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

Status:	Draft Final Amended Report for Panel Review
Release Date:	May 13, 2016
Panel Date:	June 6-7, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, Ivan Boyer, Ph.D., Senior Toxicologist, 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: May 13, 2016
Subject: Draft Final Amended Report on the *Chamomilla recutita*-derived Ingredients

At the March 31-April 1, 2016 CIR Expert Panel meeting, the Panel concluded that the 11 *Chamomilla recutita*-derived ingredients are safe in the present practices of use and concentration in cosmetics when formulated to be non-sensitizing, and issued a Tentative Amended Report with this conclusion. The current safety assessment is identified as *chamom062016rep* in the pdf document. Report comments received from the Council have been addressed.

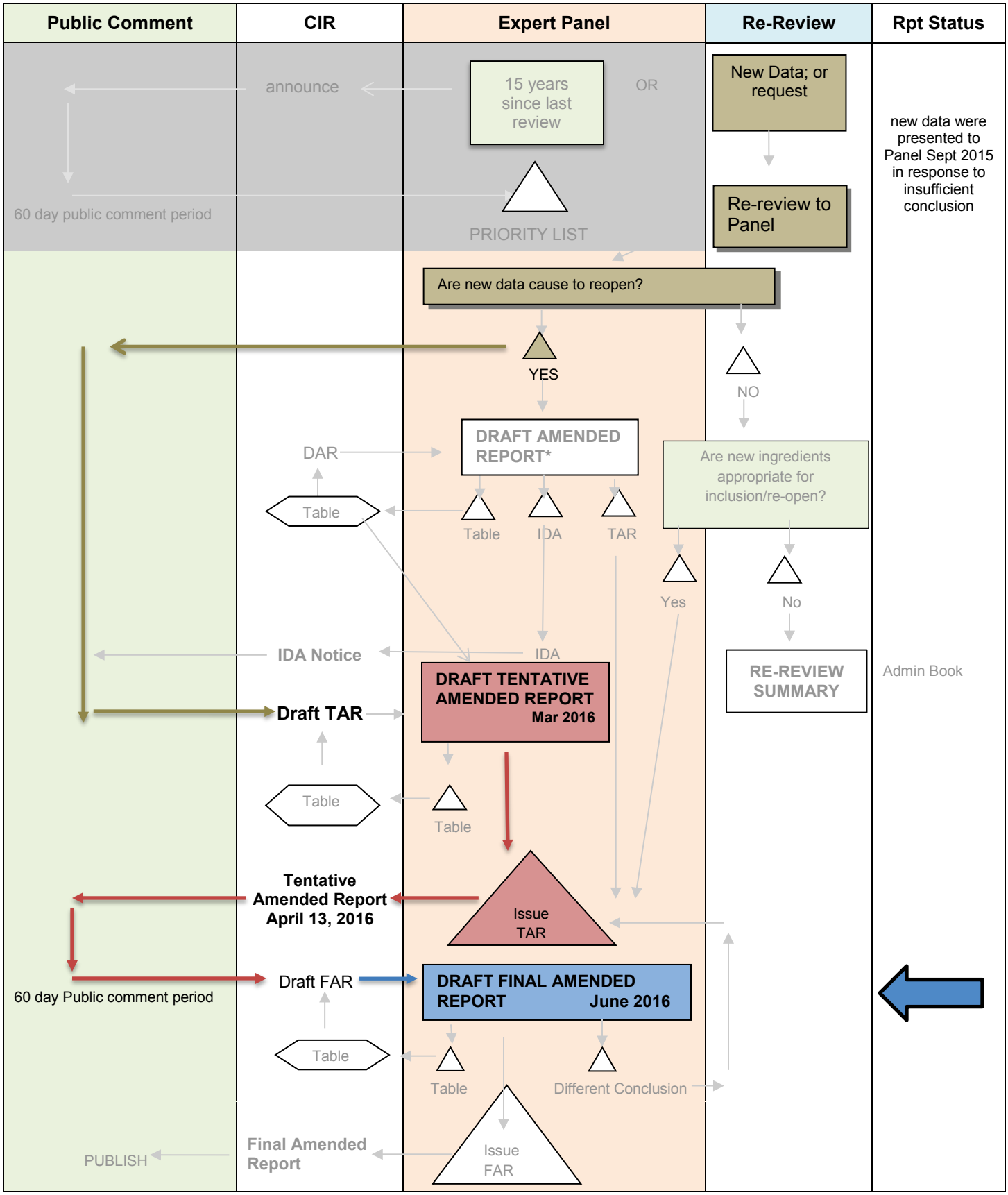
Included in this package for your review is the Draft Final Amended Report (*chamom062016rep)*, the CIR report history (*chamom062016hist)*, Literature search strategy (*chamom062016strat)*, Ingredient Data profile (*chamom062016prof)*, 2016 FDA VCRP data (*chamom062016FDA)*, Minutes from prior Expert Panel Meetings on *Chamomilla recutita*-derived ingredients (*chamom062016min)*, and comments received from the Council (*chamom062016pcpc1).*

After considering the data included in this safety assessment, the Panel will need to determine whether a final report with the conclusion stated at the beginning of this memorandum should be issued.

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY *Chamomilla recutita*-derived Ingredients

MEETING June 2016



RE-REVIEW FLOW CHART

INGREDIENT/FAMILY *Chamomilla recutita*-derived Ingredients

MEETING June 2016

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

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.

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.

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.

Draft Tentative Report, Belsito and Marks Teams/Panel: September 21-22, 2015

Chamomile recutita-Derived Ingredients – reopened

Industry provided additional information to support the safety of ingredients derived from other plant parts. Based on the additional information, the Panel voted to reopen the report. The Panel is still concerned about the lack of information on the composition of the roots. Therefore, while ingredients containing leaves and stems may be moved to the safe when formulated to be non-sensitizing conclusion, the whole plant extract, Chamomilla Recutita (Matricaria) Extract may remain with an insufficient data conclusion.

The additional information provided by industry (referred to above) included: (1) Unpublished IR and UV spectral analyses of chamomile (*Chamomilla recutita*) aqueous extract – whole plant (including roots) versus the flower extract; (2) Composition data on the following *Matricaria chamomilla* plant parts (plant samples from Eastern

Croatia) : flower heads, yellow florets, petals, stems and leaf – published report; (3) Ocular irritation data (*in vitro* data) on a mascara containing 0.01% chamomilla recutita (matricaria) extract (whole plant aqueous extract) – unpublished data; (4) HRIPT data (unpublished) on the following: a mascara containing 0.01% chamomilla recutita (matricaria) extract (whole plant aqueous extract) and a tradename mixture containing 10% chamomilla recutita (matricaria) aqueous extract (whole plant extract – includes roots, diluted to 0.5%); and (5) Home use study on the acnegenic/comedogenic potential of a foundation containing 0.01% chamomilla recutita (matricaria) extract (whole plant aqueous extract).

Draft Tentative Amended Report, Belsito and Marks Teams/Panel: March 31 - April 1, 2016

After the September 2015 Panel meeting, the following data were received: HRIPT data on an eye lotion containing 0.4% chamomilla recutita (matricaria) extract (whole plant aqueous extract) (received on 1-27-2016), data relating to the composition of the root (essential oil of the root) (received on 1-28-2016), and use concentration data on *Chamomilla recutita*-derived ingredeints (received on 2-9-2016). This information has been added to the safety assessment.

The Panel issued a tentative amended report for public comment with the conclusion that these 11 *Chamomilla recutita*-derived ingredients are safe in the present practices of use and concentration in cosmetics as described in this safety assessment, when formulated to be non-sensitizing.

The Panel reviewed the additional data submitted to support the safety of 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, which were found to be insufficient at the December 9-10, 2013 CIR Expert Panel meeting. Because the data submitted addressed the Panel's concerns, the previous conclusion was revised to state that these 6 ingredients are safe in the present practices of use and concentration in cosmetics, when formulated to be non-sensitizing.

Draft Final Amended Report, Belsito and Marks Teams/Panel: June 6-7, 2016

Comments from the Council were received and have been incorporated.

Chamomile Ingredients Check List for June, 2016. 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				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 *Chamomilla recutita*-derived Ingredients (1/9/2016)

SciFinder/PubMed Searches

Search Terms

Chamomilla Recutita (Matricaria) Extract
Chamomilla Recutita (Matricaria) Flower
Chamomilla Recutita (Matricaria) Flower Extract
Chamomilla Recutita (Matricaria) Flower Juice
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) Leaf Extract
Chamomilla Recutita (Matricaria) Flower Water
Chamomilla Recutita (Matricaria) Oil

Search Updates

Search updated on 4/27/16

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

Chamomilla recutita-derived Ingredients

Dr. Belsito: So, that gets us up to chamomilla recutita.

MR. JOHNSON: Dr. Belsito, I have a brief handout on that ingredient.

DR. BELSITO: Okay. So, this is from the IFRA dossier on linalool.

MR. JOHNSON: On linalool, yes.

DR. BELSITO: So, basically the issue that -- to put this in perspective for people who might not know what's going on with IFRA and the issue with linalool is whether linalool is the sensitizer or whether it's the peroxides, and I think Halyna, you were actually at that. That was the May meeting, and the production of peroxides and hydro peroxides and the linalool that seemed to be much more potent sensitizers than linalool. So, there's a limit on the peroxide levels to 20 millimoles per liter, and the recommendation that anti-oxidants such as VHT or tocopherols be added to prevent oxidation in final products. So, that's what Wilber essentially has just handed out for linalool.

So, I looked through this and in terms of final I thought safe, again with it formulated to be non- sensitizing. Here's one where we need to add in the botanical boilerplate, and to put into the discussion what our concerns were and move on from there.

I'm trying to look other than linalool, I know that there were some additional concerns we had, and I'm trying to find them.

MR. JOHNSON: And Dr. Belsito, I must mention that with respect to other botanical constituents of concern, in searching the IFRA website, I only found information in the standards library on linalool but none of the other constituents of concern.

DR. BELSITO: Okay, well, one of the constituents of concern was azyline that we previously concluded the data weren't sufficient, but we dealt with that with the TTC in these products. The kersatan was a genotoxic carcinogenic, and really the only two that we pointed out were pharnacine, linalool and linalool acetate, so, I mean, the peroxide generation is the same issue for linalool acetate. I believe that the IFRA dossier for linalool includes the other related ingredients like linalool acetate, so I think that we could perhaps add this from the RIFM dossier that -- or not. Again, the issue here is that the levels of linalool as present in German chamomile, chamomile recutita are not of concern. The concern would be adding in other botanicals that would also have linalool or linalool acetate, so the -- what I'm not seeing here is what the maximum concentration uses are. And the other issue becomes, as we look to IFRA guidelines for setting limits if we're actually going to talk about a limit to go, you know, IFRA uses -- RIFM who recommends to IFRA guidelines -- IFRA actually institutes the guidelines, uses QRA, so the limits vary depending upon the type of product. So, the levels of linalool that would be allowed in a deodorant are going to be less than the levels of linalool that are allowed in a scented candle which will be higher.

So, that is actually going to be rather complex for us to, as I think about it, going back to what Paul was saying, you know, we should put some guidelines and limits, it's going to be very complex in our discussion because for many of these fragrance ingredients that are in botanicals, when you go to the IFRA standards they're going to vary from product type to product type. So, it may be better just as a boilerplate for these where IFRA has set standards on limits, formulators should refer to the IFRA standards rather than for us to repeat the IFRA standards for several reasons because sometimes if you look at, for instance, I see ugenol, there have been in the last 10 years 5 different standards set for that, so they change. They set a standard and boom, someone starts reporting problems. They go back and look at it and then they reopen it and they set a new standard. I think it's safer for our documents, particularly at least for fragrance ingredients.

Now, when we're dealing with neurotoxins or developmental toxins, if we have levels we can state those. But I think for the fragrances we should probably just refer back to IFRA standards for that.

DR. SNYDER: I think that's a good approach, and I think that's consistent with what we do with impurities, saying these are established guidelines for food consumption, things like that that we do for other impurities. So, I think that would be consistent, and I like that

approach.

DR. BELSITO: So, I mean, probably in the discussion where we talk about components of chamomile ricutita flower oil, it's usually going to be from the oil's fragrance materials. We could put, for example, the fragrance materials beta pharmacy and linalool and linalool that may be sensitizers, you know, formulators should refer to the IFRA standards for proper guidance or something to that effect.

DR. LIEBLER: I also agree with that approach. I think that's sufficient and makes a lot of sense.

MR. JOHNSON: Dr. Belsito, again, that first paragraph there's a statement indicating that with respect to those botanical constituents of concern, they should not exceed any limitations that may have been established by IFRA. Is your statement replacing that one?

DR. BELSITO: Where are you, Wilbur?

MR. JOHNSON: This is in the discussion, the first paragraph, fifth line from the bottom.

DR. BELSITO: On 48?

MR. JOHNSON: 49.

DR. BELSITO: Fifth line from the bottom?

MR. JOHNSON: Yes, sir, first paragraph of the discussion.

DR. BELSITO: First paragraph. I'm sorry. No, I mean, but I don't think you need to add anything there. It's been said. Yeah. I think we've got that. Anything else?

MR. JOHNSON: Dr. Belsito, on PDF page number 34, there's an underlying paragraph in the toxical kinetics section, and I'd like to know whether or not that information is useful? You know, whether or not it should remain in the safety assessment?

DR. BELSITO: So, this is the components of the oil that could pass through membranes under different conditions?

MR. JOHNSON: Yes.

DR. BELSITO: I guess it's, I mean, it's some absorption data of a form. That's not really my area of expertise within dermatology. That would be something I would normally ask Bob Bronoughter to comment on if he were at the meeting. I think it's information. I don't think that it causes any concern, but Dan, are you following where Wilbur is?

DR. LIEBLER: Yeah, no, I'm looking at it. I think it's got its limitations, but it's relevant enough to include.

DR. BRESLAWEC: I might just suggest that the discussion should specify what the membrane is, what kind of membrane it is.

DR. BELSITO: It's a cellophane membrane.

DR. KLAASEN: Yeah, I think it's somewhat useful. I think it could be shortened a little bit. I don't think how -- the important point is the phs of this buffered solutions, but I don't think you really need to indicate how they made those solutions. They can just say one at 7.5 and one at whatever it is, 7.1.1, et cetera.

DR. LIEBLER: I agree with Kurt.

MR. JOHNSON: Should that be included in the summary -- any mention of that in vitro study?

DR. KLAASEN: Go ahead, Dan.

DR. LIEBLER: Maybe one sentence at most.

DR. KLAASEN: I'd say one sentence at most and possibly none.

MR. JOHNSON: Okay, thank you.

DR. SYNDER: I would just like to say I like the presentation of the impurities and composition data that you did here. I think that was -- the sourcing and the different processing methods and things was very nicely presented, Wilbur, so that was a nice job there.

MR. JOHNSON: Thank you.

DR. BELSITO: I had nothing else except for some little minor edits.

MR. JOHNSON: Excuse me, Dr. Belsito, just one more thing. We received two new studies from industry; two skin irritation and a sensation studies, on PDF page number 38.

DR. BELSITO: The facial cleanser, 0.01.

MR. JOHNSON: Yes.

DR. BELSITO: And then the hair gel at 0.006. I mean, it didn't add anything to the document. It didn't change anything. Rachel?

MS. WEINTRAUB: I just had one question about whether these were meaningful considering actual concentrations of use? It's sort of hard to figure out how useful it was.

DR. BELSITO: In terms of because these two studies were at such low concentrations?

MS. WEINTRAUB: Exactly.

DR. BELSITO: I don't think it adds anything in the sense that it doesn't allow us to go to a higher concentration, but to the extent that they were submitted, I guess we shouldn't exclude them from the report.

MS. EISENMANN: See the previous conclusion was insufficient for ingredients derived from the stem and leaf, and these two ingredients have some stem and leaf in them, and that's why they were summited because we didn't get any composition information, so I don't know what you're going to do with the stem and the leaf. If you would want to include a limit on those up to the concentration that -- I don't remember what the highest concentration of the two studies was.

DR. BELSITO: It was 0.0006.

MS. EISENMANN: I thought there was a slightly higher one. 0.01, I think that sounds (inaudible).

MR. JOHNSON: That was a facial cleansing and make-up remover.

MS. EISENMANN: For ingredients derived that have leaf and stem in them, if it's a leaf and stem product. That's the reason why somebody submitted those. We were not able to find any -- I should say I didn't look -- I did not receive any composition information on the leaf and stem.

DR. BELSITO: Okay, so basically we don't have composition on the leaf and stem, and looking at the ingredients that we're reviewing here, we have a flower/leaf extract. We have a flower/leaf/stem extract. We have flower/leaf/stem water. We have a leaf extract, and then I was just looking at concentrations of use, and we don't really have any -- do we have products that are using those? Presumably, we do now that we have a study on the product.

So, we receive the VCRP uses and use concentration data for the extract, flower, flower extract, flower/leaf extract, and flower oil. And the concentration of use for the flower/leaf extract, VCRP data for the flower, water, and oil, use concentration for the flower powder, and no VCRP for the leaf/stem extract, leaf/stem/water, or the leaf extract.

MS. EISENMANN: So, just principally that flower/leaf extract for which the concentration you've got a 0.01 HRIPT.

DR. BELSITO: Right.

DR. SYNDER: 0.02 is the max.

DR. BELSITO: I guess that gets us back to what we were discussion with rosemary and I missed that, so we have no composition data on stem, and no composition data on leaf, so it's just the opposite with rosemary where we had none on the flower, and we're saying the flower is insufficient for composition and concentration of use, so we've got some data on the flower leaf extract. We at least have a sensitization, irritation study, and we have absolutely no data on the flower/leaf/stem extract, the stem water, or the pure leaf extract. So, do we need to go insufficient for compensation and concentration of use on those three ingredients?

DR. BRESLAWEC: You could either go insufficient or you could put a use limit of 0.01 for ingredients derived from plant parts other than the flower because you have a maximum use concentration for the whole plant is 0.61 percent.

DR. BELSITO: I'm sorry, Halyna. We have a maximum use concentration for --

DR. BRESLAWEC: The whole plant extract at 0.061 percent.

DR. BELSITO: So, we have the whole plant which would include the flower at 0.61, and then we have the flower/leaf at 0.01.

MR. JOHNSON: 0.02.

DR. BELSITO: 0.02, and then how do we rationalize coming at.01 when we're doing --

MS. EISENMANN: Well, the.01 would probably be just applied to the flower/leaf extract.

DR. BRESLAWEC: Or you could say insufficient data.

DR. BELSITO: Well, the flower/leaf extract, I mean, we have, was that point --

MR. JOHNSON: 0.00 -- You're talking about data (inaudible)?

DR. BELSITO: Yes.

DR. SNYDER: 0.06.

MR. JOHNSON: 0.06, yes.

DR. BELSITO: So, round it up to 0.01 is what you're saying for the flower/leaf extract, but what I'm talking about are the three ingredients for which we have no reported VCRP or use concentration which includes leaf and stem for which we have no composition either.

DR. BRESLAWEC: Although the whole plant extract, you have data on 0.01 percent, and that would be the justification for extending 0.01 percent --

DR. SYNDER: I think the 0.01 is fine.

DR. BRESLAWEC: -- to the flower/leaf extract, which is actually a little lower than the reported concentration of use but that's fine.

DR. GILL: Halyna, that's the HRAPT data on (inaudible) you're looking at as the 0.01 percent for the whole plant?

MR. JOHNSON: Actually, for the whole plant it's 0.61 percent in the table 6. That's the highest reported use concentration for that.

DR. LIEBLER: We have no composition for anything but the flower, flower (inaudible), right? We have nothing for leaf or whole plant or leaf stem?

DR. BELSITO: Correct.

DR. LIEBLER: Isn't that the issue you're asking about, Don?

DR. BELSITO: Yes.

DR. LIEBLER: I think that's still glaring a hole here. I'm not sure how we use the whole plant extract to cover that. We don't have any composition on anything but flower.

DR. BELSITO: Yeah, because this is sort of a flip because with rosemary what you use when you're using it as a spice is the leaf. With chamomile, when you're using it as a tea, you actually use the flowers.

MS. EISENMANN: Actually, can I -- in my attempt to find data I asked the tea company first of all what species, and then they volunteered the information that they're using the whole cut for their chamomile tea. They're using the species, and they're using the whole cut which means they're using flowers, leaves, and stems. So -- and then I went further and asked them, oh, what's the composition, and of course they didn't reply after that. So --

DR. BELSITO: When I've been to Asia and had chamomile tea, it's the flower bud they put in the tea.

MS. EISENMANN: A major U.S. supplier of chamomile tea is using the whole cut which includes the leaves and the stems, so I'm not sure that the leaves and the stems have that much -- at 0.01 percent have that much difference in composition, but that's just an observation, what a tea company told me.

DR. LIEBLER: I think we don't have very much to go on. If we had a composition from the whole plant, we wouldn't have a problem here. I'm sure we could interpolate over, but all we have is the flower, and we kind of have an anecdotal on, you know, that other stuff that's used, other parts of the plant are used in some cases, but we don't have any composition on anything but the flower, and yet we've got ingredients that include whole plant.

DR. BRESLAWEC: Again, we have problem with an insufficient data on the ones where you don't have composition data.

DR. BELSITO: Yeah, I mean, I think that the flower and the oil is expressed from the flower, so really what we're getting are the, primarily -- and what we're looking at are going to be all flower ingredients.

And I think even when you get to a flower/leaf extract, the ingredients of the flower are probably equal to or overwhelming the leaf there, but when you start getting into stems and leaves, I'm just not -- again, going back to the rosemary report, I think we don't know what we're dealing with, and we don't know the levels of use that are being proposed, and all we have is

one U.S. manufacture of chamomile tea that say they throw the whole thing in, and my experience has been that's not the case. The chamomile tea that I've seen brewed in Asia has been brewed with pure flowers with no leaves and no stems, so -- and then they couldn't come back to you and tell you the composition for something that they're selling as a food product.

DR. BRESLAWEC: Again, we have no problem with insufficient on this.

DR. BELSITO: Okay. So, I mean, I guess I would propose safe as used and for the chamomile flower/leaf/stem extract, flower/leaf/stem water, leaf extract, insufficient for composition and concentration of use.

DR. LIEBLER: I agree.

DR. BELSITO: And then, when formulated to be non- sensitizing. Okay, anything else with these?

MR. JOHNSON: Just one more comment, Dr. Belsito. The Council in its comments had recommended including additional information in the discussion, and based upon those concerns, text is underlined in the discussion.

DR. BELSITO: Page, Wilbur?

MR. JOHNSON: That's PDF page 49, second paragraph.

DR. BELSITO: I thought that was perfect because here the issue of susquiterpene lactones which is a whole body of different chemicals, and if you look at the literature it's not clear as to what happens when you take chemicals that are susquiterpene lactones but are not the identical chemicals and put them together, do you increase the sensitization capabilities of that mixture?

So, for instance, in patch testing we use something called a Compositae Mix which is a mixture of three different susquiterpene lactones that are actually tested at a level in the mix that are lower than when you're testing them individually for patch testing. So, I like that that the Council is pointing out that here it's a broad range of chemicals that belong to the family that are called susquiterpene lactones, and you need to be aware of that, and look for it in other plant products that you might be adding. And I think the wording is very well crafted. Other issues?

So, basically, with the conclusion, last time we concluded that the available data were insufficient for chamomile recutita extract. We're now saying that that's sufficient. Is that correct, looking at the prior conclusion? The flower/leaf extract we're going safe as used. The flower/leaf/stem extract, the flower/leaf/stem water, the leaf extract, we're keeping as insufficient, and the oil safe.

MR. JOHNSON: Is that different than what is stated in the conclusion?

DR. BELSITO: Yeah, because right now the only ones we're stating are insufficient are the flower/leaf/stem extract, the flower/leaf/stem water and the leaf extract, whereas before we said it was insufficient for the whole plant extract. The flower/leaf extract which we're now bringing into sufficient because we have the flower/leaf at 0. --

MR. JOHNSON: Well, the test data on 0.00006 percent.

DR. BELSITO: And the use level is --

MR. JOHNSON: 0.61.

DR. BELSITO: No, no, no --

MR. JOHNSON: That's whole plant.

DR. BELSITO: That's whole plant.

MR. JOHNSON: Let's see -- I thought it was 0.02, 0.02 percent.

DR. BELSITO: Okay, well, let's just go through this before -- so our prior conclusion was the whole plant extract was insufficient. We're comfortable now. We have data at 0.61 that it's sufficient, correct?

Then let's go to page 50 where the existing conclusion from the last meeting was. So, we said the panel also concluded the available data are insufficient to make a determination that chamomile recutita matricaria extract -- so all of these were insufficient. So, we're now saying the extract is sufficient, correct?

DR. BRESLAWEC: The whole plant?

DR. BELSITO: Yeah.

DR. GILL: Because we had data at --

DR. BELSITO: Data at 0.61.

MS. EISENMANN: No, the data are only up to 0.01 that's used up to 0.61.

DR. BELSITO: Oh, okay.
MS. EISENMANN: So, the thought maybe you'd want to set a limit.
DR. BELSITO: Okay.
MS. EISENMANN: If you wanted to say that, but it would also be all right if you want to keep it as insufficient.
DR. BELSITO: Okay, so then the first one that we had previously said was insufficient, the whole plant extract, data at 0.01, use at 0.61. So, you're asking us to go 60 times higher than the data --
MS. EISENMANN: No, saying you can set the limit.
DR. BELSITO: Right.
DR. BRESLAWEC: Or --
DR. BELSITO: Or say insufficient, but we have some data, so why would we say insufficient? So, what you're suggesting that we do is say safe as used, chamomile recutita matricaria extracts safe up to 0.01 percent, okay, for the whole plant. Moving to the next one, chamomile recutita flower/leaf extract, we have data at 0. --
MR. JOHNSON: (inaudible) 0.006 percent.
MS. EISENMANN: Almost nothing.
DR. BELSITO: Right. And use?
MR. JOHNSON: That was up to 0.02 percent.
DR. SNYDER: If the basis for the whole plant extract is (inaudible) and we put in there formulated to be non-sensitizing?
DR. BELSITO: Well, the basis for the whole plant extract is we don't know really the ingredients in the leaf and the stem.
DR. SYNDER: So it's really (inaudible).
DR. BELSITO: So, part of it is composition.
DR. SYNDER: Okay. So, I don't think we can -- but then we can't go 0.01 even then, right, because it's still insufficient for composition?
DR. BELSITO: Well, what we know is at 0.01, I mean, were there any constituents that we're concerned about in terms of issues other than sensitization and irritation?
DR. SYNDER: I don't see the composition.
DR. BELSITO: Yeah, I guess you're right. So, I guess we need to go insufficient.
DR. SYNDER: I think so.
DR. BELSITO: So then the conclusion really doesn't change. So, --
DR. SYNDER: We were amiss. Last time we didn't catch the composition gaps we should have caught. We were going on the safe as used on sensitization, and I think that's where we're getting stuck.
DR. BELSITO: Okay, so going through this list then, chamomile recutita extract, whole plant we don't know composition. Flower/leaf extract, again, we got some data, but we don't know the composition because we don't know the composition of the leaf. The flower/leaf/stem extract is the same. The flower/leaf/stem water is the same issue. The leaf extract is the same, but the oil is really going to come from the flower, is it not?
MS. EISENMANN: It's called flower oil
(inaudible).
DR. BRESLAWEC: It's called flower oil.
MS. EISENMANN: No, actually there's two oils, so the one without a plant part is whole plant.
DR. BELSITO: Okay, but, I mean I would think -- then again, there's no data.
MS. EISENMANN: So, put it as insufficient.
DR. BELSITO: Okay. Fine. So then, the conclusion that exists on page 50 of the PDF stays the same.
MR. JOHNSON: With that in mind, Dr. Belsito, does the discussion section provide a sufficient basis for the conclusion; the safe issue as well as the insufficiencies?
DR. BELSITO: I think that in the discussion we basically need to point out that we received some new data on the whole plant, a sensitization study of 0.01, but it's used up to 0.61, number one.

And number two, while the major concern seems to be sensitization, irritation, based upon the information that we have on the composition of the flower, we have no composition data on other parts of the plant that might contain chemicals that would be of concern beyond the sensitization and irritation issue.

I mean, I think that needs to be brought out to the discussion. And that that's what's bogging us down is that when you start getting into whole plant extracts and stems and leaves, about which we know nothing, then our concern is "we don't know." You have sensitization as a concern, but are there parts of the stem, in particular, that have chemicals that we would be concerned about when combined with other chemicals and other plant stems, so we don't know. So, I guess, that needs to just be brought out.

The major issue is not necessarily that they give us an HRIPT up to 0.61 on the whole plant. The major issue -- because what we're concerned about now is sensitization, and we could cover that when formulating not to be sensitizing. The major issue is we need composition for stem, leaf, and --

DR. SYNDER: Stem and leaf.

DR. BELSITO: Stem and leaf. Dan, any comments?

DR. LIEBLER: No, I agree with everything that's been said. It's (inaudible) insufficient. The conclusion doesn't change.

DR. BELSITO: Okay, anything else? Okay. So, next we go to Roman chamomile, anthemis nobilis.

So, in September we went with the conclusion, "Safe in the present practice of use in concentration cosmetics," Again, formulated it would nonsensitizing. Data on the flower extract at 4 percent was not received as requested in the insufficient announcement, but I guess we felt that the 3 percent data that we had combined with information received on essential oils at 4 percent covered the flower extract and also the nonsensitizing that we put into the conclusion. So, issues with this particular ingredient, I basically said okay, safe for unformulated to be nonsensitizing.

DR. LIEBLER: I agree. It looks good.

MR. JOHNSON: Just one observation in the discussion section.

DR. BELSITO: Page?

MR. JOHNSON: Page 27. The Council had also recommended additional text for the discussion, which is underlined.

DR. LIEBLER: I've got no problem with that. I think it looks fine.

DR. BELSITO: I mean, again, I think it's the same sesquiterpene lactone issue that we just discussed for German chamomile.

Anything else? Paul?

DR. SNYDER: Nope.

DR. BELSITO: Okay.

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

Chamomilla recutita-derived Ingredients

DR. MARKS: At any rate, so the next is a draft final report on chamomilla recutita. And in September, the Panel concluded that all these components of the flower extract, the powder, et cetera, are safe in the present practices of use and concentration described in this safety report when formulated to be non-sensitizing. It's insufficient for a number of other of these ingredients, which, again, is in the memo from Wilbur, the extract the whole plant, the flower and leaf extract, et cetera. And we'd need an HRIPT at 0.4 percent for the extract to be safe. And that would be insufficient.

DR. BERGFELD: Do we have that comment in our discussion about why it's insufficient, what was needed?

DR. MARKS: No.

DR. BERGFELD: Because I think you have to put that in the discussion.

DR. MARKS: Yeah, I have that here. We did get some comments from the Council. We had towelettes with 0.01 percent extract, so very low. And then a hair gel with too little to smell here almost,.00006 percent of lower leaf extract was okay for HRIPT. But when I reviewed it, it looked like we would need an HRIPT of 0.4 percent for the extract to be safe.

Now, it's interesting. We could either do the "insufficient" or, as you suggested earlier, Jay, go to a concentration limit of 0.4 percent for the extract, and put the whole thing as "safe when formulated to be non- sensitizing." I think it's interesting because as we go to the Roman chamomile, e say it's non-sensitizing, and we don't have the data for all the various components of this botanical. So it's non-sensitizing in some ways, in my mind. Why do you have "insufficient" for some of the botanical or plant parts in the other when you just say if it's non-sensitizing. But at any rate, that's sort of my rambling preamble to how I saw it.

So Ron Shank, the conclusion was "safe." Or I should say the conclusion as Wilbur has stated here is fine. Tom, what do you feel?

DR. SLAGA: I think with the new data, I think it could be safe, but we could put the limit on if you want and still be formulated to be non-sensitizing.

DR. MARKS: Yeah. Instead of the insufficient portion of this conclusion, just say that with the limit for everything that we say is insufficient, just put a limit of 0.4 percent. I believe that's the right concentration, is that correct, for the extract. That was the highest concentration for the extract, 0.4 percent?

MS. FIUME: This is Wilbur's, not me.

DR. MARKS: Oh, yeah. And I didn't write a page that I could immediately go to the use table. Usually I do do that. Do you know what page the use table is, concentration on these? Did you find it? It's obviously towards the end.

DR. HELDRETH: PDF page 61.

DR. MARKS: Sixty-one, okay. Let's just confirm where I got that, yeah. I got it from Table 6. If you look at leaf -- I went for the leave-on concentration. If you go under the extract, the highest concentration on a rinse-off is.61, but for a leave-on it was 0.4. So I chose that as my maximum concentration. Do you see where we are, Tom, on page 61?

DR. SLAGA: Yeah.

DR. MARKS: That's how I got, if I we want to set a limit or if we want to know what we need to remove the insufficient, it would've been having an HRIPT of that concentration. What's your sense? Do you want to just leave the conclusion as is, or do you want to put a -- if we put a limit, I think the limit would have to be, what is it,.0 -- what do we have to test that?

DR. BERGFELD: 0.4.

DR. MARKS: No, it's not 0.4. Where is it in -- it was in the memo what we have there, 0.01. Yeah, I know.

DR. HILL: Well, 0.01 or "when formulated to be non-sensitizing."

DR. MARKS: Yeah, exactly.

DR. HILL: I mean, I guess we've done that approach before.

DR. SLAGA: "Formulated to be non-sensitizing."

DR. HILL: If you say "non-sensitizing," somebody has to prove that, right? But

if you say.01, you're good. They can use it. What if you made it either/or? I mean, I don't know how practical.01 is for anybody anyway.

DR. MARKS: Yeah. So Ron Hill, Tom, what's your sense? Ron Shank was the conclusion as it is now. And obviously the manufacturers could come back and give us proof that it's safe at that concentration of 0.4 in leave- ons,.06 percent for rinse-offs. Leave the conclusion as is?

DR. SLAGA: Yeah.

DR. HILL: Yeah.

DR. MARKS: Okay, good. Let me see who presents that tomorrow. I do. Okay. So we'll do a final report with the conclusion as stated, and then under what's insufficient, we can put in the discussion for an HRIPT for the extract. Okay.

DR. ANSELL: So --

DR. MARKS: Yeah. Actually when I went back and looked at it and re-thought it, Jay, we could only use "safe" up to 0.01 percent. I didn't think that would be very helpful because that's what we have the HRIPT data on. Okay. Why don't we leave it the same? We'll see what the Belsito team thinks tomorrow. We know what the need is, so I would move that we issue a final report. Wilma, any comments?

DR. BERGFELD: No, that was my comment, put it in the discussion.

DR. MARKS: Okay.

DR. ANSELL: I actually think it would be okay, the 0.01 for the plant parts in which it was insufficient.

DR. BERGFELD: So you're requesting it be 0.01 for everything.

DR. ANSELL: That it not be.

DR. BERGFELD: And be non-sensitizing.

DR. MARKS: Yeah, it may be non-sensitizing, and for the ones where it's insufficient, we actually wouldn't put an "insufficient." It would be formulated to be non-sensitizing, and for all those ingredients we have "insufficient," the limit would be 0.01.

MS. FIUME: So were data received on all of those plant particles?

DR. MARKS: No, in my mind, the extract represents all those others, you know, because it's really --

DR. ANSELL: And the 0.01 was on a whole plant.

DR. MARKS: Yeah. Ron, since, Jay, you feel that would be --

DR. HILL: Yeah. I will reconfirm that.

DR. BERGFELD: Yeah, just like before.

DR. HILL: Well, no. My notes say --

DR. BERGFELD: Okay.

DR. HILL: We put a use limit.

SPEAKER: Yeah, that will protect some uses.

DR. HILL: Yeah.

DR. MARKS: Okay. Trying to do that for you, Jay, here.

DR. ANSELL: Okay.

DR. MARKS: Unfortunately, let's try this one.

MS. FIUME: So, Dr. Marks, I can let Wilbur know 0.01 on the extract.

DR. MARKS: Well, all those. Where it says "available data," are --

MS. FIUME: Because of the data that changed the "insufficient" to 0.01?

DR. MARKS: That towelette down below.

MS. FIUME: On the extract.

DR. MARKS: Yes. I look at the extract to be representative of those three others because it's the whole plant, so it should have all the ingredients within it that you're extracting out.

MS. FIUME: And you've had extract data in the report at a higher concentration, isn't that correct?

DR. MARKS: Yes. Yes. It was up to 0.04 percent in the use table.

MS. FIUME: But under dermal irritation and sensitization, weren't there higher data already in the report last time?

DR. MARKS: For the ones that we say are safe, that was the flower. All of it

was relevant to the flower and not the extract. You'll notice we said it's "safe" for the flower. The flower extract, the flower powder, the flower water, and the flower oil are "safe." And then the problem we had was, okay, we had we have that as supporting the flower, but we don't have data for the whole plant. And so now what we're going to do with the rest of it is just have a use limit of 0.1 percent.

DR. HILL: 0.01 percent.

DR. MARKS: I'm sorry, 0.01. Thank you.

DR. HILL: I just wanted to make it's clear.

DR. MARKS: Yes. Thank you. It's important to have the right numbers.

DR. HILL: Those are important.

DR. MARKS: Yeah, instead of "insufficient." Okay. Any other comments? Monice, does that answer your question?

MS. FIUME: I think so (inaudible).

DR. MARKS: Yeah, I hate to surprise Wilbur, that's for sure. Okay. Let me see if I can move this here. Let me put that on here. Okay. Next is the Roman chamomile, anthemis nobilis. And so in September, the Panel came to issue a draft final report with these ingredients, having a conclusion of "safe when formulated to be non- sensitizing." And now we're at the point at issuing a final report.

And it's interesting. This gets into -- this is what I'm going to ask Don tomorrow is are these ingredients okay with no sensitization on the powder and the water. I guess because it's more of the plant, he feels it's okay.

DR. BERGFELD: It's all the flower, isn't it?

DR. MARKS: Yeah. And with a non-sensitizing conclusion. So, Tom, move forward? Let me see what Ron Shank has to say. "Conclusion okay, 'safe, formulated to be non-sensitizing." Ron Hill?

DR. HILL: It's okay.

DR. MARKS: Okay. Tom?

DR. SLAGA: Okay.

DR. MARKS: Okay. Good.

DR. BERGFELD: Okay with me, too.

DR. MARKS: Wilma, Jay, Wilbur's surrogate, all set. Okay. Let's go ahead.

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

Chamomilla recutita-derived Ingredients

The Panel issued a final safety assessment with the conclusion that the five *Chamomilla recutita*-derived ingredients listed below are safe in the present practices of use and concentration in cosmetics when formulated to be non-sensitizing.

chamomilla recutita (matricaria) flower
chamomilla recutita (matricaria) flower extract
chamomilla recutita (matricaria) flower powder
chamomilla recutita (matricaria) flower water
chamomilla recutita (matricaria) flower oil

The available data are insufficient for determining the safe use in cosmetics for the following six *Chamomilla recutita*-derived ingredients:

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
chamomilla recutita (matricaria) oil

The Panel reviewed new skin irritation and sensitization data on 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, but agreed that the available data remain insufficient for evaluating the safety of ingredients from the whole plant, stem, or leaf in cosmetic products. The Panel reiterated that their insufficient data determination is based on the need for composition data on ingredients derived from *Chamomilla recutita* leaf, stem, or the whole plant.

The Panel expressed concern that cosmetics containing *Chamomilla recutita*-derived ingredients may be sensitizing because the levels of potentially sensitizing constituents in the ingredients (e.g., sesquiterpene lactones) can vary (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. Because final product formulations may contain multiple botanical ingredients, each containing potentially sensitizing constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. The Panel also emphasized that final product formulations containing *Chamomilla recutita*-derived ingredients should meet all applicable or relevant and appropriate International Fragrance Association (IFRA) limits and guidelines established for the constituents of concern.

Day 1 of the September 21-22, 2015 CIR Expert Panel Meeting – Dr. Belsito's Team

Chamomilla recutita-derived Ingredients

DR. BELSITO: And that was the one that wanted us to look at it the first time around. So chamomile, we're now being asked -- what page are we one for this?

DR. LIEBLER: PDF 41.

DR. BELSITO: Forty-one. So --

DR. SNYDER: We have new data.

DR. BELSITO: Yeah.

DR. SNYDER: We were going to say flower was safe --

DR. BELSITO: Right.

DR. SNYDER: -- although (inaudible) sufficient (inaudible) competition.

DR. BELSITO: So this industry has submitted additional data. So what I wrote here was the last use concentration for whole plant extract was.4 percent for eye and.61 percent for mucus membrane. The data we have here is a maximum of.05 percent for the eye. Are we satisfied that the remainder of the plant is equal to flower? The maximum use of that is.5. If so we can go safe, otherwise we need to reopen. Oh, otherwise no need to reopen. So I guess what industry gave us was top position for a plant but not flower, is that correct?

DR. SNYDER: The whole plant, leaf, and stem.

DR. BELSITO: Right.

DR. SNYDER: Yeah.

DR. BELSITO: But not flower.

DR. SNYDER: Right.

DR. BELSITO: Which has a maximum concentration of use of 0.5 percent. And then their question is has -- have the use concentrations changed since the -- what's being reported as maximum concentration of use now is significantly less than what it was in the prior report. And also that AMA Laboratory Study 2015 50 Human Subject Repeat Insult Patch, a mixture containing 10 percent chamomile. That title is misleading because the chamomile at 10 percent was then diluted to five percent. So the final concentration was.05 percent. It was not a negative irritation and sensitization at 10 percent. It was negative at.05.

And I guess since I'm not one who looks at stack spectrum graph reports, I'm assuming it is possible that the flowers were so predominant versus stem, leaf, and root that they influenced the results. But would we see different spikes with all those spikiness going on? I mean, I don't know.

DR. LIEBLER: Well there are pretty useless. They don't convince me of anything.

DR. BELSITO: Uh-huh.

DR. LIEBLER: I think what they're attempting to show -- I -- first of all a stacked spectrum graph, I'm not sure what that means. If it just -- if this is just a UV plot on the upper panel for flower and a UV plot or you mean this. Sorry, UV visible spectrum plot on the upper panel for flower and one for whole plant extract, there are no features in this below about 375. This -- you essentially have maxed out the absorbance. It means the solution's too concentrated to (inaudible) anything. So I'm -- this is completely uninformative. So this doesn't tell you that a whole plant flower are the same. And the IR -- I think these are the IR spectra that are tilted over on their side on the next page which is PDF 44. I would make pretty much the same argument about. You see some -- you see features that look similar but this is a very insensitive way to demonstrate the similarity of the chemical mixtures, so.

DR. SNYDER: So in your interpretation we didn't get relevant composition data.

DR. LIEBLER: No.

DR. SNYDER: Okay, so were still insufficient.

DR. BELSITO: Yeah, and so, yeah. And I don't think any of our data needs to have -- changed, right? So we're not going to reopen. Is that correct?

DR. LIEBLER: Right.

DR. SNYDER: That was the consensus for the (inaudible).

DR. BELSITO: Yep.
DR. SNYDER: Yep.
DR. BELSITO: Yeah, so weren't not reopening either.

Day 1 of the September 21-22, 2015 CIR Expert Panel Meeting – Dr. Marks' Team

Chamomilla recutita-derived Ingredients

Dr. Marks: Okay. Let's see. Administrative still. We have two new data on two ingredients. Methylisothiazolone and chamomille. Let me see, I have Page 41 for the first one. Request to reconsider the safety of chamomille recutita derived ingredients with insufficient data conclusion. We've got composition spec HRIPT of whole extract was okay. Do we want to reopen for the remaining ingredients and now with a safe conclusion formulate to be non-sensitizing? I have that would be on Page 117.

So Tom, Rons, what do you feel? Did you get enough new data to extend this safe conclusion, and if we go on 117 you see that the conclusion was that we had a number of safe ingredients, but the available data was insufficient to make the determination on the extract, the flower leaf, the flower leaf stem extract, the flower leaf steam water, leaf extract, and oil are safe under the intended conclusions. The flower extract, flower powder, flower water, flower oil and they say were safe when formulated to be non-sensitizing. This first group of ingredients are insufficient. Clarify that. Tom, Rons, with the new data can we take those insufficient leaf, steam, whole plant which we thought were insufficient.

DR. SHANK: Well, I was quite surprised that the ultraviolet and (inaudible) were basically the same for the flower and whole plant. That, intuitively, I'm not a chemist, but I did study chemistry a long time ago. Intuitively, that doesn't add up to me. But if that is the case then I think it's reasonable to open it up again and have the new ingredients.

DR. MARKS: Actually, not new ingredients, the ones that we called insufficient.

DR. SHANK: Okay. Sorry. But to expand --

DR. MARKS: That they would become safe.

DR. SHANK: -- and then see what the conclusion is going to change or not.

DR. MARKS: Ron Hill? Tom?

DR. HILL: So the deal that we would be reopening and then looking at this again at the next meeting is that -- as a change conclusion or we're going to put it to bed at this meeting?

DR. MARKS: I would think --

DR. HILL: With the new language?

DR. MARKS: Yes, I would think we would reopen it and we would reissue another tentative final which would state that now all the ingredients --

DR. HILL: Yes.

DR. MARKS: -- are safe with formulate to be non- sensitizing for all the plant parts, and then we would get to review that final draft. Is that reasonable in terms of the CIR process?

DR. HELDRETH: Yes, absolutely. We have to reopen the report.

DR. MARKS: Yes.

DR. HELDRETH: So they can create a new final conclusion.

DR. MARKS: Yes, and the final conclusion would be safe, formulate to be non-sensitizing for all the plant parts now with this new information.

DR. BERGFELD: Well, that's your intent, but that may not be real if you look at all the data then.

DR. MARKS: Yeah.

DR. SHANK: That's right.

DR. MARKS: So, Ron, you expressed concern.

DR. HILL: Well --

DR. MARKS: And so that needs to be answered. I thought the sensitization was fine. The whole extract was good, so I don't need any more sensitization data. What were the data in the (inaudible) is insufficient? I was looking to see if that was -- that's 117. What was the memo here? Let's see, that's 41. You were concerned, Ron, that the UV and the IR spectrums. How can they be the same?

DR. SHANK: They're exactly the same.

DR. MARKS: Is that all we needed in terms of the insufficient data needs? Along with sensitization?

DR. HILL: I wouldn't have thought so because we said formulate to be non-sensitizing don't we?

DR. SHANK: Yeah.

DR. MARKS: Yeah, exactly.

DR. HILL: But I was trying to find what was the list of needs. Is it in this what we've got here? I didn't go back otherwise and look.

DR. MARKS: Let's see here. So if we go on Page 116 under the discussion paragraph, the panel was concerned that cosmetics contain these ingredients be formulated to be non- sensitizing because of levels of potentially sensitizing constituents and ingredients for its ample sesqueturpping lactones can be quite variable. So that's why we add that non-sensitizing now to the conclusions on these botanicals. So I don't -- provide the patch testing. Panel determined available -- I don't see -- chemical composition data on these ingredients are needed, so do the data we have -- that was the only thing that we wanted was chemical composition, and that's in the end of --

DR. SHANK: With given the spectrum.

DR. MARKS: Yeah, with given the spectrum. That was the end of the next paragraph which starts with in response. That's on Page 116, and if you look at the last sentence beginning with however. We wanted the chemical composition for the leaf stem and whole plant.

DR. SHANK: Well, we didn't get it for the leaf and stem. We got the spectra for whole plant and flower water extracts. They were almost identical.

DR. EISENMAN: There was also a published paper in there that looked at composition. (inaudible) non-essential oils of the various plant parts.

DR. HILL: The composition in the plant parts doesn't tell you the composition in the particular extract. That's the problem. So with that method of manufacture that includes information about that you're trying to read across from an extract for flower where we have data with an extract that, you know, a composition might be pretty similar, but we don't know about the actual extract. Now I remember the issues.

DR. EISENMAN: But then you do have the comparison of the actual extracts of the whole plant and the flower, so you --

DR. HILL: Consistent with the ones that are sold to the cosmetic industry --

DR. EISENMAN: Correct.

DR. HILL: -- that's --

DR. EISENMAN: Correct.

DR. HILL: -- because I don't --

DR. EISENMAN: That's the spectra were from a supplier of cosmetic ingredients.

DR. HILL: That's right.

DR. EISENMAN: But then --

DR. HILL: I've done enough IR spectra in my life to not be compellingly convinced from IR spectra. I want LCMS, basically done quantitatively on the extracts themselves if I were going to read across.

DR. EISENMAN: Well,.001 percent concentration.

DR. HILL: No, no. I didn't go back to the original report to see are they all concentration of use.005 percent.

DR. EISENMAN: Well, one's.01.

DR. HILL: All right.

DR. EISENMAN: I think the highest concentration.

DR. HILL: So, yes, you're right.

DR. MARKS: So the small concentration is reassuring?

DR. HILL: Yes, very. And so --

DR. MARKS: Ron?

DR. HILL: -- we'll reopen. We're going to look at it. At least that's what we're saying we want to do, yes.

DR. MARKS: Right. Yeah. Well, at this point we hadn't finished the

discussion, so I didn't want to presume we're going to reopen --

DR. HILL: And we'll have --

DR. MARKS: -- until we're sure at least what we have now we think we can come to a conclusion to change. We don't know for sure. But, okay, so there's Ron Shank, Tom, do you like the idea of reopen?

DR. SHANK: Yes.

DR. MARKS: And if we reopen do we want to -- technically it would be a tentative amended report since it's already been issued as a final report, correct?

DR. HELDRETH: I think it would be an amended final report. I don't think we need to go back a stage before. I mean, I guess when it comes to the panel table it's going to be a final report again, but it will go out as a tentative.

DR. BURNETT: I'm not sure. We'll have to check with Elyse on the procedure.

DR. MARKS: Okay.

DR. BURNETT: It might need to go through to reviews.

DR. MARKS: I'll let you figure that out. I'll propose tomorrow, if I'm the one doing this, no. Actually Belsito, so perhaps I will be seconding reopen with a safe conclusion formulate to be non-sensitizing for all the plant parts, and we'll see where it goes? Any other comments?

Day 2 of the September, 2015 CIR Expert Panel Meeting – Full Panel

Chamomilla recutita-derived Ingredients

DR. MARKS: Yeah. So, with that one in December of 2013 the Panel issued a final report on chamomilla recutita, that these ingredients -- the flower-derived ingredients -- were safe when formulated being on sensitizing while the data were insufficient for the other plant parts. And what the Panel requested was chemical composition data on the ingredients derived from the whole plant and the leaves and the stem.

The memo from Beth Lange, including industry data on composition mass. spec., our team felt was adequate. There was an HRIPT of the whole plant abstract. That was okay. So, we felt, our team, that we could reopen this with a safe inclusion for all plant parts when formulated to be nonsensitizing. So, I think that's a little different than the conclusion your team came to. You didn't want to reopen it.

DR. BELSITO: We were -- I mean, I'll let Dan address it, but those (inaudible) we thought didn't really help us assess anything about what the composition of those materials were so that we were still insufficient for composition. The last use concentrations we had for a whole plant extract were.4 for eye,.61 for mucous membrane. The data we received were from a maximum of.05 percent for eye.

It's a little bit misleading as it was shown in the report, because it would lead you to believe that the product tested had 10 percent, but it was tested at a 5 percent dilution of products, so the actual ingredient was tested at.005 percent not 10 percent. So we thought it was still insufficient for pretty much all the reasons we had asked before. Dan, in particular, was not convinced that those (inaudible) provided us with any information as to what was in the product.

DR. LIEBLER: I think the intention of what is called the stacked spectrum graphic port, which is essentially -- I don't know what "stacked" means, it looks like there's one plot on top of the other -- is that the stacking? I don't know. But, anyway, the UV VIS spectra are essentially uninformative. They have no -- other than -- you can see that they used a borosilicate glass (inaudible).

And then in the IR spectra, again they have some generic features. They -- you know, significant differences between the compositions of those mixtures would not necessarily show up in these UV and IR plots. So, you know, I felt that the submitted information wasn't really enough to establish the substantial similarity between these ingredients.

DR. EISENMANN: Was the published paper at all helpful that looked at -- it kind of showed that in those components they looked at, the composition of the flowers wasn't always greater than the composition of the stems and the leaves?

DR. LIEBLER: Right. They -- as I recall -- I'm looking for where that paper is -- but we tested -- they were basically able to look only at real things.

DR. EISENMANN: Correct, but those were on some of the important onus and --

DR. LIEBLER: Right.

DR. MARKS: Yeah, I think that's what swayed our team, not the mass. spec., and all it was (inaudible).A of the data that was in that paper with it constituents that were in the paper higher in a flower than the other plant parts. So, that's why we --

DR. LIEBLER: I did look at that.

DR. EISENMANN: You could also limit it to the concentration that was tested in most studies, the very, very low --

DR. LIEBLER: Can somebody give me a PDF page?

DR. HILL: 119 is where that starts.

DR. LIEBLER: Okay, I wasn't yet close.

DR. HILL: Administrative book, but that's not where the table is. The table is a couple pages down.

DR. MARKS: I mean, we could reopen, unless we can settle the issue quickly now, and then close it next meeting.

Thank you for clarifying the HRIPT concentrations, Don. That wasn't one of our data needs, but I found that reassuring until you clarified --

DR. BELSITO: Well, I mean, if say formulated to be nonsensitizing or nonirritating, that might go away.

DR. MARKS: That's what we --

DR. BELSITO: And I think it was just a little bit misleading. If you look at simply the data we received, you would think that we received an HRIPT on the ingredient at 10 percent, and it wasn't. It was product that contained percent that was tested at 5 percent.

DR. MARKS: Right. Right. Now, as I said, thank you, Don, for clarifying that, even though that wasn't a data need --

DR. BELSITO: Right.

DR. MARKS: -- and even though the final conclusion as the -- included formulate to be nonsensitizing, which we're using for essentially all plans now.

Dan, maybe you --

DR. BERGFELD: And Ron Hill has something.

DR. HILL: Right, so, let's say that I was so offended by the crappy graphs that we were presented with were obviously uninformative, that I've now regained my composure (laughter), and would that be at the paper that's got the table titles in English and Croatian, which is interesting. So, there are data suggesting essentially that the flower -- the concentration of chamazoline, pharmasan, bisabolol, bisabolol oxides A and B, and a couple of other things are pretty much uniformly higher in the flower.

DR. BELSITO: But they didn't have all plant parts. It was flower versus --

DR. MARKS: Stems and leaves.

DR. BERGFELD: Stems and leaves, petals.

DR. BELSITO: Right.

DR. LIEBLER: Flower heads versus petals and stems and leaves. I mean, the data were overlapping and similar in terms of magnitude. You know, so I guess I would withdraw my objection on the analysis, and if we want to reopen it, we can reopen it, at least from my standpoint.

DR. MARKS: And then I guess if we did without reassurance, the whole -- what does the whole plant contain --

DR. BELSITO: Right.

DR. MARKS: -- besides the flower, stem, and leaf?

DR. BELSITO: Right, at their roots.

DR. MARKS: I guess it's their root, and if there isn't root then we could say the whole plant but that we need to -- we would -- one, if we reopen and we want to --

DR. BELSITO: I'm comfortable with reopening, and we're not going to make a decision of safe or unsafe.

DR. MARKS: Correct.

DR. BELSITO: But we -- insufficient right now to understand what does whole plant consist of.

DR. MARKS: Yes.

DR. BERGFELD: So, that's a motion to reopen?

DR. BELSITO: Yes.

DR. BERGFELD: And a second?

DR. BELSITO: Second.

DR. BERGFELD: All right, and the need that you need is --

DR. BELSITO: We need to understand whether the whole plant includes the root.

DR. BERGFELD: Okay. And Ron Hill?

DR. MARKS: And would the -- what would I say, the notice that we're going to more than likely expand the safe to at least the stem leaf to include -- along --

DR. BELSITO: Yeah, I mean, the issue is the whole plant.

DR. HILL: Yes.

DR. BERGFELD: Right. Ron Hill?

DR. HILL: I just had a general issue, which is the pragmatic implementation of the formulated to be nonsensitizing, because we actually I think pretty much got started since I've been on the Panel. So, we allow somebody to run HRIPTs to document that or conclude that --

not document, conclude; run a QRA -- that's pretty much it, right, that you would look at the people who use a QRA or they run an HRIPT to decide that they know that this is safe, and I'm just sort of thinking that pragmatically if I'm a mom and pop cosmetic shop, maybe I'll just put it in there and see if people start reacting to my product. So, I'm not trying to cast dispersion, because I believe in those small businesses. I'm just making sure that we think about how this is pragmatically implemented, and that's really --

DR. BERGFELD: I guess we'll see that when we reopen it and ask for some more information.

So, I'm going to call the question. All those in favor of reopening, please raise your hand -- with the needs that have been so outlined.

GROUP: Yes.

Day 1 of the March 31-April 1, 2016 CIR Expert Panel Meeting – Dr. Marks' Team

***Chamomilla recutita*-derived Ingredients**

Okay. Chamomilla. So this is a draft tentative amended report. And I'm not sure we had a conclusion at the last meeting. That's what I question, that there really wasn't a conclusion. So the second paragraph that we concluded in December was maybe a little bit bold. Now I have -- our motion the last time was that all ingredients, the whole plant, flower, leaf, stem, are safe when formulated to be non sensitizer. The Belsito Team, and specifically Don, wanted insufficient for the whole plant. That's what sort of delayed things, what's the composition of the whole plant. And we have HRIPTs, a blow from the memo at the bottom where a whole extract, including the root, had HRIPT that was okay. And then also an eye lotion. So team, do you want to -- we'll be seconding tomorrow, but we'll see if the motion is that all the ingredients are safe.

SPEAKER: (Inaudible).

DR. MARKS: Pardon?

DR. SLAGA: They'll say it's all safe tomorrow.

(Laughter)

DR. MARKS: Do you --

DR. SLAGA: I mean that's what we originally said.

DR. MARKS: Right, exactly. So, team, do you feel the same? All ingredients are safe when formulated to be non sensitizing.

DR. SLAGA: I even question that, but there's a lot of data in there.

DR. MARKS: Yes. Okay. Any other comments about -- I don't know whether we're getting tired or fast, or both.

SPEAKER: Hang on, hang on.

DR. SLAGA: Both.

SPEAKER: Hang on.

DR. MARKS: Okay. So we'll see what the Belsito team -- their motion tomorrow is.

MR. BEST: I just have one basic question. So one of the questions before was the composition of the root and these new studies where they do the special analysis of the whole thing, including the root, that's giving you the data you need? I just want to make sure I understand what's happening.

DR. MARKS: Right.

MR. BEST: Okay.

DR. MARKS: The HRIPT, which includes the --

MR. BEST: From this whole mixture now gives you what you were concerned about, about the root before.

DR. MARKS: Yes.

MR. BEST: Okay. Thank you.

Day 1 of the March 31-April 1, 2016 CIR Expert Panel Meeting – Dr. Belsito's Team

Chamomilla recutita-derived Ingredients

Okay the next one is chamomile tea test. So in 2013 we had a final report that five of the flower ingredients were safe in the use when formulated to be non sensitizing, insufficient for the whole plant extract, the flower leaf extract, flower leaf stem extract, flower leaf stem water, leaf extract in the oil and in 2015 we reopened it and we actually if I recall correctly if this was the document then added a few more of the ingredients safe and that conclusion was not updated yet so we added some additional ingredients so the safe list at the September 2015 meeting. That wasn't put into this document. I thought that we got information on the whole plant and we got some information on the root that allowed me to go as a safe as used for the entire family at this point when formulated to being non sensitizing.

DR. SNYDER: I agree.

DR. LIEBLER: Yes.

DR. JOHNSON: Well there was a question as to whether or not the whole plant included the root.

DR. BELSITO: But we have data now looking at root and there also is information that the whole plant included the root, Page 30. It says so composition and impurities, it says because some of the data includes the extract of the whole plant including the roots. Do you see that paragraph under composition and impurities, the fourth paragraph the first two lines and I have a note that this information needs to be added to your table.

DR. JOHNSON: I see composition impurities.

DR. BELSITO: Because some of the data include in the safety and assessment of the extracts of the whole plant including the roots and then we also have data on the composition of the roots themselves which is listed there and needs to be added to your table where you getting compositions and the different portions of the plant. So the root oil contains blah, blah.

DR. JOHNSON: So basically add this to the table.

DR. BELSITO: Right. So your abstract now you need to get rid of your last sentence to now determine that available data is insufficient and we need to take in all of the new information that we had put in the September 2015 report or discuss in September 2015 when we added a few more ingredients as safe. We need the usual botanical boiler plate in our discussion and cosmetic use section. We really covered the maximum concentrations of use with sensitization and irritation data that we had. We have the inhalation boiler plate that needs to be added so inhalation and botanical in discussion.

DR. SNYDER: Under the reproductive development toxicity section there is an epidemiologist that doesn't belong there that needs to go under on of those other relevant studies.

DR. BELSITO: What page are you at?

DR. SNYDER: I'm in the Word document.

DR. BELSITO: It is going to be after Page 33 I guess. So that's the epidemiologic study?

DR. SNYDER: Yes.

DR. BELSITO: Yeah I made the same comment.

DR. ANSELL: What page of the PDF?

DR. BELSITO: PDF 35. I mean basically it is an epidemiologic study looking at pregnancy outcomes in women who drank chamomile tea versus women who did not. It was a pretty weak study. And then I made a note about the grass status but we all know Rachel's point about grass status. Wilbur on Page 33 of the PDF on toxic of kinetics the fourth line down it has concentrations as high as 41.45 is that 41.45 or is that 41 to 45 because that seems like a weird concentration to use.

DR. JOHNSON: I can check on that.

DR. BELSITO: Check and if it is correct then nothing needs to be done and if it is not correct then there in the summary it again occurs as 41.45.

DR. JOHNSON: Okay.

DR. BELSITO: Under skin irritation and sensitization under animal the first

study that chamomilla recutita I don't even know if this is relevant. So what they're doing is they're taking animals that are allergic to another susquiterpene lactone carabrone and then they're seeing would they also react to chamomilla recutita and there were no cross reactivity between chamomilla recutita and carabrone. So what the heck does this tell us about chamomilla recutita at all?

DR. JOHNSON: What page is that?

DR. BELSITO: Page 38. So I thought that entire study should be deleted as totally irrelevant to what we're looking at here. I mean do we really care whether individual sensitized carabrone will react to chamomilla recutita?

DR. LIEBLER: I was wondering about that and I didn't know enough to say whether it would considered to be irrelevant so if you say it is irrelevant it is irrelevant in my book as well.

DR. BELSITO: I think it is irrelevant and should just be deleted. We have an HRIPT on the whole plant extract at.01 but it as used at.4 percent. And then we have another one at.5 which is even better. So in your discussion is that where we are we obviously need to make the changes on PDF Page 49 the first full paragraph the last sentence that we determine the available data are insufficient, we need to get rid of that since we're going sufficient and then your 41.45 comes up again so if that is incorrect you'll need to correct that. We have inhalation boiler plate so it is in lipsticks where there is incidental ingestion it's grass do we want to mention that in the discussion? We have very limited oral toxicity as we just discussed. The repro was not really a repro it was an epidemiologic study of women who drank chamomile tea and didn't know what their pregnancy outcomes were. So do we need a discussion about incidental ingestion or not?

DR. LIEBLER: It doesn't hurt anything.

DR. BELSITO: Okay so safe as used. Inhalation, boiler plate, botanical boiler plate, this one is stacking a susquiterpene lactones so to minimize sensitization the usual safe as used when formulated to minimize sensitization or whatever the boiler plate is we use for botanicals.

DR. JOHNSON: That's for the conclusion?

DR. BELSITO: Yes. And then the usual botanical boiler plates in terms of stacking of allergens of heavy metals, pesticides and then inhalation boiler plate.

DR. SNYDER: What about this asaline here at the beginning of the discussion? The second line where we have asaline it says insufficient?

DR. BELSITO: I think those are all going to be below the level of toxicologic concern when formulated. I mean asaline has been --

DR. SNYDER: Because we didn't really address that.

DR. LIEBLER: So we already say later in that paragraph in the middle the panel concluded that these components are not at levels of toxicologic concerns in cosmetics.

DR. BELSITO: Okay I thought that was covered. Is there anything else? Okay good.

DR. KLAASEN: Fine.

DR. BERGFELD: Okay, moving on to the next ingredient, Dr. Belsito, chamomilla?

DR. BELSITO: Okay, so this is chamomilla recutita or German chamomile. Remember, we split this off from Roman chamomile and that 2013 meeting we issued a final report with the conclusion that chamomilla recutita flower ingredients were safe in the present use of concentration when formulated to be non-sensitizing. We concluded that the available data were insufficient for all of the remaining components of chamomile and I will review all of those at this time point. We reopened that in 2015, we added safety for a few more individual ingredients but not everything. We did, again, get some additional data here and we felt that based upon that, that we can go safe as used when formulated to minimize sensitization and in the discussion, the standard botanical boiler plate and I believe inhalation. The usual inhalation boiler plate. Lip, we didn't really feel we needed to discuss the GRAS status on it in the discussion so safe was used when formulated to be non-irritating discussion, inhalation and botanical boilerplates.

DR. BERGFELD: Where did you put the minimal sensitizing, I am confused?

DR. BELSITO: As part of our usual botanical conclusion when formulated to be non-sensitized.

DR. MARKS: Second.

DR. BERGFELD: Second. Any further discussion? I am still confused though, you had both should not be irritating and should be minimally --

DR. BELSITO: No, not irritation.

DR. BERGFELD: Well you said --

DR. BELSITO: Safe as used when formulated to be non-sensitizing.

DR. BERGFELD: Okay, that's what we are voting on. Thank you, I'll call for the vote then. All those in favor of this conclusion? Unanimous, thank you.

(Motion passed unanimously)

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

Status:	Draft Final Amended Report for Panel Review
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The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, Ivan Boyer, Ph.D., Senior Toxicologist, 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. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Industry should use good manufacturing practices to limit impurities that could be present in botanical ingredients. The Expert Panel concluded that the *Chamomilla recutita* -derived ingredients are safe in the present practices of use and concentration in cosmetics, when formulated to be non-sensitizing.

INTRODUCTION

This report presents information relevant to evaluating the safety of the following 11 chamomile (German chamomile [*Chamomilla recutita* (*matricaria*)])-derived 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
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.[3] The Panel concluded, in 1999, that bisabolol is safe as used in cosmetic products; reported use concentrations ranged from 0.001% to 1%. At the March 16-17, 2015 CIR Expert Panel meeting, the Panel reaffirmed their original conclusion that bisabolol is safe as used in cosmetic formulations.[4]

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*.[5] 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.

In addition to the data presented in Table 3, both ultraviolet (UV) and infrared (IR) spectral analyses of chamomile (Chamomilla recutita) aqueous extract – whole plant (including roots) versus the flower extract are available. Separate UV spectral analyses for the whole plant (including roots) extract and flower extract indicate absorbance in the 200 to 350 nm range, and the spectra appear to be identical.[6] Similarly, the IR spectra for the whole plant aqueous extract (including roots) and the flower extract appear to be identical.[7]

Method of Manufacture

Chamomilla Recutita (Matricaria) Flower Oil

Chamomilla Recutita (Matricaria) Flower Oil is produced via steam distillation of chamomile (*Chamomilla recutita*) flowers.[8,9] According to another publication, Chamomilla Recutita (Matricaria) Flower Oil is prepared by steam distillation of the flowers and stalks of *Chamomilla recutita* (*Matricaria*).[10] 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 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.[11] Another trade name mixture associated with Chamomilla Recutita (Matricaria) Flower Extract has the name, propylene glycol (and) water (and) Chamomilla Recutita (Matricaria) Flower Extract (see Table 4). This trade name mixture is manufactured by hydroglycolic extraction.[12]

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.[13]

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.

Composition data on the following *Matricaria chamomilla* plant parts (plant samples from Eastern Croatia) are presented in Table 6: flower heads, yellow florets, petals, and stems and leaf.[14] Because some of the data included in this safety assessment are on the extract of the whole plant (*Chamomilla recutita* [Matricaria], including the roots), composition data on the essential oil from *Chamomilla recutita* roots are presented in Table 7.[15,16]

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:[17] 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.[18] 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.

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.[19] 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 Plant Line

A study was performed to characterize the 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.[20] 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 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.[21] 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.[21]

Chamomilla Recutita (Matricaria) Flower

*Chamomilla Recutita (Matricaria) Flower*s contain a volatile oil (0.24 to 2.0%) that is blue in color.[22] 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.[23] *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.[24] 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.[25] 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

A trade name material (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) Flower*s, and pure Chamomilla Recutita (Matricaria) Oil (plant part source not stated) were analyzed (using HPLC) to identify the coumarin derivatives umbelliferone and herniarin. The trade name material contained 41.8 µg umbelliferone/ml and 93.1 µg herniarin/ml, and the hydroalcoholic extract of *Chamomilla Recutita (Matricaria) Flower*s contained 36.0 µg umbelliferone/ml and 114.0 µg herniarin/ml. Pure Chamomilla Recutita (Matricaria) Oil contained 540 µg herniarin/ml.[26] Information on content of the trade name material 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, it may contain Roman chamomile (also known as *Chamaemelum nobile* or *Anthemis nobilis*) or German chamomile (also known as *Matricaria recutita* or *Chamomilla recutita*):[27] "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 a specific trade name contains German chamomile, while a product with the same name marketed in Britain contains Roman chamomile."

USE

Cosmetic

The safety of the *Chamomilla recutita* (Matricaria)-derived ingredients included in this safety assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by Industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category. Collectively, the use frequency and use concentration data indicate that 8 of the 11 ingredients in this safety assessment are currently being used in cosmetic products (Table 8). According to these data, Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Extract, Chamomilla Recutita (Matricaria) Flower/Leaf/Stem Water, and Chamomilla Recutita (Matricaria) Leaf Extract are not being used in cosmetic products.

According to 2016 VCRP data, the greatest reported use frequency is for Chamomilla Recutita (Matricaria) Extract (1054 product formulations, mostly leave-on products), followed by Chamomilla Recutita (Matricaria) Flower/Leaf Extract (359 product formulations, mostly leave-on products) (Table 8).[28] The results of a concentration of use survey provided in 2016 indicate that Chamomilla Recutita (Matricaria) Flower Powder has the highest maximum concentration of use; it is used at concentrations up to 1% in rinse-off products (cleansing skin care preparations) (Table 8). The highest reported maximum use concentration of *Chamomilla recutita* (Matricaria)-derived ingredients in leave-on products is being reported for Chamomilla Recutita (Matricaria) Flower Extract (0.5% in makeup preparations).[29]

Cosmetic products containing *Chamomilla recutita* (Matricaria)-derived ingredients may be applied to the skin and hair or, incidentally, may come in contact with the eyes (e.g., Chamomilla Recutita (Matricaria) Extract at maximum use concentrations up to 0.4% in eye area cosmetics) and mucous membranes (e.g., Chamomilla Recutita (Matricaria) Flower Extract at maximum use concentrations up to 0.8% in bath oils, tablets, and salts). Additionally, some of these ingredients are being used in products that may result in incidental ingestion. For example, Chamomilla Recutita (Matricaria) Extract is being used in dentifrices at maximum use concentrations up to 0.025%, and Chamomilla Recutita (Matricaria) Flower Extract is being used in lipstick at maximum use concentrations up to 0.2%. 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 = 0.066% Chamomilla Recutita (Matricaria) Flower Oil in body and hand spray): Chamomilla Recutita (Matricaria) Extract (0.0000933% maximum in pump hair spray), Chamomilla Recutita (Matricaria) Flower (0.0022% maximum in pump hair spray), Chamomilla Recutita (Matricaria) Flower Extract (0.011% maximum in pump hair spray), and Chamomilla Recutita (Matricaria) Flower Oil (0.066% maximum in body and hand spray). Additionally, the following 2 ingredients are used in face powders: Chamomilla Recutita (Matricaria) Flower Extract (highest maximum use concentration = 0.0032%) and Chamomilla Recutita (Matricaria) Flower/Leaf Extract (0.002% maximum). Because some of these ingredients are used in spray and loose-powder cosmetic products , 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.[30,31,32,33] 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.[30,31] Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[34,35,36]

Non-Cosmetic

Chamomilla Recutita

The chamomile species used in medicine is *Chamomilla recutita*, and hydroalcoholic extracts of chamomile flowers are often used in tradename ointments or creams. Additionally, trade name bath additives and mouth sprays containing chamomile extracts as the active ingredient are offered for topical and oral treatment.[17] The use of chamomile in aroma therapy for the treatment of patients with dementia has also been reported.[37] 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.[38]

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.[39] 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.[40]

*Chamomilla Recutita (Matricaria) Flower*s 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.[41] 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.[42]

FDA has determined that the available data are inadequate for establishing general recognition of safety and effectiveness of chamomile (genus and species not stated) flowers as used in digestive aid drug products.[43]

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.[44] Additionally, 2 tradename ointments 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*).[27]

TOXICOKINETICS

In vivo 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 the absorption of 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.

Using an *in vitro* membrane (cellophane membrane) diffusion model, Chamomilla Recutita (Matricaria) Oil was tested to identify components of the oil that are able to pass through membranes under different conditions.[45] The components of Chamomilla Recutita (Matricaria) Oil examined were: chamazulene, (-)-α-bisabolol, α-farnesene, β-farnesene, and matricin. In the diffusion model, the buffer solution (pH 1.1) used to represent the stomach was: 1 N HCl, NACl, and glycocol in water. The following buffer solution (pH = 7.5) was used to represent the plasma: Na_2HPO_3 and KH_2PO_4 in water. 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. Transfer of the oil to the acidic moiety was faster than its transfer from buffer pH =1.1 to buffer pH = 7.5. Regarding transfer from aqueous solution to buffer pH = 1.1, 36.4% of the oil passed through the membrane; a value of 13.7% was reported in the case of transfer from buffer pH =1.1 to buffer pH = 7.5. With the exception of chamazulene, most of the components passed through the membranes.

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.[46] Each group received a single oral dose of 720 or 440 mg/kg, and was 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).[47] 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.[48]

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).[49] The essential oil 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).[47] 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.[50] 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.[51] 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.[52] 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.

GENOTOXICITY

In Vitro

Chamomilla Recutita (Matricaria) Flower Extract

One of the trade name mixtures associated with Chamomilla Recutita (Matricaria) Flower Extract has the name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) Chamomilla Recutita (Matricaria) Extract (see Table 4 for composition). It 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.[53] The mixture was tested at doses up to 5,000 µg/plate. Dimethyl sulfoxide (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.

In Vivo

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 (in corn oil) of 10, 100, and 1000 mg/kg, respectively.[49] 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 (MMS; 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 (SCEs) was comparable to that noted in bone marrow cells from control animals (i.e., not more than 1.1). A high incidence of SCEs 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.

Antigenotoxicity

Chamomilla Recutita (Matricaria) Flower Oil

Chamomilla Recutita (Matricaria) 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: 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 Chamomilla Recutita Flower Oil (500 mg/kg), and 3 groups treated with DAU and Chamomilla Recutita Flower Oil (5, 50, and 500 mg/kg), respectively.[54] Specifically, the effect of the 3 doses of essential oil on the rate of SCE induced by DAU in spermatogonia was studied. Chamomilla 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).

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 orally with corn oil**,** SCEs induced by DAU were decreased in mice pre-treated with crude Chamomile Recutita (Matricaria) Flower Oil at doses ranging from 5 to 500 mg/kg.[49] Administration of the crude oil to DAU-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.[55] 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).[55]

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 Extract (distilled water extract).[56] 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.[57] 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.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Skin Irritation

Animal

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).[47]

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.[10] 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 name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) Chamomilla Recutita (Matricaria) Extract (see Table 4 for composition). It 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.[58] 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 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 name, propylene glycol (and) water (and) Chamomilla Recutita (Matricaria) Flower Extract (see Table 4 for composition). It 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.[59]

The skin irritation potential of a trade name mixture associated with Chamomilla Recutita (Matricaria) Flower Extract (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.[60] The trade name mixture (extraction solvents were 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.[10]

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.[61] 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

Human

Predictive Testing

Chamomilla Recutita (Matricaria) Flower Extract

A human repeated insult patch test (HRIPT) on a shave balm containing 0.2% Chamomilla Recutita (Matricaria) Flower Extract was performed using 105 subjects (males and females; mean age = 47).[62] 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 HRIPTusing 107 healthy subjects (males and females; between 18 and 70 years old).[63] 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).[64] 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.

A mascara containing 0.01% Chamomilla Recutita (Matricaria) Extract (whole plant aqueous extract) was evaluated in an HRIPT involving 106 healthy subjects.[65] A semi-occlusive patch containing the product was applied to the upper back for a total of 9 24-h induction applications. The dose/concentration per cm^2 was not stated. Following a 2-week non-treatment period, a challenge patch was applied to a previously untreated site on the back. Reactions were scored at 24 h, 48 h, and 72 h post-application. The mascara tested did not demonstrate a potential for eliciting dermal irritation or sensitization.

The skin irritation and sensitization potential of an eye lotion containing 0.4% Chamomilla Recutita (Matricaria) Extract (whole plant aqueous extract) was evaluated in an HRIPT using 107 healthy subjects according to the procedure in the preceding study.[66] The eye lotion did not demonstrate a clinically significant potential for eliciting dermal irritation or sensitiozattion.

A trade name mixture containing 10% chamomilla recutita (matricaria) aqueous extract (whole plant extract – includes roots) was evaluated for skin irritation and sensitization potential in an HRIPT involving 50 healthy subjects.[67] The mixture was diluted to a concentration of 5% in distilled water (effective test concentration = 0.5%) prior to testing. An occlusive patch containing 0.2 ml of the test substance was applied to infrascapular regions of the back for a total of 9 24-h

consecutive induction applications. The dose/concentration per cm^2 was not stated. After a 10- to 14-day non-treatment period, a challenge patch was applied to a previously untreated site. Reactions were scored at 24 h and 48 h post-application. There was no evidence of any type of adverse reaction during the study.

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).[68] 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).[69] 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.[70] 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) Extract (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) Extract (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.[71] 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 (Matricaria) 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.[72] 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.[73] 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.[74] 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).[75] *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).[76] 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.[76]

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.[77] 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.[78] 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.[79] 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).[80] 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).[81] 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 (matricaria) 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.[82] 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.[83] 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:[84] 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.

Comedogenicity

Chamomilla Recutita (Matricaria) Extract

The acnegenic/comedogenic potential of a foundation containing 0.01% Chamomilla Recutita (Matricaria) Extract (whole plant aqueous extract) was evaluated in a home use study using 23 healthy female subjects. The foundation was used by each subject once daily for 6 weeks. Each subject was then examined by a dermatologist, who identified and counted the number of lesions on the face and forehead and determined an acne score. Any evidence of skin irritation or dryness was reported after initiation of product use. At 3 weeks, skin irritation, dryness, the acne score, and lesion counts were evaluated by a trained technician. Neither skin irritation nor dryness was observed during the study. The mean acne grade was 0 at 3 weeks and 0.04 at 6 weeks. Furthermore, a slight increase in the mean acne grade after 4 weeks of product use was noted, but this finding was not considered clinically significant because the mean value remained below 1. Slight increases in mean open comedone and papule counts and a decrease in closed comedone counts were noted at week 3. A decrease in open and closed comedone counts and a slight increase in papules were observed at week 6. Because the mean values corresponding to these findings remained below 1, they were not considered clinically significant. Based on the results of this study, the foundation tested was considered “non-acnegenic/comedogenic”.[85]

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.[86] 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.[87] 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*).[88] 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.[89] 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.[90] 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.[91] 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.[44]

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.[74] 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.[92] 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.[93] 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 a trade name material (oily extract of *Chamomilla Recutita (Matricaria) Flower*s).[94] The extraction solvent was not stated. Urticaria, larynx edema, tachycardia, and hypotension followed, indicative of an anaphylactic reaction. In the skin prick test, the trade name material 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*).[95] 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.[96] 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) Extract (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.[70]

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.[97] 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.[98] 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.

Ocular Irritation

In Vitro

Chamomilla Recutita (Matricaria) Extract

The ocular irritation potential of a mascara containing 0.01% Chamomilla Recutita (Matricaria) Extract (whole plant aqueous extract) was evaluated using the following assays (all alternative methods to the Draize test): neutral red release (NRR) assay, the reconstituted human epithelial culture (REC) assay, and the hen's egg test on the chorioallantoic membrane (HET-CAM).[99] The results of these 3 assays supported the estimated classification that the mascara tested is slightly irritating to the eye. However, the author noted that, based on experience with the type of product (mascara, a make-up product) that was tested, the mascara is as well-tolerated as other test items that belong to this product category. It was also noted that a warning relating to the ocular irritation potential of this product is not considered necessary.

Chamomilla Recutita (Matricaria) Flower Oil

The HET-CAM assay was used to determine the irritation potential of Chamomilla Recutita (Matricaria) Flower Oil.[100] 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 CAM.

Animal

Chamomilla Recutita (Matricaria) Flower Extract

One of the trade name mixtures associated with Chamomilla Recutita (Matricaria) Flower Extract has the name, mineral oil (and) prunus armeniaca (apricot) kernel oil (and) Chamomilla Recutita (Matricaria) Extract (see Table 4). It 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.[58] 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 name, propylene glycol (and) water (and) Chamomilla Recutita (Matricaria) Flower Extract (see Table 4 for composition). It 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.[59] 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 (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.[60] The trade name mixture (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.

EPIDEMIOLOGY

Chamomile

An epidemiology study examined the use of herbal products by pregnant women in Italy and pregnancy outcome.[101] 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.

A questionnaire-based study was performed to measure the prevalence and predictors of herb use among a group of 120 pregnant women and the possible influence of herbal consumption on pregnancy outcomes.[102] Most of the women (90%) consumed more than one herb during pregancy. The most commonly used herbs were anise (*Pimpinella anisum*) (61.7%), chamomile (*Matricaria recutita*) (53.3%), sage (*Salvia officinalis*) (55%), mixture of herbs (33.3%), and thyme (*Thymus vulgaris*) (29.2%). A group of 180 pregnant women did not use herbs during pregnancy. There were no statistically significant differences in pregnancy outcomes between users and non-users of herbs during pregnancy. The authors concluded that the infrequent use of herbs during pregnancy seems to be safe and beneficial.

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.[103] 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):[104] 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.[104]

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. [50] 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*))-derived 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 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 for Chamomilla Recutita (Matricaria) Flower Powder (up to 1% in rinse-off products [cleansing skin care preparations]). The highest reported maximum use concentration of *Chamomilla recutita* (Matricaria)-derived ingredients in leave-on products is being reported for Chamomilla Recutita (Matricaria) Flower Extract (0.5% in makeup preparations).

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 [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 [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. The essential oil of the roots of *Chamomilla recutita* contains sesquiterpenes and polyenes.

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. Both IR and UV spectral analyses of chamomile (*Chamomilla recutita*) aqueous extract – whole plant (including roots) versus the flower extract were essentially identical.

In vivo 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. However, data relating to the absorption of and systemic exposure to bisabolol, a major component of Chamomilla Recutita (Matricaria) Flower Oil, were considered. Using an *in vitro* membrane diffusion model, most of the components of Chamomilla Recutita (Matricaria) Oil, except for chamazulene, passed through the cellophane membrane.

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 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. Results from the following *in vitro* assays suggested that a mascara containing 0.01% Chamomilla Recutita (Matricaria) Extract (whole plant aqueous extract) was a slightly irritating to the eye: neutral red release (NRR) assay, the reconstituted human epithelial culture (REC) assay, and the HET-CAM assay. 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, and chamomilla recutita (matricaria flower extract). Each was classified as a non-irritant.

Skin irritation was observed in an acute dermal toxicity study and 24 h skin irritation test 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.

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 (50 subjects), and a hair gel styling mist containing 0.00006% Chamomilla Recutita (Matricaria) Flower/Leaf Extract (103 subjects) were negative for skin irritation and sensitization. Negative HRIPT results were also reported for the following: a mascara containing 0.01% Chamomilla Recutita (Matricaria) Extract (whole plant aqueous extract) (106 subjects), an eye lotion containing 0.4% Chamomilla Recutita (Matricaria) Extract (whole plant aqueous extract) (107 subjects), and a trade name mixture containing 10% chamomilla recutita (matricaria) aqueous extract (whole plant extract – includes roots, diluted to 0.5%) (50subjects).

In a home use study, a foundation containing 0.01% Chamomilla Recutita (Matricaria) Extract (whole plant aqueous extract) was neither acnegenic nor comedogenic. Additionally, skin irritation was not observed.

In provocative tests, skin sensitization was observed in 18 of 24 patients patch tested with 1% Chamomilla Recutita (Matricaria) Extract (ether extract) and in 4 of 5 patients and 48 of 85 patients patch tested with 2.5% Chamomilla Recutita (Matricaria) Extract (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 Extract (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 (Matricaria) 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) Extract (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 of preterm labors were 21.6% higher when compared to non-users (group of 283); many of the subjects also consumed licorice. In a questionnaire-based study, there were no statistically significant differences in pregnancy outcomes between users (120 women) and non-users (180 women) of herbs during pregnancy. The most commonly used herbs were anise (*Pimpinella anisum*) (61.7%), chamomile (*Matricaria recutita*) (53.3%), sage (*Salvia officinalis*) (55%), mixture of herbs (33.3%), and thyme (*Thymus vulgaris*) (29.2%).

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 (Matricaria) 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

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 constituents 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.

Negative HRIPT results were also reported for the following products: a hair gel styling mist containing 0.00006% Chamomilla Recutita (Matricaria) Flower/Leaf Extract, a mascara containing 0.01% Chamomilla Recutita (Matricaria) Extract (whole plant aqueous extract), an eye lotion containing 0.4% Chamomilla Recutita (Matricaria) Extract (whole plant aqueous extract), and a trade name mixture containing 10% chamomilla recutita (matricaria) aqueous extract (whole plant extract – includes roots, diluted to 0.5%). These data were considered sufficient for evaluating the skin irritation and sensitization potential of ingredients derived from the leaf/stem or whole plant.

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 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 droplets/particles from spray and loose-powder cosmetic products 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.

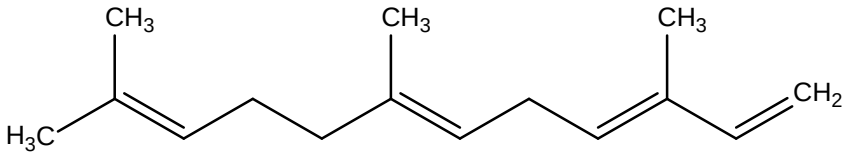
CONCLUSION

The CIR Expert Panel concluded that the following cosmetic ingredients are safe in the present practices of use and concentration in cosmetics, described in this safety assessment, when formulated to be non-sensitizing:

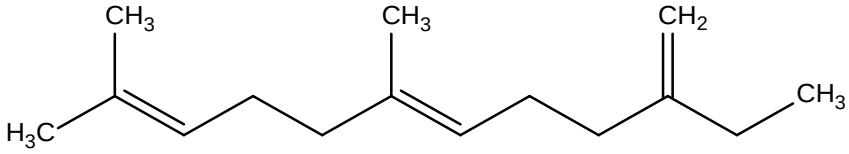
Chamomilla Recutita (Matricaria) Flower
Chamomilla Recutita (Matricaria) Flower Extract
Chamomilla Recutita (Matricaria) Flower Powder
Chamomilla Recutita (Matricaria) Flower Water
Chamomilla Recutita (Matricaria) Flower Oil
Chamomilla Recutita (Matricaria) Extract
Chamomilla Recutita (Matricaria) Flower/Leaf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

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

1. Farnesene

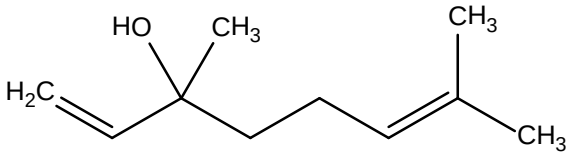


alpha-farnesene

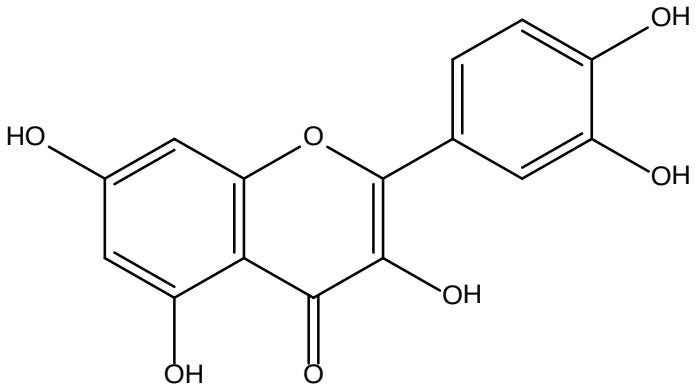


beta-farnesene

2. Linalool



3. Quercetin



4. Azulene

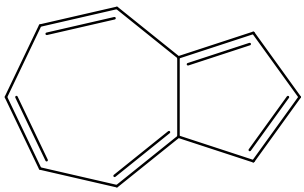


Figure 1. Structural formulas for some of the constituents of Chamomilla Recutita (Matricaria) Flower Oil and extract.

Table 1. Data from CIR Final Safety Assessment on Bisabolol.[3]

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.[105]
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.[105]
		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.[106]
		Acute Oral Toxicity	
(-)-α-Bisabolol	Mice (number and strain not specified)	Oral dosing (procedure not stated)	LD_{50} = 15.1 ml/kg.[107]
(-)-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).[107]
(±)-α-Bisabolol	Rats (number and strain not stated)	Oral dosing (procedure not stated)	LD_{50} > 5 g/kg.[108]
		Acute Parenteral Toxicity	
(±)-α-Bisabolol	12 rats (strain not stated)	Exposed for 7 h to aerosolized test substance.	No deaths or lesions at necropsy.[109]
(±)-α-Bisabolol (in emulsion)	Mice (number and strain not specified)	Intraperitoneal dosing	LD_{50} = 633 mg/kg.[110]
		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.[107]
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".[107]
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. [107]
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.[107]

Table 1. Data from CIR Final Safety Assessment on Bisabolol.[3]

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.[111]
		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.[112]
		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.[113]
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.[114]
Product containing 0.1% bisabolol	25 panelists	Maximization test (occlusive patches)	Neither irritation nor sensitization observed.[115]
		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.[116]
		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.[117]
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.[118]
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.[118]

Table 1. Data from CIR Final Safety Assessment on Bisabolol.[3]

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.[107]
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.[107]

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[48,119]

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.[13]

INCI Name	Composition (%)	Extraction Solvent
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
Butylene glycol (and) water (and) Chamomilla Recutita (Matricaria) Flower Extract	> 50, 25 to 0, and 5 to 9.9, respectively	Butylene glycol and water
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
Propylene glycol (and) water and Chamomilla Recutita (Matricaria) Flower Extract	>50, 25 to 50, and 5 to 9.9, respectively	Propylene glycol and water
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.[5,8,25,48,120,121,122,123,124,125]

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%	
β-Caryophyllene		< 0.1 to 0.9%	
Caryophyllene oxide		0.70%	
Chamazulene		0.2 to 24.50%	530 to 13,200 ppm

Table 5. Composition of Chamomilla Recutita Ingredients.[5,8,25,48,120,121,122,123,124,125]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
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%	
Germacrene-D		0.16 to 5.78%	
Glucose			70,000 ppm
2-Heptanone		< 0.1%	
Herniarin			320 to 915 ppm

Table 5. Composition of Chamomilla Recutita Ingredients.[5,8,25,48,120,121,122,123,124,125]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
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%	
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%	

Table 5. Composition of Chamomilla Recutita Ingredients.[5,8,25,48,120,121,122,123,124,125]

Data	Ingredients		
Components/Impurities	**Chamomilla Recutita (Matricaria) Flower Extract**	**Chamomilla Recutita (Matricaria) Flower Oil**	**Chamomilla Recutita (Matricaria) Flower**
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. Composition Data on *Matricaria chamomilla* Plant Parts.[14]

Components (w/%)	Flower Heads	Stems and Leaf	Petals	Yellow Florets
Essential Oil	0.43	0.08	0.28	0.49
Chamazulene	6.94	4.75	5.14	10.35
Farnesen	7.84	8.37	12.91	9.49
Bisabolol	2.08	1.85	1.84	2.21
Bisabolol Oxide A **(w*/%)**	26.49	25.51	19.67	28.5
Bisabolol Oxide B **(w*/%)**	19.11	18.76	14.85	19.5
En-in-Dicyclo Ethers **(w*/%)**	7.99	9.39	11.25	2.93
Flavonoids	0.93	0.86	2.58	1.1

* Mass fraction in essential oil

Table 7. Composition of *Chamomilla recutita* Roots.[15,16]

Sesquiterpenes	Chamomillol
	β-Caryophyllene
	cis-Caryophyllene
	Caryophyllenepoxide
	Caryophyllene Oxide
Polyenes	Chamomillaester I
	Chamomillaester II
Other Components	Linalool
	Nerol
	Geraniol
	β-Elemene
	(E)-β-Farnesene
	α-Farnesene
	Spathulenol
	τ-Cadinol
	τ- Muurolol
	Hexadec-11-yn-11,13-diene
	cis-en-yn-Dicycloethers
	trans-en-yn-Dicycloethers

Table 8. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[28,126]

	Chamomilla Recutita (Matricaria) Extract		**Chamomilla Recutita (Matricaria) Flower**		**Chamomilla Recutita (Matricaria) Flower Extract**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	1054	0.000002-0.61	14	0.00001-0.2	156	0.0000005-0.8
Duration of Use						
Leave-On	675	0.000002-0.4	12	0.002-0.2	77	0.000004-0.5
Rinse off	361	0.00017-0.61	2	0.00001-0.018	79	0.0000005-0.2
Diluted for (bath) Use	18	0.0009	NR	NR	NR	0.0003-0.8
Exposure Type						
Eye Area	58	0.0001-0.4	2	NR	15	0.0001-0.2
Incidental Ingestion	7	0.002-0.025	NR	NR	1	0.0001-0.2
Incidental Inhalation- Sprays	286*	0.000002-0.02	6	0.0022	26*	0.000004-0.11
Incidental Inhalation- Powders	40**	0.002-0.13**	2**	0.002**	7	0.0015-0.2**
Dermal Contact	689	0.0001-0.61	11	0.00001-1	84	0.0000005-0.8
Deodorant (underarm)	3	NR	NR	NR	NR	0.0035
Hair - Non-Coloring	158	0.000002-0.026	NR	0.00025-0.2	24	0.00000063-0.12
Hair-Coloring	18	NR	NR	NR	15	0.000005-0.059
Nail	1	NR	NR	NR	NR	0.000033-0.3
Mucous Membrane	93	0.61	1	NR	5	0.0000005-0.8
Baby Products	29	0.02	NR	NR	NR	0.0005-0.0006
	Chamomilla Recutita (Matricaria) Flower/Leaf Extract		**Chamomilla Recutita (Matricaria) Oil**		**Chamomilla Recutita (Matricaria) Flower Oil**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	359	0.0002-0.1	154	0.00005	NR	0.00001-0.29
Duration of Use						
Leave-On	240	0.002-0.1	89	NR	NR	0.01-0.2
Rinse off	115	0.0002-0.02	56	0.00005	NR	0.00001-0.29
Diluted for (bath) Use	4	NR	9	NR	NR	NR
Exposure Type						
Eye Area	8	0.1	7	NR	NR	0.001-0.015
Incidental Ingestion	5	0.01-0.1	6	NR	NR	0.04
Incidental Inhalation- Sprays	192*	NR	65*	NR	NR	0.01-0.11
Incidental Inhalation- Powders	69**	0.002	47**	NR	NR	0.015-0.2
Dermal Contact	274	0.002-0.1	113	NR	NR	0.001-0.29
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	68	0.0002	33	0.00005	NR	0.00001-0.11
Hair-Coloring	5	0.02	1	NR	NR	0.015
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	31	0.01-0.1	36	NR	NR	0.04-0.29
Baby Products	5	NR	7	NR	NR	NR
	Chamomilla Recutita (Matricaria) Flower Powder		**Chamomilla Recutita (Matricaria) Flower Water**			
	# of Uses	Conc. (%)				
Totals/Conc. Range	NR	0.5-1	14	NR		
Duration of Use						
Leave-On	NR	NR	10	NR		
Rinse off	NR	0.5-1	4			
Diluted for (bath) Use	NR	NR	NR	NR		
Exposure Type						
Eye Area	NR	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation- Sprays	NR	NR	8	NR		
Incidental Inhalation- Powders	NR	NR	7	NR		
Dermal Contact	NR	0.5	12	NR		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	2	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	NR	NR	1	NR		
Baby Products	NR	NR	NR	NR		

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

*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.
** It is possible that these products may be powders, but it is not specified whether the reported uses are powders.
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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2016 FDA VCRP Data

Matricaria Chamomilla (German Chamomile) Extract

01A - Baby Shampoos	6
01B - Baby Lotions, Oils, Powders, and Creams	13
01C - Other Baby Products	10
02A - Bath Oils, Tablets, and Salts	10
02B - Bubble Baths	4
02D - Other Bath Preparations	4
03A - Eyebrow Pencil	2
03B - Eyeliner	9
03C - Eye Shadow	5
03D - Eye Lotion	15
03E - Eye Makeup Remover	7
03F - Mascara	1
03G - Other Eye Makeup Preparations	19
04A - Cologne and Toilet waters	178
04B - Perfumes	12
04E - Other Fragrance Preparation	49
05A - Hair Conditioner	61
05B - Hair Spray (aerosol fixatives)	2
05D - Permanent Waves	2
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	52
05G - Tonics, Dressings, and Other Hair Grooming Aids	25
05H - Wave Sets	4
05I - Other Hair Preparations	19
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	16
06C - Hair Rinses (coloring)	1
06D - Hair Shampoos (coloring)	1
07A - Blushers (all types)	13
07B - Face Powders	10
07C - Foundations	15
07E - Lipstick	5
07F - Makeup Bases	5
07H - Makeup Fixatives	1
07I - Other Makeup Preparations	15
08A - Basecoats and Undercoats	1
08B - Cuticle Softeners	5
08C - Nail Creams and Lotions	1
08F - Nail Polish and Enamel Removers	2
08G - Other Manicuring Preparations	2
09A - Dentifrices	2
10A - Bath Soaps and Detergents	50
10B - Deodorants (underarm)	3
10E - Other Personal Cleanliness Products	18
11A - Aftershave Lotion	7

11E - Shaving Cream	12
11G - Other Shaving Preparation Products	1
12A - Cleansing	78
12B - Depilatories	13
12C - Face and Neck (exc shave)	81
12D - Body and Hand (exc shave)	30
12F - Moisturizing	76
12G - Night	13
12H - Paste Masks (mud packs)	21
12I - Skin Fresheners	14
12J - Other Skin Care Preps	25
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	3
13C - Other Suntan Preparations	3
Total	**1,054**

Matricaria Chamomilla (German Chamomile) Flower Extract

03B - Eyeliner	3
03C - Eye Shadow	1
03D - Eye Lotion	4
03E - Eye Makeup Remover	4
03F - Mascara	1
03G - Other Eye Makeup Preparations	2
04B - Perfumes	3
04E - Other Fragrance Preparation	17
05A - Hair Conditioner	8
05C - Hair Straighteners	3
05F - Shampoos (non-coloring)	10
05G - Tonics, Dressings, and Other Hair Grooming Aids	4
05I - Other Hair Preparations	1
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	13
06G - Hair Bleaches	1
06H - Other Hair Coloring Preparation	1
07B - Face Powders	4
07C - Foundations	2
07E - Lipstick	1
07I - Other Makeup Preparations	1
10A - Bath Soaps and Detergents	3
10E - Other Personal Cleanliness Products	1
11G - Other Shaving Preparation Products	11
12A - Cleansing	13
12C - Face and Neck (exc shave)	10
12D - Body and Hand (exc shave)	7
12F - Moisturizing	5
12G - Night	4
12H - Paste Masks (mud packs)	8

12I - Skin Fresheners	7
12J - Other Skin Care Preps	2
13A - Suntan Gels, Creams, and Liquids	1
Total	**156**

Matricaria Chamomilla Flower

03D - Eye Lotion	2
04A - Cologne and Toilet waters	1
04B - Perfumes	1
04C - Powders (dusting and talcum, excluding aftershave talc)	1
04E - Other Fragrance Preparation	3
10C - Douches	1
12A - Cleansing	1
12C - Face and Neck (exc shave)	2
12F - Moisturizing	1
12I - Skin Fresheners	1
Total	**14**

Matricaria Chamomilla 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	1
03E - Eye Makeup Remover	2
03G - Other Eye Makeup Preparations	4
04A - Cologne and Toilet waters	24
04B - Perfumes	1
04E - Other Fragrance Preparation	91
05A - Hair Conditioner	22
05B - Hair Spray (aerosol fixatives)	3
05C - Hair Straighteners	1
05F - Shampoos (non-coloring)	30
05G - Tonics, Dressings, and Other Hair Grooming Aids	5
05H - Wave Sets	2
05I - Other Hair Preparations	8
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	4
06D - Hair Shampoos (coloring)	1
07B - Face Powders	3
07C - Foundations	6
07E - Lipstick	4
07F - Makeup Bases	1
07I - Other Makeup Preparations	2
09A - Dentifrices	1

10A - Bath Soaps and Detergents	12
10C - Douches	2
10E - Other Personal Cleanliness Products	8
11A - Aftershave Lotion	1
12A - Cleansing	21
12B - Depilatories	1
12C - Face and Neck (exc shave)	34
12D - Body and Hand (exc shave)	3
12F - Moisturizing	22
12G - Night	4
12H - Paste Masks (mud packs)	8
12I - Skin Fresheners	5
12J - Other Skin Care Preps	8
13A - Suntan Gels, Creams, and Liquids	2
13B - Indoor Tanning Preparations	1
13C - Other Suntan Preparations	1
Total	**359**

Matricaria Chamomilla (German Chamomile) Flower Water

05F - Shampoos (non-coloring)	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
07F - Makeup Bases	1
07I - Other Makeup Preparations	1
10E - Other Personal Cleanliness Products	1
12A - Cleansing	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	2
Total	**14**

Chamomilla Recutita (Matricaria) Oil

01A - Baby Shampoos	2
01B - Baby Lotions, Oils, Powders, and Creams	4
01C - Other Baby Products	1
02A - Bath Oils, Tablets, and Salts	3
02B - Bubble Baths	6
03D - Eye Lotion	2
03E - Eye Makeup Remover	1
03G - Other Eye Makeup Preparations	4
04A - Cologne and Toilet waters	3
04B - Perfumes	1
04E - Other Fragrance Preparation	7
05A - Hair Conditioner	6

05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	12
05G - Tonics, Dressings, and Other Hair Grooming Aids	10
05I - Other Hair Preparations	2
06F - Hair Lighteners with Color	1
07E - Lipstick	6
07F - Makeup Bases	1
10A - Bath Soaps and Detergents	20
10E - Other Personal Cleanliness Products	1
11A - Aftershave Lotion	1
12A - Cleansing	8
12C - Face and Neck (exc shave)	15
12D - Body and Hand (exc shave)	13
12F - Moisturizing	11
12G - Night	2
12H - Paste Masks (mud packs)	4
12I - Skin Fresheners	2
12J - Other Skin Care Preps	2
13C - Other Suntan Preparations	2
Total	**154**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 18, 2016

SUBJECT: Comments on the Tentative Amended Report: Safety Assessment of Chamomilla Recutita-Derived Ingredients as Used in Cosmetics (posted April 11, 2016)

Acute Exposure, Oral - Please provide a reference for the acute oral study of "a lyophilized water extract of *Chamomilla Recutita (Matricaria) Flowers*". If italics are going to be used, they should only be used for the genus species name, not the common name and plant parts.

Skin Irritation, Chamomilla Recutita (Matricaria) Flower Extract - The units of ml^2 do not make sense, so the reference (57) was checked. In the original reference the superscript 2 refers to a footnote that describes the dosing syringe. The superscript 2 should be deleted from the CIR report.

Summary - Please correct the following sentence: "Skin irritation was observed in an acute dermal toxicity study on , and Recutita (Matricaria) Flower Oil involving rabbits."

Table 2 - Please update the reference for this table from the 14th edition of the Dictionary (reference 118), to the 16th edition of the Dictionary (reference 1).

Table 5 - The 1% reported use concentration of Chamomilla Recutita (Matricaria) Flower Powder for paste masks and mud packs from the Council's concentration of use survey should also be shown in the Dermal Contact row.

Reference 1 - The 2016 edition of the Dictionary is the 16th edition, not the 14th edition as stated in reference 1.

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