ranged from 0.001% to 1%. The following data on bisabolol are included in this report to support the safety of chamomilla recutita (matricaria) flower oil in cosmetic products: skin penetration, skin penetration enhancement, acute inhalation toxicity, acute oral and intraperitoneal toxicity, repeated dose oral and dermal toxicity, ocular irritation, skin irritation and sensitization, photosensitization, genotoxicity, and reproductive and developmental toxicity data.

The Panel discussed the issue of incidental inhalation exposure from propellant and pump hair sprays and face powders and sprays. Inhalation toxicity data were not available. However, the Panel considered pertinent data indicating that incidental inhalation exposures to these ingredients in such cosmetic products would not cause adverse health effects, including acute inhalation toxicity data on bisabolol and data characterizing the potential for these ingredients to cause acute and repeated dose oral toxicity, and ocular or dermal irritation or sensitization. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

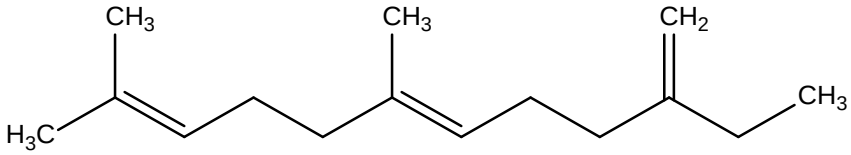
CONCLUSION

The CIR Expert Panel concluded that chamomilla recutita (matricaria) flower, chamomilla recutita (matricaria) flower extract, chamomilla recutita (matricaria) flower powder, chamomilla recutita (matricaria) flower water, chamomilla recutita (matricaria) flower oil are safe in the present practices of use and concentration, described in this safety assessment, in cosmetics, when formulated to be non-sensitizing. The Panel also concluded that the available data are insufficient to make a determination that chamomilla recutita (matricaria) extract, chamomilla recutita (matricaria) flower/leaf extract, chamomilla recutita (matricaria) flower/leaf/stem extract, chamomilla recutita (matricaria) flower/leaf/stem water, chamomilla recutita (matricaria) leaf extract, and chamomilla recutita (matricaria) oil are safe under the intended conditions of use in cosmetics.

1. Farnesene

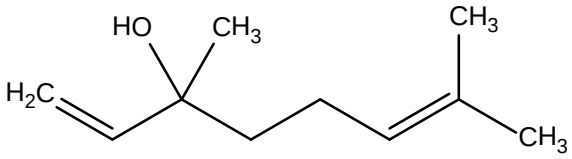


alpha-farnesene

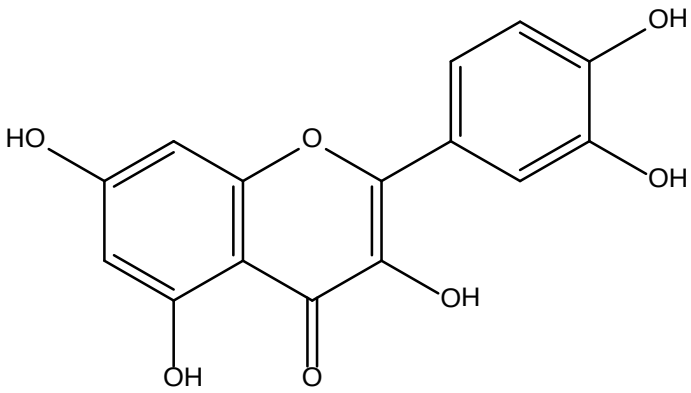


beta-farnesene

2. Linalool



3. Quercetin



4. Azulene

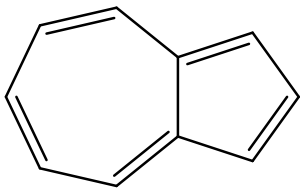


Figure 1. Structural formulas for some of the constituents of chamomilla recutita (matricaria) flower oil and extract.

Table 1. Data from CIR Final Safety Assessment on Bisabolol

Test Substance	Animals/Subjects/ Tissues/Cells Studied	Procedure	Results
		Skin Penetration Enhancement	
1:1 α-Bisabolol:propylene glycol mixture	Epidermis from abdominal human cadaver skin	Pretreatment of epidermis with test substance, followed by application of 5-fluorouracil (5-FU) or triamcinolone acetonide.	Increased permeability of 5-FU and triamcinolone acetonide by 17- and 73-fold, respectively.[90]
α-Bisabolol	Epidermis from abdominal human cadaver skin	Pretreatment of epidermis with test substance, followed by application of 5-FU.	5-fold increase in 5-FU permeability. α-Bisabolol altered the transition enthalpy of skin lipids.[90]
		Skin Penetration	
^{14}C-Levomenol [(-)-6-methyl-2-(4-methyl-3-cyclohexen-1-yl)-5-hepten-2-ol and (-)-α-Bisabolol]	Mice (number and strain not specified)	^{14}C-Levomenol solution, delivered with either arlatone or acetone as a solubilizer, applied to shaved skin (radioactive dose = 40.6 kBq).	After 1 h, 80% of applied radioactivity (from arlatone solution) remained at application site. By 3 h and 5 h, radioactivity at application site decreassed to 57% and 50%, respectively. Similar results with acetone solution. ^{14}C-Levomenol detected in fatty and muscle tissues of the neck.[91]
		Acute Oral Toxicity	
(-)-α-Bisabolol	Mice (number and strain not specified)	Oral dosing (procedure not stated)	LD_{50} = 15.1 ml/kg.[92]
(-)-α-Bisabolol	Rats (number and strain not stated)	Oral dosing (procedure not stated)	LD_{50} = 15.6 ml/kg (females) and 14.9 ml/kg (males).[92]
(±)-α-Bisabolol	Rats (number and strain not stated)	Oral dosing (procedure not stated)	LD_{50} > 5 g/kg.[93]
		Acute Parenteral Toxicity	
(±)-α-Bisabolol	12 rats (strain not stated)	Exposed for 7 h to aerosolized test substance.	No deaths or lesions at necropsy.[94]
(±)-α-Bisabolol (in emulsion)	Mice (number and strain not specified)	Intraperitoneal dosing	LD_{50} = 633 mg/kg.[95]
		Repeated Dose Toxicity	
Bisabolol (85% pure oily liquid)	Groups of 20 Wistar Br 46-II rats (10 per sex)	1 ml/kg by stomach tube 7 days/week for 6 weeks.	No intolerance reactions observed.[92]
Bisabolol (85% pure oily liquid)	2 groups of 40 Sprague-Dawley rats (20 per sex)	2 ml/kg or 3 ml/kg by stomach tube 7 days/week for 4 weeks.	Slight and increased motor agitation at 2 ml/kg and 3 ml/kg, respectively; 20% mortality and decreased body weight gain at 3 ml/kg. Inflammatory changes (more severe at 3 ml/kg) in liver, trachea, spleen, thymus, and stomach; characterized as an"infection defense weakness triggered by the emaciation".[92]
Bisabolol (85% pure oily liquid)	2 mixed breed dogs	1 ml/kg body weight by stomach tube 7days/week for 2 weeks.	No intolerance reactions observed. [92]
Bisabolol (85% pure oily liquid)	Groups of 6 dogs (3 per sex)	2 ml/kg or 3 ml/kg (increased to 4 ml/kg at week 2) oral dose 7 days/week for 4 weeks.	Appetite loss and reduced feed intake at 2 ml/kg; both more severe at 4 ml/kg. At necropsy, liver weight-relative-to-body-weight significantly increased.[92]

Table 1. Data from CIR Final Safety Assessment on Bisabolol

Test Substance	Animals/Subjects/ Tissues/Cells Studied	Procedure	Results
α-Bisabolol (87.5% pure, in olive oil)	10 Wistar rats (5 per sex)	Applied to clipped skin (under semiocclusive dressing) at doses of 50, 200, and 1000 mg/kg body weight. Doses applied 7 days/week (6 h/day) for 4 weeks.	No treatment-related effects in low- and mid-dose groups. Slight decrease in body weight gain and feed efficiency in all rats of high-dose group only on day 7; also, decreased mean terminal body weight (high-dose males and females). High-dose female rats also had transient, moderate erythema. NOAEL = 200 mg/kg/day.[96]
		Ocular Irritation	
(-)-α-Bisabolol (undiluted)	3 rabbits	Instilled into 1 conjunctival sac of each animal; eyes not rinsed.	Well-defined conjunctival redness in all rabbits at 1 h, 24 h, and 48 h, but not at 72 h.[97]
		Skin Irrritation and Sensitization	
(-)-α-Bisabolol (undiluted)	3 white Vienna rabbits	Semiocclusive patches with test substance applied for 4 h to clipped back or flank.	At 4 h reading, very slight erythema in all rabbits. Well-defined erythema in 2 rabbits at 24 h, and very slight erythema in 1 rabbit at 72 h.[98]
Bisabolol (5% in petrolatum)	Patients (total number not stated) suffering from or suspected of suffering from cosmetic product contact allergy	Patch test (procedure not stated)	No skin irritation in 1 to 20 patients. According to source, these preliminary results were from an unpublished, ongoing study.[99]
Product containing 0.1% bisabolol	25 panelists	Maximization test (occlusive patches)	Neither irritation nor sensitization observed.[100]
		Photosensitization	
Bisabolol (3% or 15% v/v in absolute alcohol or olive oil)	Groups of 5 male white Pirbright guinea pigs	Test substance (in absolute alcohol) applied to shaved skin of neck. Application followed by irradiation with light at 240-540 nm wavelengths (7.9 kilolumens for 15 min). Protocol followed for 5 days, then a 9-day non-treatment period. Protocol then repeated (vehicle changed to olive oil) for 2 successive days, followed by 12-day non-treatment period. Bisabolol solutions (dissolved in commercial soap) then applied to left leg, followed by irradiation, and procedure repeated for 3 days.	No evidence of photosensitization.[101]
		Genotoxicity	
Bisabolol (86.8% pure, in DMSO)	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537	Ames standard plate test (doses up to 5,000 µg/plate); preincubation protocol (doses up to 1,500 µg/plate). Both protocols with and without metabolic activation.	Non-genotoxic in both assays.[102]
Bisabolol (86.8% pure, in DMSO)	Chinese hamster V79 cells	Chromosome aberrations assay. Doses up to 31.25 µg/ml (with metabolic activation) and up to 3.13 µg/ml (without metabolic activation).	Non-genotoxic.[103]
Bisabolol (86.8% pure, in DMSO)	Chinese hamster V79 cells	Chromosome aberrations assay. Doses up to 40 µg/ml (with metabolic activation) and up to 4 µg/ml (without metabolic activation).	Non-genotoxic.[103]

Table 1. Data from CIR Final Safety Assessment on Bisabolol

Test Substance	Animals/Subjects/ Tissues/Cells Studied	Procedure	Results
		Reproductive and Developmental Toxicity	
Bisabolol (98% pure)	Pregnant rats (number and strain not stated)	Oral (stomach tube) doses up to 3.0 ml/kg body weight on days 6-15 of gestation.	No effect on prenatal development at doses ≤ 1.0 ml/kg. Significant reduction in fetal number and subsequent increase in resorption rate at 3.0 ml/kg. No deformities observed. Lowest toxic dose for both fetuses and dams between 1 and 3 ml/kg body weight perorally.[92]
Bisabolol	Pregnant New Zealand rabbits (number not stated)	Oral (stomach tube) doses up to 3.0 ml/kg body weight on days 6-15 of gestation.	No effect on prenatal development at doses ≤ 1.0 ml/kg. Reduction in number of living fetuses at 3.0 ml/kg; no deformities or dead fetuses. Lowest toxic dose for both fetuses and dams between 1 and 3 ml/kg body weight perorally.[92]

Table 2. Definitions and functions of the ingredients in this safety assessment[1]

Ingredient, CAS No.	Definition	Function
Chamomilla Recutita		
Chamomilla Recutita (Matricaria) Extract	Chamomilla Recutita (Matricaria) Extract is the extract of the whole plant, *Chamomilla recutita*.	Skin-conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Flower	Chamomilla Recutita (Matricaria) Flower is the flower of *Chamomilla recutita*.	Skin-conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Flower Extract [84082-60-0]	Chamomilla Recutita (Matricaria) Flower Extract is the extract of the flowerheads of the matricaria, *Chamomilla recutita*.	Fragrance ingredients; skin-conditioning agents-miscellaneous; skin conditioning agents-occlusive
Chamomilla Recutita (Matricaria) Flower/Leaf Extract	Chamomilla Recutita (Matricaria) Flower/Leaf Extract is the extract of the flowers and leaves of *Chamomilla recutita*.	Cosmetic Biocides
Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Extract	Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Extract is the extract of the leaves, flowers and stems of *Chamomilla recutita.*	Flavoring agents; oral care agents; skin conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Water	Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Water is an aqueous solution of the steam distillate obtained from the flowers, leaves and stems of *Chamomilla recutita*.	Fragrance ingredients
Chamomilla Recutita (Matricaria) Flower Oil [8002-66-2]	Chamomilla Recutita (Matricaria) Flower Oil is the volatile oil obtained from the flowers of *Matricaria recutita*.	Fragrance ingredients; skin-conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Flower Powder	Chamomilla Recutita (Matricaria) Flower Powder is the powder obtained from the dried, ground flowers of *Chamomilla recutita.*	Skin-conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Flower Water	Chamomilla Recutita (Matricaria) Flower Water is an aqueous solution of the steam distillate obtained from the flowers of *Chamomilla recutita*.	Fragrance ingredients
Chamomilla Recutita (Matricaria) Leaf Extract [84082-60-0]	Chamomilla Recutita (Matricaria) Leaf Extract is the extract of the leaves of *Chamomilla recutita.*	Fragrance ingredients; skin-conditioning agents-miscellaneous
Chamomilla Recutita (Matricaria) Oil	Chamomilla Recutita (Matricaria) Oil is the volatile oil obtained from the whole plant, *Chamomilla recutita.*	Fragrance ingredients

Table 3. Chemical and Physical Properties[38,104]

Properties	Chamomilla Recutita (Matricaria) Flower Oil
Form	Deep blue or blue-green liquid with strong, characteristic odor
logP	5.29
Specific gravity	Between 0.910 and 0.950
Solubility	Soluble in most fixed oils and in propylene glycol. Insoluble in glycerin and in mineral oil
Acid value	Between 5 and 50 mg KOH/g oil
Ester value	Between 65 and 155 KOH/g oil
Saponification number	≈ 43
UV absorption maximum	285 nm

Table 4.Composition Data on *Chamomilla Recutita* (Matricaria) Trade Name Materials.[10]

Trade Name	INCI Name	Composition (%)	Extraction Solvent
Vegetol matricaria 4140 oily	Mineral oil (and) prunus armeniaca (apricot) kernel oil (and) chamomilla recutita (matricaria) flower extract	> 75.0, 10 to 24.9, and 1 to 4.9, respectively	Mineral oil and prunus armeniaca (apricot) kernel oil
Vegetol matricaria GR 337 Hydro	Butylene glycol (and) water (and) chamomilla recutita (matricaria) flower extract	> 50, 25 to 0, and 5 to 9.9, respectively	Butylene glycol and water
Vegetol matricaria MCF 793 hydro	Propylene glycol (and) water (and chamomilla recutita (matricaria) flower extract	50.0 to 75.0, 25 to 50, and 5 to 9.9, respectively	Propylene glycol and water
Vegetol matricaria ME 106 hydro	Propylene glycol (and) water and chamomilla recutita (matricaria) flower extract	>50, 25 to 50, and 5 to 9.9, respectively	Propylene glycol and water
Vegetol SP GR 051 hydro	Propylene glycol and water, salvia officinalis (sage) leaf extract,and chamomilla recutita (matricaria) flower extract	25 to 50, 25 to 50, 1 to 4.9, and 0.1 to 0.9, respectively	Propylene glycol and water

Table 5. Composition of Chamomilla Recutita Ingredients.[4,5,19,38,105,106,107,108,109,110]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
Apigenin	3.0 to 95.1 µmol/l		6 to 8400 ppm
Apigenin-7-glucoside	94.1 to 216.2 µmol/l		
Artemesia alcohol		< 0.1% to 0.2%	
Artemisia ketone		< 0.1 to 7.8%	
Azulene		0.40%	
Benzaldehyde		< 0.1%	
Benzyl alcohol		< 0.1%	
cis-En-yn-bicycloether		3.6 to 17.7%	
Bicyclogermacrene		0.10%	
β-Bisabolenal		0.80%	
cis-α-Bisabolene		0.30%	
cis-α-Bisabolene epoxide		< 0.05% to 3.8%	
α-Bisabolene oxide A		1.31 to 10%	
β-Bisabolene		0.2 to 19.6%	
(Z)-γ-Bisabolene		0.50%	
trans-γ-Bisabolene		0.10%	
Bisabolol			600 to 5,000 ppm
α-Bisabolol		0.7 to 13.15%	725 to 10,000 ppm
(-)-α-Bisabolol		1.59 to 41.45%	
α-Bisabolol acetate		1.80%	
α-Bisabolol oxide A		< 0.05% to 55.9%	
Bisabolol-oxide A		0.42 to 36.27%	
Bisabolol oxide B		4.64% to 11.17%	
α-Bisabolol oxide B		1.2 to 25.1%	
β-Bisabolol		0.1 to 2.5%	
Bisabolone-oxide		0.55 to 4.13%	
α-Bisabolone oxide A		< 0.05% to 13.6%	
Borneol		0.80%	
Butyl phthalate		15.10%	
Cadina-1,4-diene		< 0.1%	
α-Cadinene		0.2 to 3.75%	
δ-Cadinene		0.1 to 5.20%	
γ-Cadinene		0.1 to 2.25%	
Caffeic acid	1.2 to 5.1 µmol/l		
α-Calacorene		< 0.1%	
trans-Calamenene		< 0.1%	
Camphor		≤ 0.1%	
trans-Carveol		0.10%	

Table 5. Composition of Chamomilla Recutita Ingredients.[4,5,19,38,105,106,107,108,109,110]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
β-Caryophyllene		< 0.1 to 0.9%	
Caryophyllene oxide		0.70%	
Chamazulene		0.2 to 24.50%	530 to 13,200 ppm
Chamo-spiroether		4.71%	
Chlorogenic acid	7.3 to 310.3 µmol/l		
Choline			3,400 to 3,800 ppm
cis-Chrysanthenol		0.10%	
1,8-Cineole		< 0.1% to 2.1%	
α-Copaene		0.2% to 0.24%	
ar-Curcumene		< 0.1%	
p-Cymene		0.05% to 1.1%	
para-Cymene-8-ol		0.70%	
Daucene		0.50%	
Decanoic acid		0.3 to 3.7%	
Dendrolasin		0.50%	
trans-Dicycle-ether		3.20%	
2,4-Dihydroxybenzoic Acid	Amount not stated	Amount not stated	Amount not stated
2,5-Dihydro-2,5-dimethylfuran		< 0.1%	
2,6-Dimethyl-5-heptenal		< 0.1%	
β-Elemene		< 0.1% to 0.9%	
δ-Elemene		0.10%	
γ-Elemene		0.70%	
Essential Oil (EO)			2,400 to 20,000 ppm
Ethyl decanoate		< 0.1%	
Ethyl hexanoate		< 0.1%	
Ethyl 2-methybutyrate		< 0.1%	
ethyl isovalerate		< 0.1%	
γ-Eudesmol		1.50%	
α-Farnesene		0.15 to 27.72%	
(*E*,*E*)-α-Farnesene		3.10%	
β-Farnesene		52.30%	
(E)-β-Farnesene		0.9 to 10.9%	
cis-β-farnesene		0.90%	
tr-β-Farnesene		7.2 to 12.8%	
trans-β-Farnesene		5.20%	
(Z)-β-Farnesene		< 0.1% to 15.97%	
Furfural		< 0.1%	
Galactose			150,000 ppm
Galacturonic Acid			750,000 ppm
Geraniol		< 0.1%	

Table 5. Composition of Chamomilla Recutita Ingredients.[4,5,19,38,105,106,107,108,109,110]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
Germacrene-D		0.16 to 5.78%	
Glucose			70,000 ppm
2-Heptanone		< 0.1%	
Herniarin			320 to 915 ppm
Hexadecanoic acid		0.3 to 23%	
Hexanal		< 0.1%	
(Z)-3-Hexanol		0.10%	
(E)-2-Hexenal		< 0.1%	
(E)-β-Ionone		0.10%	
Isorhamnetin	0.1 to 3.6 µmol/l		
Juniperol		0.90%	
Kaempferol	0.2 to 0.9		
Ledol		< 0.1%	
Limonene		0.1% to 0.2%	
Linalool		0.10%	
Linalool acetate (dihydro)		3.39%	
cis-Linalool oxide (furanoid)		< 0.1%	
trans-Linalool oxide (furanoid)		< 0.1%	
cis-Linoleic acid		< 0.05% to 11.9%	
Luteolin	0.6 to 9.2 µmol/l		
Methyl decanoate		< 0.1%	
Methyl guaiacol		< 0.1%	
6-Methyl-5-hepten-2-ol		< 0.1%	
6-Methyl-5-hepten-2-one		0.10%	
Methyl hexadecanoate		2.60%	
5-Methyl-2-hexanal		< 0.1%	
Methyl linoleate		1.00%	
Methyl linolenate		1.10%	
Mucilage			100,000 ppm
α-Muurolene		0.8 to 3.41%	
γ-Muurolene		1.31%	
α-Muurolol		0.30%	
Myrcene		< 0.1%	
(E)-Nerolidol		0.20%	
Nonanal		< 0.1%	
n-Nonanal		0.10%	
Nonanoic acid		0.30%	
3-Nonen-2-one		< 0.1%	
(E)-β-Ocimene		0.10%	
(Z)-β-Ocimene		0.20%	

Table 5. Composition of Chamomilla Recutita Ingredients.[4,5,19,38,105,106,107,108,109,110]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
trans-β-Ocimene		1.73%	
(E,E)-3,5-Octadien-2-one		< 0.1%	
Octanal		< 0.1%	
2-Octanol		< 0.1%	
3-Octanol		< 0.1%	
1-Octen-3-ol		< 0.1%	
3-Octen-2-one		< 0.1%	
2-Phenylethanol		0.20%	
α-Pinene		< 0.1% to 0.12%	
β-Pinene		< 0.1%	
Pinocarvone		< 0.1%	
Quercetin	0.5 to 6.5 µmol/l		
Quercetin-3-glucoside	1.7 to 10.6 µmol/l		
Quercitrin	limit of detection		
Rutin	0.7 to 2.9 µmol/l		
cis-Sabinene hydrate		0.20%	
Sabinene		< 0.1%	
Safrole		< 0.1%	
Salicylates			0.6 ppm
Salvial-4(14)-en-1-one		0.1 to 4.1%	
(Z)-β-Santalol		1%	
β-Selinene		1%	
Spathulenol		0.46 to 9.4%	
Spiroether		1.10%	
cis-Spiroether		3.43 to 7.48%	
cis-en-yn-Spiroether		0.73%	
trans-Spiroether		0.9 to 6.01%	
Terpinen-1-ol		< 0.1%	
Terpinen-4-ol		< 0.1%	
γ-Terpinene		< 0.1% to 0.3%	
α-Terpineol		0.10%	
4-Terpineol		0.10%	
α-Thujone		< 0.1%	
2,2,6-Trimethylhexanone		< 0.1%	
Umbelliferone	1.0 to 53.1 µmol/l		20 to 290 ppm
α-Ylangene		< 0.1%	
Yomogi alcohol		< 0.1%	

Table 6. Frequency and Concentration of Use According to Duration and Type of Exposure[22,23]

	Chamomilla Recutita (Matricaria) Extract		**Chamomilla Recutita (Matricaria) Flower**		**Chamomilla Recutita (Matricaria) Flower Extract**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	2	0.0001-0.4	1	NR	58	0.0001-0.2
Incidental Ingestion	NR	0.002	NR	NR	3	0.0002-0.5
Incidental Inhalation- Sprays	NR	0.1	NR	0.02	115	0.00001-0.01
Incidental Inhalation- Powders	1	0.0004	NR	NR	20	NR
Dermal Contact	4	0.0001-0.61	1	NR	700	0.000025-0.2
Deodorant (underarm)	NR	NR	NR	NR	3	NR
Hair - Non-Coloring	2	NR	NR	0.02-0.5	234	0.00001-0.25
Hair-Coloring	NR	NR	NR	0.02-0.3	20	0.00001-0.02
Nail	NR	NR	NR	NR	7	0.002-0.3
Mucous Membrane	NR	0.002-0.61	1	NR	100	0.000025-0.5
Baby Products	1	NR	NR	NR	26	0.0097
Duration of Use						
Leave-On	4	0.0001-0.4	1	0.02	507	0.00001-0.5
Rinse off	2	0.01-0.61	NR	0.02-0.5	440	0.00001-0.25
Diluted for (bath) Use	NR	NR	NR	NR	19	0.0051
Totals/Conc. Range	6	0.0001-0.61	2	0.02-0.5	966	0.00001-0.5
	Chamomilla Recutita (Matricaria) Flower/Leaf Extract		**Chamomilla Recutita (Matricaria) Flower Oil**		**Chamomilla Recutita (Matricaria) Flower Water**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	9	NR	6	0.001	1	NR
Incidental Ingestion	1	0.01	4	0.03	NR	NR
Incidental Inhalation- Sprays	100	0.0001	12	0.007-0.066	NR	NR
Incidental Inhalation- Powders	4	0.002	3	NR	NR	NR
Dermal Contact	251	0.002-0.02	93	0.0001-0.2	11	NR
Deodorant (underarm)	1	NR	NR	NR	NR	NR
Hair - Non-Coloring	89	0.0001	28	0.007-0.1	NR	NR
Hair-Coloring	6	NR	NR	0.06	NR	NR
Nail	NR	0.01	NR	NR	NR	NR
Mucous Membrane	37	0.01	34	0.0001-0.03	1	NR
Baby Products	5	NR	5	NR	NR	NR
Duration of Use						
Leave-On	218	0.0001-0.02	67	0.001-0.2	9	NR
Rinse off	127	NR	49	0.0001-0.06	2	NR
Diluted for (bath) Use	4	NR	9	NR	NR	NR
Totals/Conc. Range	349	0.0001-0.02	125	0.0001-0.2	11	NR
	Chamomilla Recutita (Matricaria) Flower Powder		**Chamomilla Recutita (Matricaria) Oil**			
	# of Uses	Conc. (%)	# of Uses	Conc. (%)		
Exposure Type						
Eye Area	NR	NR	1	NR		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation- Sprays	NR	NR	NR	NR		
Incidental Inhalation- Powders	NR	NR	NR	NR		
Dermal Contact	NR	1	8	NR		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	3	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	NR	NR	NR	NR		
Baby Products	NR	NR	NR	NR		
Duration of Use						
Leave-On	NR	NR	10	NR		
Rinse off	NR	1	1	NR		
Diluted for (bath) Use	NR	NR	NR	NR		
Totals/Conc. Range	NR	1	11	NR		

Table 6. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2013

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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2013 FDA VCRP Data

Chamomilla Recutita (Matricaria) Extract

01A - Baby Shampoos	1
03G - Other Eye Makeup Preparations	2
05F - Shampoos (non-coloring)	1
07B - Face Powders	1
07I - Other Makeup Preparations	1
Total	**6**

Chamomilla Recutita (Matricaria) Flower

03D - Eye Lotion	1
10C - Douches	1
Total	2

Chamomilla Recutita (Matricaria) Flower Extract

01A - Baby Shampoos	7
01B - Baby Lotions, Oils, Powders, and Creams	15
01C - Other Baby Products	4
02A - Bath Oils, Tablets, and Salts	10
02B - Bubble Baths	4
02D - Other Bath Preparations	5
03A - Eyebrow Pencil	2
03B - Eyeliner	8
03C - Eye Shadow	6
03D - Eye Lotion	17
03E - Eye Makeup Remover	5
03F - Mascara	2
03G - Other Eye Makeup Preparations	18
04A - Cologne and Toilet waters	77
04E - Other Fragrance Preparation	24
05A - Hair Conditioner	76
05B - Hair Spray (aerosol fixatives)	2
05C - Hair Straighteners	1
05D - Permanent Waves	2
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	57
05G - Tonics, Dressings, and Other Hair Grooming Aids	30
05H - Wave Sets	5
05I - Other Hair Preparations	20
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	35
06C - Hair Rinses (coloring)	1
06D - Hair Shampoos (coloring)	1
07A - Blushers (all types)	11
07B - Face Powders	8
07C - Foundations	15
07E - Lipstick	5

07F - Makeup Bases	4
07H - Makeup Fixatives	1
07I - Other Makeup Preparations	15
08A - Basecoats and Undercoats	1
08B - Cuticle Softeners	6
08C - Nail Creams and Lotions	1
08F - Nail Polish and Enamel Removers	2
08G - Other Manicuring Preparations	1
09A - Dentifrices	2
10A - Bath Soaps and Detergents	56
10B - Deodorants (underarm)	3
10D - Feminine Deodorants	3
10E - Other Personal Cleanliness Products	19
11A - Aftershave Lotion	3
11E - Shaving Cream	12
11G - Other Shaving Preparation Products	1
12A - Cleansing	77
12B - Depilatories	13
12C - Face and Neck (exc shave)	72
12D - Body and Hand (exc shave)	30
12F - Moisturizing	86
12G - Night	15
12H - Paste Masks (mud packs)	22
12I - Skin Fresheners	14
12J - Other Skin Care Preps	27
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	3
13C - Other Suntan Preparations	2
Total	**966**

Chamomilla Recutita (Matricaria) Flower/Leaf Extract

01B - Baby Lotions, Oils, Powders, and Creams	1
01C - Other Baby Products	4
02B - Bubble Baths	1
02D - Other Bath Preparations	3
03B - Eyeliner	1
03D - Eye Lotion	2
03E - Eye Makeup Remover	1
03G - Other Eye Makeup Preparations	5
04A - Cologne and Toilet waters	9
04E - Other Fragrance Preparation	74
05A - Hair Conditioner	26
05B - Hair Spray (aerosol fixatives)	4
05C - Hair Straighteners	2
05F - Shampoos (non-coloring)	35
05G - Tonics, Dressings, and Other Hair Grooming Aids	12
05H - Wave Sets	2

05I - Other Hair Preparations	8
06A - Hair Dyes and Colors (all types requiring caution statem	4
06D - Hair Shampoos (coloring)	1
06G - Hair Bleaches	1
07B - Face Powders	3
07C - Foundations	2
07E - Lipstick	1
07F - Makeup Bases	2
07I - Other Makeup Preparations	2
10A - Bath Soaps and Detergents	15
10B - Deodorants (underarm)	1
10C - Douches	2
10D - Feminine Deodorants	5
10E - Other Personal Cleanliness Products	10
11A - Aftershave Lotion	1
11E - Shaving Cream	1
12A - Cleansing	19
12B - Depilatories	1
12C - Face and Neck (exc shave)	25
12D - Body and Hand (exc shave)	3
12F - Moisturizing	28
12G - Night	2
12H - Paste Masks (mud packs)	7
12I - Skin Fresheners	6
12J - Other Skin Care Preps	10
13A - Suntan Gels, Creams, and Liquids	4
13B - Indoor Tanning Preparations	2
13C - Other Suntan Preparations	1
Total	**349**

Chamomilla Recutita (Matricaria) Flower Oil

01A - Baby Shampoos	1
01B - Baby Lotions, Oils, Powders, and Creams	3
01C - Other Baby Products	1
02A - Bath Oils, Tablets, and Salts	3
02B - Bubble Baths	6
03D - Eye Lotion	3
03E - Eye Makeup Remover	1
03G - Other Eye Makeup Preparations	2
04A - Cologne and Toilet waters	3
04E - Other Fragrance Preparation	7
05A - Hair Conditioner	6
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	11
05G - Tonics, Dressings, and Other Hair Grooming Aids	8
05I - Other Hair Preparations	1
07C - Foundations	1

07E - Lipstick	4
07F - Makeup Bases	1
10A - Bath Soaps and Detergents	20
10E - Other Personal Cleanliness Products	1
11A - Aftershave Lotion	1
12A - Cleansing	7
12C - Face and Neck (exc shave)	7
12D - Body and Hand (exc shave)	12
12F - Moisturizing	8
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	1
12J - Other Skin Care Preps	2
13C - Other Suntan Preparations	2
Total	**125**

Chamomilla Recutita (Matricaria) Flower Water

03C - Eye Shadow	1
07F - Makeup Bases	1
07I - Other Makeup Preparations	1
10E - Other Personal Cleanliness Products	1
12C - Face and Neck (exc shave)	1
12D - Body and Hand (exc shave)	2
12F - Moisturizing	2
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	1
Total	**11**

Chamomilla Recutita (Matricaria) Oil

03G - Other Eye Makeup Preparations	1
05F - Shampoos (non-coloring)	1
05I - Other Hair Preparations	2
12C - Face and Neck (exc shave)	3
12F - Moisturizing	2
12G - Night	2
Total	**11**

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Memorandum

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

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

DATE: July 22, 2013

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

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

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

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

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

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

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

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

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

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

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

		rinse-off	3%

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

†Product category codes used by FDA

Information collected in 2013

Table prepared: May 2, 2013

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

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

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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 21, 2013

SUBJECT: Summaries of HRIPTs on Products Containing *Chamomilla recutita*-Derived Ingredients

Anonymous. 2005. Summary of an HRIPT of towelettes containing 0.01% Chamomilla Recutita (Matricaria) Extract.

Anonymous. 2012. Summary of an HRIPT of a hair gel styling mist containing 0.00006% Chamomilla Recutita (Matricaria) Flower/Leaf Extract.

Chamomilla recutita (Matricaria) Extract

Summary of HRIPT

Facial cleansing and makeup remover towelettes containing 0.01% *Chamomilla recutita* (Matricaria) Extract were tested using Modified Draize Human Repeated Insult Patch Test (HRIPT) procedure to determine the potential of this product to induce irritation and contact sensitization. The product was tested as a mixture of the wipe fabric and the material with which the wipe was impregnated under occlusive conditions.

The HRIPT consisted of three phases: induction phase, rest phase and challenge phase. During the induction phase, patches were applied on the subject's back and were removed 24 hours after each application. A trained examiner scored skin responses after each patch removal. Patches were applied at the same site 3 times a week for 3 consecutive weeks for a total of 9 applications. Following the 9th application, a rest period of 2 weeks elapsed after which a challenge phase started. Challenge patches were applied in the same manner and the same site used for the induction phase. Patches were removed after 24 hours and test sites were scored at 24, 48 and 72 hours after patch application.

A total of 50 subjects satisfactorily completed the study. Under the conditions previously described, no skin reactivity was observed in any of the 50 subjects during the course of the study. Under the conditions of a Modified Draize HRIPT procedure, the tested product containing 0.01% *Chamomilla recutita* (Matricaria) Extract was not associated with skin irritation or allergic contact dermatitis.

This study was conducted by The Institute for Skin Research, Tel Aviv, Israel from February 10 through March 20, 2005 in accordance with the Good Clinical Practice and Standards established by the International Standardization Organization (ISO) and the standard operating procedures of the Institute for Skin Research.

Chamomilla recutita (Matricaria) Flower/Leaf Extract

Summary of HRIPT

A hair gel styling mist containing 0.00006% *Chamomilla recutita* (Matricaria) Flower/Leaf Extract was tested using Modified Draize Human Repeated Insult Patch Test (HRIPT) procedure to determine the potential of this product to induce irritation and contact sensitization. The product was tested neat under semi-occlusive conditions.

The HRIPT consisted of three phases: induction phase, rest phase and challenge phase. During the induction phase, patches were applied on the subject's back and were removed 24 hours after each application. A trained examiner scored skin responses when subjects returned to the testing facility for next patch application. Patches were applied at the same site 3 times a week for 3 consecutive weeks for a total of 9 applications. Following the 9th application, a rest period of approximately 2 weeks elapsed after which a challenge phase started. Challenge patches were applied to adjacent virgin sites and removed after 24 hours. The test sites were scored at 24 and 72 hours after application.

A total of 103 subjects satisfactorily completed the study. Under the conditions of a Modified Draize HRIPT procedure, the tested product containing 0.00006% *Chamomilla recutita* (Matricaria) Flower/Leaf Extract was not associated with skin irritation or allergic contact dermatitis.

This study was conducted by Essex Testing Clinic, Inc. Verona, NJ from April to June, 2012 in accordance with the spirit of Good Clinical Practice regulations described in 21 CFR, Part 50 (Protection of Human Subjects-Informed Consent).

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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 Tentative Report on *Chamomilla recutita*-Derived Ingredients

Key Issues

The Discussion should include information as to why the CIR Expert Panel concluded that the flower-derived ingredients are safe when formulated to be non-sensitizing. Although there are sensitization data on a number of flower extracts in the report, 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, *Chamomile recutita* is in the Asteraceae family, a family of plants that contains sesquiterpene lactones which are known to be sensitizers. The CIR Expert Panel also thought the "safe when formulated to be non-sensitizing" conclusion would reinforce their concern about products that contain plant-derived ingredients from multiple species.

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

This report needs a complete reference check as several randomly selected studies (noted under additional comments) did not appear to be cited to the correct reference based on the information in the report and the title of the reference.

Additional Comments

Throughout the report, when referring to the plant (rather than a cosmetic ingredient), *Chamomilla recutita* should be italicized and the common names, such as matricaria and German chamomile should not be italicized.

p.1 - In the Introduction, please indicate the maximum use concentration for Bisabolol reported in the 1999 CIR report.

p.2 - Please delete the study on the impurities found in plants grown in Croatia. Unless there are additional studies, this study, published in 1999, as summarized in the CIR report, adds no information to the variability in composition based on "country of origin". If the study is left in the report, it should be indicated that the information is from an abstract of a study in Croation. If the study has been translated into English, the concentrations of the impurities should be stated.

p.3 - What was the country of origin of the 34 chamomile preparations for which anthecotulide was not detectable (reference 19)?

p.5 - Rather than citing a secondary reference (reference 30) and stating that "Reportedly, chamomile (*Matricaria recutita*) is listed as an official drug in the pharmacopeias of 26 countries...", it should be confirmed that *Matricaria recutita* is listed in the pharmacopeias and they should be cited directly. The 2008 edition of the British Pharmacopeia is in John Krowka's office (German chamomile is listed under matricaria).

p.5 - These ingredients are mixtures. Therefore, it is not possible to study the kinetics of mixtures. It is possible to study the kinetics of components of mixtures. The statement that there are no data on the absorption, metabolism, and excretion of chamomile ingredients is not correct. A quick search of PubMed with the terms chamomile and kinetics revealed the following papers:

Merfort I, Heilmann J, Hagedorn-Leweke U, et al. 1994. In vivo skin penetration studies of camomile flavones. Pharmazie 49(7): 509-11.

Abstract: "In vivo skin penetration studies of the Camomile flavones apigenin, luteolin and apigenin 7-O-beta-glucoside were carried out with nine healthy, female volunteers. During seven hours the decline of flavonoid concentration in a saturated aqueous alcoholic solution filled in glass application chambers were repeatedly measured by spectrophotometry at fixed time periods. The maximal fluxes were calculated. From the graph of the maximal flux values as a function of time it was concluded, that the flavonoids are not only adsorbed at the skin surface, but penetrate into deeper skin layers. This is important for their topical use as antiphlogistic agents."

Szentmihályi K, Forgács E, Hajdú M, et al. 2001. In vitro study on the transfer of volatile oil components. J Pharm Biomed Anal 24(506): 1073-80.

Abstract: "The following volatile oils were tested in vitro: chamomile (Matricaria recutica L.), peppermint (Mentha piperita L.) and sage (Salvia officinalis L.) to obtain information on which components of volatile oils or minerals are able to pass through the membranes under different conditions. The transfer of chamomile and peppermint oil from aqueous volatile oil to the stomach (pH=1.1) and then to the plasma (pH=7.5) was studied, and the transfer of sage oil through the skin (from pH=5.5 to pH=7.5) was examined. The transfer of some

components was more favorable than that of others. The transfer of chamomile oil was faster to buffer pH=1.1 than from buffer pH=1.1 to buffer pH=7.5 and most of the components, except for chamazulene, passed through the membranes. In the case of peppermint the components went through the membranes in the first 15 min although the main components mostly remained in the initial solution. The sage oil transferred showed the same characteristics as the starting oil. A small amount of metal present in the volatile oils also passed through the membranes. The transfer of metals varied, depending on the time, type of the oil, metal quality and the conditions applied.

Tschiersch K, Hölzl J. 1993. [Absorption and excretion of apigenin, apigenin-7-glycoside and herniarin after oral administration of extracts of Matricaria recutita (L.) (syn. Chamomilla recutita (L.) Rauschert)]. Pharmazie 48(7): 554-555 (article in German - no abstract available).

Additional references would likely be found if searches were completed for main components (such as Bisabolol or apigenin) of this plant.

If kinetic data are not added to the report, it should not be because there "are no data".

p.5 - "Extract" needs to be added to the first heading in the Acute Exposure Oral section.

p.6, 14-15 - Based on the method of manufacture, and the title of the study, the material tested in reference 39 was an essential oil of the flowers, not an "oil extract". Although the study authors may have stated that they "extracted" the oil from the plant, the method of manufacture, vapor distillation, is consistent with the method for manufacturing an essential oil, and is not consistent with how the Dictionary defines ingredients named as "extracts". Please delete Extract from the headings and refer to the material tested as an essential oil, not an "oil extract".

p.6-7 - Reference 43, titled "Efficacy of anise oil, dwarf-pine oil and chamomile against thymidine-kinase-positive and thymidine-kinase-negative herpes viruses" does not appear to be the correct reference for the HET-CAM assay of Chamomilla Recutita (Matricaria) Flower Oil.

p.7-8 - In the sections on Chamomilla Recutita (Matricaria) Flower Extract (Ocular Irritation, Skin Irritation) describing the materials tested is sufficient. It is not necessary to include the trade names.

p.7 - The title of reference 47 says "Chamomile oil Roman." Therefore, either the information under Skin Irritation (flower oil) cited to this reference is not correct, or the reference is not correct.

p.9 - The reference for the HRIPT of the eye lotion containing 0.4% Chamomile Recutita (Matricaria) Flower Extract is not stated.

p.10 - Please provide more information about the subjects tested in reference 56 (36 patients). Where were these subjects from? What conditions were observed in these subjects?

P.10 - In the description of reference 58, the significance of "Andujar honey" is not clear. The abstract of this study indicates that Andujar honey was from a specific region and it had high levels of sunflower pollen (compared to honey from Granada, another region).

p.11 - Please include the species of arnica tested in reference 63.
p.14 - It should be stated if the information cited to reference 79 is only based on an abstract of a Japanese language study.
p.14 - The abstract of reference 80 indicates that the women drank tea derived from *Anthemis nobilis* so this study should be deleted from this report.
p.16 - Please correct "dosed i.p. to the extract"
p.18 - In the Summary, Bisabolol should also be listed as a component of the essential oil.
p.18 - In the Summary, please give some indication of the concentrations of the ingredients tested in the dermal irritation and sensitization studies.
p.19 - The first paragraph of the Discussion is not appropriate for this group of ingredients as there is no structure-property relationship discussed in this report.
p.19 - It is not clear why quercitrin is mentioned in the Discussion when quercetin is shown in Figure 1 (and there are higher concentrations of quercetin compared to quercitrin in the essential oil).
p.19 - Please see the following for a review of the safety of quercetin:
Harwood M, Danielwska-Nikiel B, Borzelleca JF, et al. 2007. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. Fd Chem Toxicol 45(11): 2179-21205.
p.19 - Where are the data that shows farnesene has insecticidal activity?
p.20 - *Chamomilla recutita* extracts are produced with multiple extraction solvents such as oils, propylene glycol, water and carbon dioxide. It is incorrect for the Discussion to imply that they are produced only by "maceration in oils".
p.20 - The information on Bisabolol should be moved to the beginning of the Discussion. Please also note the maximum use concentration reported in the 1999 CIR report.
p.21 - Is the structure for farnesene in Figure 1 β-farensene, as ChemID has a slightly different structure for α-Farnesene? ChemID also shows the one of the hydroxyl groups of quercetin to be in a different position than the structure shown in Figure 1.
p.22-23, Table 1 - Please include the maximum use concentrations reported in the 1999 CIR report. Please include the concentration of Bisabolol used in the skin penetration enhancement studies. If reference 93 is an inhalation exposure study, please put it in a separate inhalation exposure section.
p.26, Table 3 - If there is no refractive index available, the heading should be deleted from the table.
p.27, Table 5 - Please delete reference 110 as the title indicates that it is about *Anthemis nobilis*.
p.36, reference 47, p.40, reference 110 - As these references concerns Roman chamomile, they should not be included in the report on German chamomile.
p.37, references 63, 72 - The format of some of the references, e.g., 63, 72, does not appear to be correct.
p.39, reference 98 - Reference 98 does not appear to be complete as it appears to be missing the book title.