Safety Assessment of Rosmarinus Officinalis (Rosemary)-Derived Ingredients as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	November 15, 2013
Panel Meeting Date:	December 9-10, 2013

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, 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 safety assessment was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Senior Scientific Analyst/Writer
Date: November 15, 2013
Subject: Safety Assessment of Rosmarinus Officinalis (Rosemary)-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Tentative Report on the Safety Assessment of Rosmarinus Officinalis (Rosemary)-Derived Ingredients as Used in Cosmetics.

The Panel reviewed this report for the first time at the September meeting, and determined that additional data were needed to make a determination of safety. The Panel issued an Insufficient Data Announcement (IDA) requesting the following:

1. Dermal sensitization data for 10% rosmarinus officinalis (rosemary) leaf extract (i.e., a human repeated-insult patch test in a sufficient number of subjects at concentration of use);
2. Chemical characterization of the flower, if available;
3. Additional information on the deodorizing process performed during preparation of some of the ingredients, including information on what by-products may form; and
4. Information as to why the *PDR of Herbal Medicines* states that rosemary preparations should not be used during pregnancy.

The Panel also asked for confirmation of whether rosmarinus officinalis (rosemary) flower/leaf/stem water, rosmarinus officinalis (rosemary) leaf water, and rosmarinus officinalis (rosemary) water are used as fragrance ingredients only. We have contacted RIFM about this issue, but have not heard back.

The following data were received from the Council since the report was last reviewed, and are included with this report; these data are indicated in the report by the inclusion of a border on either side of the paragraph:

1. Studies on a product containing 0.2% rosmarinus officinalis (rosemary) leaf extract; memo dated September 10, 2013.
    a. KGL, Inc. (Ivy Laboratories). 1998. An evaluation of the contact sensitization potential of a topical coaded produced in human skin by means of the maximization assay (product contains 0.2% rosmarinus officinalis (rosemary) leaf extract).
    b. Anonymous. 1998. Human patch test of a product containing 0.2% rosmarinus officinalis (rosemary) leaf extract.
2. HRIPT on a product containing rosmarinus officinalis (rosemary) leaf oil; memo dated October 8, 2013.
    a. Clinical Research Services. 2007. Human repeat insult patch test of a massage oil containing 1.5% rosmarinus officinalis (rosemary) leaf oil.

3. Summary of an HRIPT of a hair spray containing 0.0013% rosmarinus officinalis (rosemary) leaf extract; memo dated October 21, 2013.
    a. Anonymous. 2009. Summary of an HRIPT of a hair spray containing 0.0013% rosmarinus officinalis (rosemary) leaf extract.

The Council also submitted, on October 25, a memo on the "Reproductive and Developmental Toxicity Concern for Rosemary Used as a Drug." Because of the date the memo was received with respect to report preparation for the meeting, the information in the memo has not been incorporated in the report. However, the memo does address one of the items of the IDA; therefore it is being included with this submission. If the information included with this memo results in changes in the safety assessment, you will receive a Wave 2 document that contains those changes.

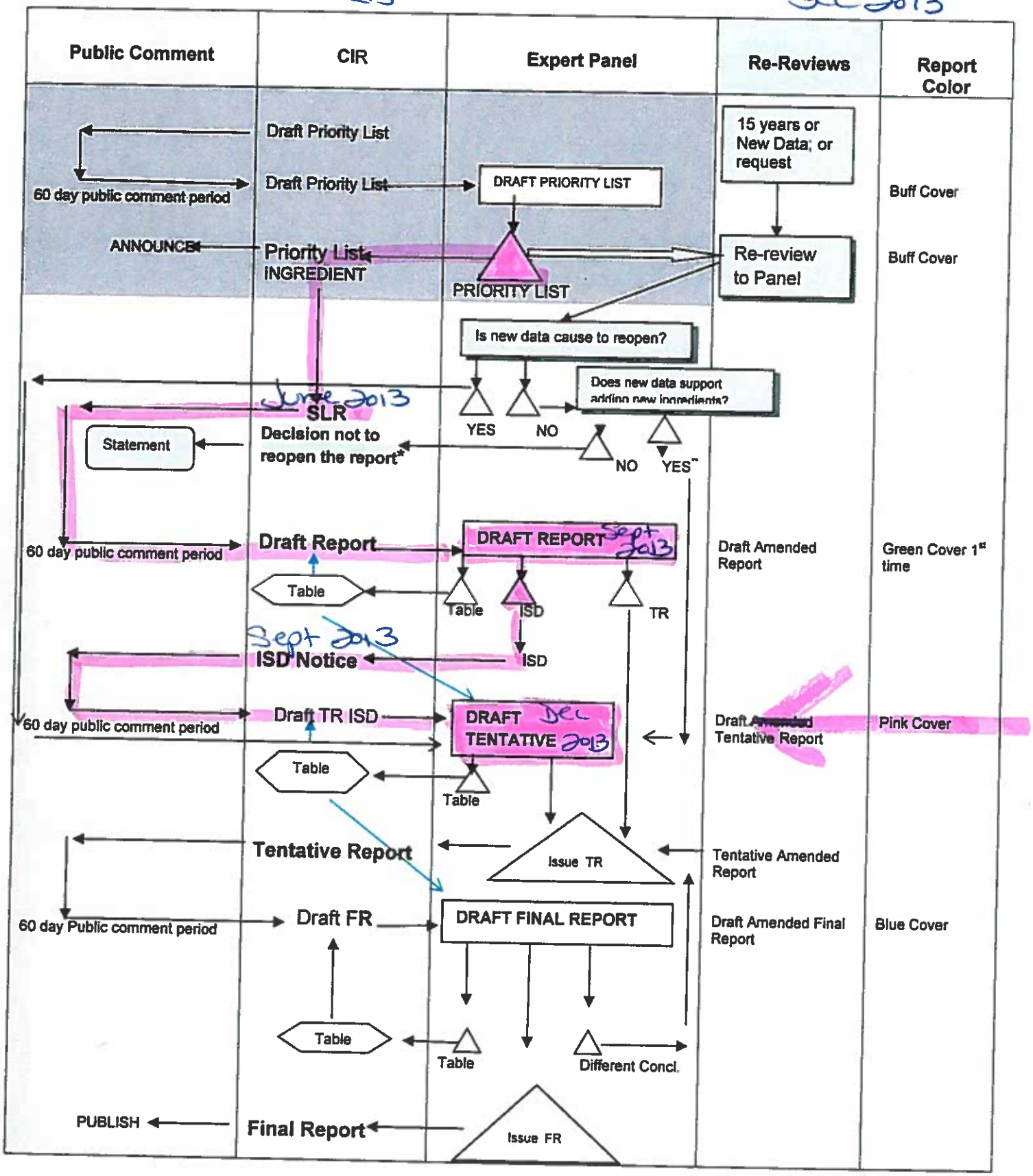
Since not all the requested data were received, the Panel should consider issuing a Tentative Report with a conclusion of insufficient data for the data needs that were not addressed, particularly, dermal sensitization data for 10% rosmarinus officinalis (rosemary) leaf extract. The Panel is also being asked to review the draft Discussion to see if it adequately addresses all concerns of the Panel.

If after further review of the report the Panel finds that the existing data are sufficient to make a determination of safety, then a Tentative Report with a conclusion of safe as used when formulated to be non-irritating should be issued.

SAFETY ASSESSMENT FLOW CHART

Rosmarinus officinalis

Dec 2013



Rosmarinus Officinalis (Rosemary)-Derived Igngredients Report History

June 7, 2013: Scientific Literature Review
The following data submissions were received from the Council:

1. Rosmarinus officinalis (rosemary) leaf extract: composition information; dated April 22.
    a. Natural Sourcing. 2013. Organic rosemary oil extract;
    b. Natural Sourcing. 2013. Rosemary antioxidant extract – 14% diterpene phenols;
    c. Natural Sourcing. 2013. Rosemary antioxidant extract – 25% diterpene phenols;
    d. Natural Sourcing. 2011. CO_2 rosemary extract select certificate of analysis;
    e. Natural Sourcing. 2012. Organic rosemary antioxidant CO_2 extract 14% diterpene phenols certificate of analysis;
    f. Natural Sourcing. 2013. Organic rosemary antioxidant CO_2 extract 25% diterpene phenols certificate of analysis;
    g. Natural Sourcing. 2012. Rosemary essential oil certificate of analysis.
2. Rosmarinus officinalis (rosemary) leaf extract; dated May 31.
    a. Flavex Naturextrakte GmbH. 2010. Rosemary antioxidant CO_2 extract 25% diterpene phenols, type no. 027.020 25% diterpene phenols;
    b. Flavex Naturextrakte GmbH. 2013. Certificate of analysis: Rosemary antioxidant extract 25% diterpene phenols, type no. 027.020;
    c. Flavex Naturextrakte GmbH. 2013. Allergen compounds according to Cosmetic Guideline 76/768/EEC Rosemary antioxidant extract 25% diterpene phenols, type no. 027.020;
    d. Official Journal of the European Union. 2010. Commission Directive 2010/69/EU of 22 October 2010 amending the Annexes to the European Parliament and Council Directive 95/2/EC on food additives other than colours and sweeteners.
3. Updated concentration of use by FDA product category: Rosemary-derived ingredients (added rosemary leaf oil). Memo dated June 14, 2013.
4. Concentration of use by FDA product category: Rosmarinic acid. Memo dated July 29, 2013.

September 9-10, 2013: Draft Report for Panel Review
The Panel determined that rosmarinus officinalis (rosemary) flower wax should be removed from the report because it is chemically dissimilar from the other ingredients and rosmarinic acid should be removed because it is a constituent that is found in other botanical sources and is not unique to rosemary.

The Panel reviewed *Rosmarinus officinalis* (Rosemary)-derived ingredients for the first time at this meeting and determined that additional data were needed to make a determination of safety. The Panel issued and IDA requesting the following:

1. Dermal sensitization data for 10% rosmarinus officinalis (rosemary) leaf extract (i.e., a human repeated-insult patch test in a sufficient number of subjects at concentration of use);
2. Chemical characterization of the flower, if available;
3. Additional information on the deodorizing process performed during preparation of some of the ingredients, including information on what by-products may form; and
4. Information as to why the *PDR of Herbal Medicines* states that rosemary preparations should not be used during pregnancy.

The Panel also asked for confirmation on whether rosmarinus officinalis (rosemary) flower/leaf/stem water, rosmarinus officinalis (rosemary) leaf water, and rosmarinus officinalis (rosemary) water are used as fragrance ingredients only. If their use is as fragrance only, they will be deleted from the conclusion of the safety assessment because they will be under the purview of the RIFM.

December 9-10, 2013: Draft Tentative Report for Panel Review
The following unpublished data were received and incorporated into the report:

1. Anonymous. 1998. Human patch test of a product containing 0.2% Rosmarinus officinalis (rosemary) leaf extract.
2. Anonymous. 2009. Summary of a hair spray containing 0.0013% Rosmarinus officinalis (rosemary) leaf extract.
3. KGL, Inc. (Ivy Laboratories). 1998. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (product contains 0.2% Rosmarinus officinalis (rosemary) leaf extract).

4. Clinical Research Services. 2007. Human repeat insult patch test of a massage oil containing 1.5% Rosmarinus officinalis (rosemary) leaf oil.

A memo regarding reproductive and developmental toxicity concern for rosemary used as a drug was also received.

Confirmation has not been received regarding whether some of the ingredients are truly fragrance only.

Rosmarinus Officinalis (Rosemary)-Derived Ingredients Data Profile* – Dec 2013 – Monice Fiume															
	Reported Use	Preparation/ Extraction	Constituents/ Impurities	Toxicokinetics	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox – Rptd Dose, Dermal	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhalaiton	Repro/Dev Tox	Genotox	Carcinogenicity/ Anti-Tumor Act	Dermal Irr/Sens	Ocular Irritation
Rosmarinus officinalis L.			X												
Rosmarinus Officinalis (Rosemary) Extract	X											X	X		
Rosmarinus Officinalis (Rosemary) Flower Extract	X		X												
Rosmarinus Officinalis (Rosemary) Flower/Leaf Stem Extract	X										X				
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Water															
Rosmarinus Officinalis (Rosemary) Leaf	X		X			X								X	
Rosmarinus Officinalis (Rosemary)Leaf Extract	X	X	X			X			X		X	X	X	X	
Rosmarinus Officinalis (Rosemary) Leaf Oil	X	X	X		X	X			X			X		X	X
Rosmarinus Officinalis (Rosemary) Leaf Powder	X														
Rosmarinus Officinalis (Rosemary)Leaf Water	X														
Rosmarinus Officinalis (Rosemary) Water	X														

*"X" indicates that data were available in a category for the ingredient

Rosmarinus Officinalis (Rosemary)-Derived Ingredients

Keep Me Posted Results are obtained weekly

SciFinder Substance Search (Feb 12, 2013)

84604-14-8
8000-25-7
Rosmarinus Officinalis (Rosemary) Extract
Rosmarinus Officinalis (Rosemary) Flower Extract
Rosmarinus Officinalis Flower/Leaf Stem Extract
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Water
Rosmarinus Officinalis (Rosemary) Flower Wax
Rosmarinus Officinalis (Rosemary) Leaf
Rosmarinus Officinalis (Rosemary) Leaf Extract
Rosmarinus Officinalis (Rosemary) Leaf Oil
Rosmarinus Officinalis (Rosemary) Leaf Powder
Rosmarinus Officinalis (Rosemary) Leaf Water
Rosmarinus Officinalis (Rosemary) Water

- 2 substances found – via above CAS No.
    - 84604-14-8 – 0 hits
    - 8000-25-7 – 49 hits/7 selected for further examination

Searched
- effects of rosemary on reproduction or fertility?
    - 178 hits; 1 selected for further examination
- Estrogenic effects of rosemary
    - 14 hits; 3 selected for further examination
- Dermal irritation and sensitization and rosemary
    - 73 hits; 3 selected for further examination

Added Rosmarinic Acid/searched Mar 7, 2013: 20283-92-5; pulled 4 hits from SciFinder – because also searched PubMed

PubMed Search (Feb 12, 2013)
(rosmarinus AND officinalis) OR rosemary – 1291 hits/44 selected for further examination

"20283-92-5" OR (rosmarinic AND acid) OR (rosemary AND acid) – (Mar 8, 2013) – 935 hits/19 selected for further examination

ChemPortal
nothing useful

IARC
Found info on constituents

NTP
Found info on constituents

The next item is rosmarinus. Dr. Belsito?

DR. BELSITO: Yes. This is the first time we're looking at these 12 ingredients of rosmarinus officinalis. And again, we thought that rosmarinic acid should be removed from this report. It has no reported uses, and, therefore, we had no sense at what concentration it might be used. And we also got some soft information that it may be present in other botanical products as well.

Having said that, we also thought that the wax should be deleted. Dr. Liebler may want to comment, but he felt this was chemically dissimilar from the other components of rosmarinus officinalis that we were reviewing. And you can comment. I'll continue going.

The water --

DR. BERGFELD: He's ready to comment.

DR. BELSITO: You ready?

DR. LIEBLER: I'd just make the comment that I'm not going to comment.

(Laughter)

DR. BELSITO: Okay. So anyway, he thought the wax was dissimilar, so we're removing those two ingredients. And then it appears that the water extracts are -- may be used only as fragrance ingredients. We're waiting for some information from RIFM. If they are, then it's not in the purview of this Panel to review them, and those would be deleted.

We had a lot of data on the whole plant, a little less on component parts. But we felt that by and large the plant data covered the compositions that we needed. And that -- but it was still insufficient for sensitization of the leaf extract at 10 percent. And since we're going with an "insufficient," if the composition of the flower, which we didn't have a lot of information on, was available, we would like to see that. In terms of helping the Panel develop a discussion, we would need the pesticide heavy metal inhalation boilerplates.

And the specific components of concern are caffeic acid, thujone, and terpenes, especially linalool/linalyl acetate acetate, limonene methyl eugenol. And then the discussion of the fact that there were reproductive effects on both males and females, but at very high doses that weren't relevant to use in a cosmetic product.

So developing a discussion, hopefully going ahead with eventually a "safe as used." But at this point, sensitization of the leaf extract at 10 percent, composition of the flower, if available.

DR. BERGFELD: So it's an insufficient notice --

DR. BELSITO: Insufficient notice.

DR. BERGFELD: -- that you're making a motion for. Is there a second?

DR. MARKS: Second.

DR. BERGFELD: Any other comments about the needs?

DR. MARKS: I think Don has addressed most of them. We were concerned in the text that said with a reference with a PDR herbal that rosemary should not be used in pregnancy. So you may have addressed it, Don, in terms of your saying, yeah, the amount should not be a safety issue, but we want that clarified. Ron Shank, if you want to comment more?

DR. SHANK: Yeah. I'd like to know what the writers of the PDR herbal had in mind when they said that rosemary preparation should not be used during pregnancy. I think that needs to be explained.

DR. HILL: And I had added to that the concern that we didn't have any reproductive toxicology data on the oil. And I'm not sure we have enough composition on the oil specifically to know how that relates to the other ingredients that we're studying in this group. So it's sort of a combined concern between those two things.

DR. MARKS: So I think it's just delve more into the pregnancy issue and the insufficient data notice.

And then the last thing was Ron Hill wanted to know what was meant by the manufacturer when you used "deodorize." So again, I think that's a minor point, but it would be perhaps nice to clarify that. If you want to comment, Ron Hill, you may.

DR. HILL: Just depending on how that process is actually conducted. I mean if it's just absorption with activated carbon, then that presents no concerns whatsoever. But if there is chemistry involved, for example, some sort of bleaching, then that creates the potential for creating new chemicals that we might like to know something about.

DR. MARKS: So I think the two big data points we need is either a max or an HRIPT for the leaf extract at 10 percent. Undiluted, the leaf extract is a sensitizer, so is it safe at 10 percent? And then the second is clarify the issue of pregnancy and repo and development toxicity.

DR. BERGFELD: Have we captured it all then? Is there something that's been left out? No?

DR. MARKS: No.

DR. BERGFELD: Lillian, are you comfortable with what we've got in that list, because it went on and on.

DR. GILL: I have it.

DR. BERGFELD: Okay. Now, I call for the question. It's going out as an insufficient data notice.

All those in favor? Thank you. Unanimous.

SEPT 2013 – BELSITO TEAM

DR. BELSITO: Okay. Parsley, sage, rosemary and thyme, sorry, Monice but this is another one I did on paper so hopefully --

MS. FIUME: That's fine.

DR. BELSITO: I thought that first of all, there were several ingredients that functioned only as fragrance ingredients. The flower wax and all of the water extracts were listed as fragrance ingredients and should we be reviewing those ingredients or should we be cutting them out?

DR. LIEBLER: So I read this and then I read the, I guess it was the wave 2 suggest or maybe the memo at the end. It was either a memo at the end or the wave 2 that suggested that we table this report and consider the possibility of issuing a report on the constituent ingredients. Right? That was a suggestion that was made?

MS. FIUME: It was. It was, it came in the main package.

DR. LIEBLER: Okay, so I encountered it. It was at the end I think. It was in the memo at the end.

MS. FIUME: Yes.

DR. LIEBLER: So that's why I encountered that after I considered the report. So I guess my question in response to that suggestion is whether or not the individual ingredients have significant uses and use concentration data to allow us to bracket our needs for data and to consider these in an actual report.

In other words, I understand the logic of focusing on some of the main potentially bioactive constituents but then is there enough actual use and data to help us figure out what data we would need to evaluate those individual ingredients?

MS. FIUME: There are data out there on some of the individual constituents, however, as we encounter more and more botanicals as a writer, if we start reviewing all the documents we start with Dr. Duke's. We find other documents that have what main constituents are and what the percentages are. But as the writer, it becomes a question of what is a main constituent? What level of those constituents are a concern? Which ones are in cosmetic use? And what is the chemical characterization of the actual cosmetic ingredient versus, like if it's the extract, versus what is out there?

DR. LIEBLER: Like carnosols, for example.

MS. FIUME: Right. And there is some information out, there is information out there. I forget. I know I looked at it but I can't remember from the BCRP how many uses it would have. As we're going through and I struggled with this and the writers have talked to it. It does become at what point is it a report of the constituents versus a report on the ingredient that's being used. So I understand what you're saying but I guess my answer is it's a confusing situation for us as well.

DR. LIEBLER: 'Cause I think of an evaluation of carnosol, if it were to be different then the evaluation of a botanical that contains carnosol's a major ingredient, then if it were to be different then we would need to know something about what kinds of products carnosol was used in and concentrations and use context to know if that was anything different than the occurrence just in botanicals. And I think this would generally apply to these other individual chemical constituents.

So although I see a potential logic of reviewing the individuals, 'cause that way we can refer to our previous reviews when we do some of the botanicals, we just might not have enough context for the use of the individual ingredients for that strategy to actually work for us. And that's what I'm concerned about. But I don't know enough about the uses and concentrations just for some of the major ones in rosemary to know if that's an issue for us to consider here and now.

MS. FIUME: So, for example, carnosic acid is listed in the database and is just listed as an antioxidant is what its use is listed as.

DR. BELSITO: But I thought that whole point was just should we be reviewing rosmarinic acid with the botanical? I didn't take it to mean we should be evaluating botanicals solely based upon their constituents. You know what I mean? So I mean, quite honestly that's what I thought and I didn't have a problem putting rosmarinic acid in here since it's a major component,

number one. Number two, we had some safety data on rosmarinic acid itself and number three, it's apparently listed in the cosmetic ingredient dictionary.

So I thought it was fine to keep it in. But --

DR. ANSELL: Well, that was our comment.

DR. BELSITO: Right.

DR. ANSELL: Although this discussion might be well worth having.

DR. BELSITO: But I don't think you can go, I mean, unless you get something like peppermint where carbone is the overwhelming, you know, principle ingredient that you can really base your safety evaluation trying to put together all the individual ingredients in these botanicals. I think that's going down a slippery slope.

On the other hand if a botanical has a major ingredient like rosmarinic acid and there's also data, safety data, on that ingredient and that ingredient as a purified ingredient is used a fragrance ingredient, I think it could be thrown in with the botanical.

DR. GILL: And I think that's the approach the writers are taking, Don.

DR. BELSITO: Right.

DR. GILL: The question, I think, from our perspective as we discussed is what's major and as we look, go down the list of components, where do we draw the line on what's major? Which is I think the comment from the council as well.

DR. BELSITO: Okay.

DR. GILL: Why rosmarinic acid and none of the others. So the discussion that Dan was having is important but I -- what you just described is how we've approached this before.

DR. LIEBLER: So, if there, for example, perhaps a good rule of thumb to deal with this is if you have a specific chemical component that is significant component of a botanical and is relatively unique to that botanical, like the rosmarinic acid for example, then we can consider it along with the botanical. But if we have something like caffeic acid or luteolin or ursolic acid, these are things that are in lots and lots of different botanicals, you know, we could keep rosemary on the back burner for ages while we do all of those.

And then that would be a clever way of avoiding ever doing botanicals, actually. We could just put them behind all the individual chemicals but that's just not going to be workable for us.

DR. BELSITO: So I guess what we're saying as a boiler plate, if it a major's constituent you need to have botanical, it's a cosmetic ingredient and there's some safety data, we'll include it. If it's not unique to that botanical, then we won't include it.

DR. LIEBLER: Right. And I'm fine with that. I was really trying to respond to the comment here in this memo 'cause I thought it was worth discussing.

DR. BELSITO: But I think that brings us back to Table 1. Again, my question where we have rosemary flower leaf stem water function fragrance ingredient, rosemary flower wax function fragrance ingredient, leaf water fragrance ingredient, water fragrance ingredient.

I thought it was not the purview of this panel to look at safety of the fragrance ingredients, so should those be in here to begin with? I can see when it, you know, benzyl alcohol is both a fragrance and something else that's a cosmetic function.

DR. ANSELL: Well, the CIR procedures address that don't they?

DR. GILL: Yes.

DR. ANSELL: And they --

DR. GILL: It is covered if it is a fragrance. I think part of the question was whether or not its whole purpose was a fragrance and we have made a connection if we're going to ask that question.

DR. ANSELL: Right. Mixed use ones are more confusing but if it were solely a fragrance it would be outside the purview of the panel.

DR. BELSITO: Okay. I mean I don't have a problem leaving them in. I mean, you know --

DR. LIEBLER: So I was going to suggest dumping the wax simply because of chemical dissimilarity from the other things. The wax is probably going to contain long chain lipids that -- it's waxy because it contains a lot of highly hydrophobic materials that -- and that the whole product will behave differently, the whole mixture will behave differently than the others.

So I just thought the wax could go. It just doesn't fit literally whereas the others could stay there and then we could still dump in the we consider them as only fragrances.

DR. BELSITO: Okay, so we're going to delete the wax because of its chemically dissimilar. They have questions regarding --

DR. SNYDER: Wouldn't we hold that same caveat then for any of these derived ingredients that have functions only related to fragrance?

DR. BELSITO: Well, that's what we're trying to figure out.

DR. ANSELL: Well, it's already the CIR procedures already state that, that materials which are exclusively fragrances are outside the scope of the panel. The place where it becomes confusing, as Lillian pointed out, is there are ingredients which may be mixed use.

DR. BELSITO: Right.

DR. ANSELL: And they may bring other functions than simply fragrance.

DR. BELSITO: Right, so we're going to --

DR. ANSELL: In which case they would be here and then CIR is supposed to coordinate with the RIFM panel to make sure that the relevant data is --

DR. BELSITO: So we're going to check with regarding the water extracts. Once we get rid of the wax which is also reported just as a fragrance, we're going to check whether the water extracts are solely fragrance ingredients or if they have mixed uses. If they're fragrance ingredients we'll delete them from our consideration, although I would say that we could still if there's data on their safety, use that data. It just wouldn't be part of the ingredients that we review.

MS. FIUME: Dr. Belsito, that is the protocol we are trying to follow now with these botanicals. If something is listed as just a fragrance ingredient, confirm with RIFM that that is its only use and see if they have a data profile or anything, a monograph on those ingredients that we can incorporate for that use.

DR. BELSITO: Okay.

MS. FIUME: For information in our report.

DR. BELSITO: Okay, and then I have a note here that I thought really do we have enough information on the constitution of the flower? Again, when you look at it it's totally empty. You know, what we have is the whole plant. Is that sufficient?

So we have great data on the plant. We just don't have any data on the flower. And what we have are we have the rosemary extract, we have a flower extract, we have a flower leaf stem extract and we have leaf, which we have at least a little more data on.

So do we have enough on the flower constitution? And really do we have enough on the leaf; it can be leaf extract is used at 10 percent which I thought were insufficient for sensitization at 10 percent of the leaf extract.

DR. LIEBLER: So the plant's mostly leaves. So I would argue that the plant data which are pretty extensive could probably cover us at least for the leaves, leave and shoots. I don't know about the flower. This is a little better situation than we had with one of the chamomiles where we had, I think it was just the flower oil, right?

And we, it was hard to interpolate that to the other plant constituents but here we have the whole plant data. I would argue that we're probably okay with that, without having extensive data on the flower. Do we have a lot of uses on the flower?

DR. BELSITO: Quite honestly, I never knew that rosemary had a flower.

DR. LIEBLER: Oh, they're really tiny.

MS. FIUME: It does. Actually when it flowers then the spice gets bitter. You don't want it to flower if you're using it as an herb is what I've been told.

DR. LIEBLER: And they are covered with bees. We used to have rosemary out in front of our house in Tucson and they'd be flowering right when I had to put the Christmas lights out.

DR. BELSITO: Okay, so rosemary flower extract we have a total of 36 uses. Flower stem we have a concentration but no reported uses and a rinse off and that's it. So not a lot of uses probably because there aren't a lot of flowers.

DR. LIEBLER: Hard to get, yes.

DR. BELSITO: Yes.

DR. LIEBLER: But really the action is rosemary extract, rosemary leaf extract and leaf boil. That's where almost all the uses are.

DR. BELSITO: So the plant data covered the composition that we need.

DR. LIEBLER: I think plant data covers that, yes.

DR. BELSITO: Okay. So then in the discussion we need the pesticide heavy metal boilerplate and we need the inhalation boilerplate. And then I guess the ingredients of concern here are caffeic acid, thujone and methyl eugenol? So when we develop the botanical boilerplate those are the things we need to address.

So the leaf extract is used up to 10 percent but we don't have sensitization which I think is an insufficiency. Or would you disagree?

DR. SNYDER: Agreed. I mean sensitization and (inaudible).

DR. BELSITO: Right, for the leaf extract. There were reproductive effects on male and females as and antiestrogenic effect but the doses were super high so that needs to go in the discussion.

DR. LIEBLER: And I think the in vitro studies described on page 16, non-human, the effect of methanol extract leaves on NaDPH, depend on microsome metabolism of estradiol and estrone in liver microsomes. I don't think that's relevant. Essentially the effect of these compounds on microsome metabolism doesn't really serve as a model for interaction with estrogen receptors or really for modulating estrogen receptor signaling.

DR. BELSITO: So where are you, Dan?

DR. LIEBLER: I'm on pdf page 16; let's see about halfway down where it says effects on estrogenic activity. In that first section, the first one, two, three paragraphs are all about microsomal dependent oxidation of estradiol or glucoronidation and all those I think are irrelevant and can go.

And then I'm okay with the CD1 mice in vivo studies but the extract --

DR. BELSITO: So you're deleting the first three paragraphs?

DR. LIEBLER: Correct. The first three paragraphs. But the fourth paragraph you can keep.

DR. BELSITO: So the group of seven or eight six week old, that's okay?

DR. LIEBLER: Yes.

DR. BELSITO: I'm going to assume that corrects the only typo I had (inaudible) fennel. You did a great job there. So you're not going to get the paper document.

MS. FIUME: Darn. I like this paper document.

DR. BELSITO: I know you were looking forward to my handwriting.

DR. LIEBLER: She'll tear the office apart looking for it. I know he had one. He always has one.

MS. FIUME: But at least it says AU so I always knew if I needed to figure it out it was marked.

DR. BELSITO: Okay so that's my list of things that I had to bring up. Oh, penetration enhancement before do we need to discuss that at all? It was really not that great. I'm just raising it. I'm not saying we need to say it shouldn't be used with things that we said didn't penetrate. I don't even know what page that's on. Penetration. Penetration enhancement, it's 14 of the pdf on aminophylline. "Did enhance the penetration of, however the increase in permeation was less than that observed with 50 percent ethanol." Okay, so no mention about penetration enhancement, okay.

DR. SNYDER: So I have a question in the summary, this third sentence that says "rosmarinic acid is a constituent of the plant as well as a cosmetic ingredient." So we talked about that but what was the final resolution. It was we're not implying that this is a safety assessment of rosmarinic acid?

DR. LIEBLER: No, we are.

DR. SNYDER: We are? So then we should state that then.

DR. LIEBLER: That's the one individual chemical that's included with this.

DR. SNYDER: Okay, so then we need to make sure that we state that. So we should say because rosmarinic acid is a major constituent of the plant as well as an individual cosmetic ingredient, for safety assessment it includes or something along those lines, right?

MS. FIUME: So, Dr. Belsito, just to make sure I have everything correct, so it's going to go IDA for an HR IPT on the leaf extract at 10 percent which is the concentration of use? Since it's going out as IDA I wasn't sure, are you requesting chemical characterization on the flower ingredients then or on the flower?

DR. BELSITO: I mean, we could if it's available but Dan said he's comfortable with the total composition of the plant particularly given the small use of the flower.

MS. FIUME: Okay, so don't put it out at all or as if available.

DR. BELSITO: If available, yes.

MS. FIUME: If available? Okay.

DR. LIEBLER: That's fine.

MS. FIUME: And then the wax will be deleted?

DR. BELSITO: Yes.

MS. FIUME: And we're double-checking on those that are just fragrance ingredients?

DR. BELSITO: Right.

DR. ANSELL: So just so I'm clear there were a series of acids that we suggested including and did we get to them?

DR. LIEBLER: Yes, we talked about that. This is in the memo at the end?

DR. ANSELL: Yes.

DR. LIEBLER: Yes. You also suggested including carnosic acid or basically raised the question why rosmarinic acid but not carnosic acid, oleanolic acid or carsolic acid, et cetera, et cetera, et cetera. And then perhaps you should a discussion including the plant components or reports concerning plant extracts or perhaps the CIR may want to consider having a report on diterpenes before a report on rosemary derived ingredients is completed. And I thought we talked about that and decided not to do that.

DR. ANSELL: To include the ingredients but not to include the discussion, I mean the discussion would have -- I tracked that. That was the inclusion of ursolic and carnosic.

DR. BELSITO: Well, it's not clear to me that those are unique to rosemary.

DR. BRESLAWEC: No, but they're present in higher concentrations than we first though, than the rosmarinic acid.

DR. BELSITO: Well, what we had said before you came in, Halyna, was that we would add a component if it was unique to that botanical and didn't cross over to other botanical products and also was listed as an ingredient in the cosmetic dictionary.

DR. LIEBLER: I mean I raised the question in response to the memo, Halyna, about whether -- if we were going to pursue that strategy of actually doing a report on some of these terpines, then I raised initially the question of do we have data on uses and use concentrations of these that would allow us to actually do a report and not get stuck at square one. And I don't think we have the answer to that and I think there's a lot of headshaking going on. So we kind of defaulted back to okay, let's do the botanical with the or let's do this ingredient with the highly characteristic/almost unique compound rosmarinic acid and that might be a rule of thumb to use in future such situations where we have a botanical ingredient and a characteristic ingredient that can be evaluated alongside it where there's some data for it. Otherwise, we're stuck.

DR. BRESLAWEC: Okay, I just -- I'm sorry coming in late to the discussion but did you include your discussion the consideration that these particular ingredients and the amount of certain components is, what's the term that you used, Carol, is standardized?

DR. EISENMANN: Right. These ingredients are normalized to carnosic and carnosol which that's probably the question to begin with because well, why, is that's (inaudible) about carnosic acid. They're very similar to rosmarinic and I'm not sure rosmarinic is really unique to rosemary. I think it's also found in sage and some other related ingredients.

DR. LIEBLER: So would we review these in sage or would we --

DR. EISENMANN: Right, right.

DR. LIEBLER: -- review in the first plant that comes --

DR. EISENMANN: And I just don't -- what's the rationale for putting rosmarinic in this report and not carnosic acid when that's the one that being -- it's 25, 17 or 25 percent. They're normalizing their extracts to carnosic and carnosol. This is in the food chemical codex.

DR. BELSITO: Well, actually, Paul just brought up a very good point. There are no reported uses or use concentrations from rosmarinic acid which is going to make this very difficult to say safe as used if we're looking at an individual ingredient based upon the safety data. Then we're back to the pre, that limited period of time where we had no use concentration data and we're setting artificial limits based upon however the wind was blowing over our finger that day. So maybe we should just drop it from this report and say --

DR. BRESLAWEC: Yes.

DR. LIEBLER: Okay, I like that better.

DR. BELSITO: I do, too.

DR. LIEBLER: Depending on how the way the suggestion was worded, what I was getting at is please consider adding all these other compounds. And what you really meant was please consider not including rosmarinic acid.

DR. EISENMANN: Well, yes.

DR. BRESLAWEC: I think actually the request was please discuss this.

DR. EISENMANN: Right. Right, I mean because this will come up for other reports.

DR. LIEBLER: But if we ran this --

DR. EISENMANN: Should you review a component with the plants when you didn't do it for licorice. You did them separate.

DR. LIEBLER: Okay. I guess I was after licorice but anyway.

DR. SNYDER: You'll have to drink some Jagermeister.

DR. BRESLAWEC: We can give you a copy of the report to read.

DR. EISENMANN: There's two reports actually.

DR. LIEBLER: Yes, send me the gift box.

DR. BELSITO: Okay, so --

DR. LIEBLER: Without the rosmarinic acid.

DR. BELSITO: We're going to delete the wax because it's chemically dissimilar. We're delete the rosmarinic acid because there are no use concentrations and we've just made a decision we're not going to review individual ingredients with a whole plant. We're going to check whether the water extracts are solely fragrance ingredients and if they are they'll be dropped from the report in terms of what we're reviewing. However, the safety data, if any, will not be dropped.

We're going to ask -- we're going to use the pesticide heavy metal inhalation, boilerplates in the discussion. Our botanical boilerplate our concerns are caffeic acid, thujone and methyl eugenol. We're going to point out that there were repro effects but at very high doses and we're going to go for insufficient for sensitization the leaf extract at 10 percent.

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DR. MARKS: Okay. Next are the rosemary-derived ingredients, rosmarinus oficinalis. And this is the first review of these 12 ingredients -- they're GRAS.

So, Rons and Tom, I guess, let's first -- shall we look at the ingredients? Are they all okay?

DR. SHANK: Well, I have here to remove rosmarinic acid.

DR. MARKS: Yes, that's the question that counsel -- if we look at Monice's memo, in the second paragraph, the counsel asked for explanations as to why rosmarinic acid is included.

DR. SHANK: It's a component of the plant, but not of the cosmetic ingredient extracts. So I think that can be deleted.

MS. FIUME: Dr. Shank, it is a cosmetic ingredient --

DR. SHANK: Oh --

MS. FIUME: -- in and of itself.

DR. SHANK: By itself.

MS. FIUME: And it is also a component. So, in the past, corn acid, coconut acid, we have, there has been precedent for including the acid. But I do want to see what you think, if it fits into this family.

DR. MARKS: So, as you mentioned, Monice, there's also --

DR. SHANK: So, the other acids, we include with the extracts? Or the other acids were reviewed separately, that you're talking about?

MS. FIUME: Most of them were included with the extracts or the oils. Whatever that family was --

DR. SHANK: Was.

MS. FIUME: Whatever the corn report was, it did have corn acid in it.

DR. SHANK: Oh, in the extract report.

MS. FIUME: Let me check coconut acid.

DR. EISENMANN: But that acid is for the fatty acids from corn oil. That's not like -- rosmarinic acid is a -- I don't what the -- I think it's a triterpene?

DR. MARKS: Yes.

DR. EISENMANN: So, if it's a -- I think it's a little bit, it's not --

DR. SHANK: So when you say "corn acid," you mean "corn fatty acids."

DR. EISENMANN: That's what they are, yes.

DR. SHANK: Okay. That's different.

DR. MARKS: So the counsel (inaudible) -- are you going to talk about the diterpenes, or reviewing them first?

DR. BRESLAWEC: No, no, no. We simply want the panel to have this discussion.

DR. MARKS: Right.

DR. BRESLAWEC: You know, if you're going to review something like rosemary-derived ingredients, do you also include components -- rosmarinic acid, or solic acid.

DR. EISENMANN: Well, what struck me is that this is one of the rare times where the industry has come out and said "we normalize this to carnosic acid and carnosol. Well, carnosic acid is also a cosmetic ingredient, and it's very structurally similar to rosmarinic acid. So why pick rosmarinic and not carnosic? I don't know the answer.

So that's why I thought maybe you wanted to -- I mean, like for licorice, what you did there is you reviewed the components of licorice first, and then you reviewed the mixtures.

So I just thought maybe you should develop some kind of a policy on when do you include a component. I mean, it's getting to be more and more components are in the dictionary. When do you review a component, versus a mixture? It didn't come up until I saw that, you know, that carnosic acid is being used to normalize these extracts.

DR. SHANK: Okay. So, let -- rosmarinic acid itself is an ingredient.

MS. FIUME: It is an ingredient. I think --

DR. EISENMANN: So is carnosic. I mean, there are other similar compounds that are in the dictionary that could be cosmetic ingredients. I don't think there's any uses of some of them, but that's -- when you pick one and not the other, I just thought you should discuss it.

DR. HILL: Right -- if rosmarinic acid is not showing up in here as a significant constituent in any of the extracts, then it doesn't, to me, make sense to be lumping it together with these extracts. On the other hand, if carnosic acid is showing up -- which it is -- as a significant constituent, and is even being used to normalize it, then we're going to put something in here that would certainly be more sensical. But whether we want to do that or not, that seems to be a more philosophical question.

To me, if these extracts are often being standardized on that ingredient, then that ingredient should be reviewed, separately reviewed. It can go through roughly at the same time, and then you can at least reference back to that in the appropriate sports, in terms of the plant extracts.

But that's just the way I see it.

DR. MARKS: So, let's take carnosic as an example. How many different botanicals would that be found in? What would you guess? A lot?

MS. FIUME: It's hard to tell. And the problem with these botanicals is, as we go through the published information -- because, often -- now, we did get information from industry that talks specifically to carnosic acid and carnosol, but from our standpoint, we don't know if that's being standardized to that, because it's being listed as antioxidant. And is that becoming a claim information, or is that relating directly to cosmetic safety?

So that's one of the issues we have as writers, because we don't want to put claim information in the safety evaluation that needs to reflect cosmetic safety.

And as we go through these botanicals -- currently we're writing a report on citrus ingredients, and the number of constituents is incredible. It's probably about 10 pages long right now. So, if we're not getting, searching the published literature for the constituent information, it depends on where it was grown, and what time of year it was grown, how much it rained that year --

DR. HILL: Of course it does. It does.

MS. FIUME: Right. So, if we're not being given constituent information each time, on the cosmetic ingredient, it becomes very difficult for us. We start searching for a needle in the haystack in writing reports on chlorogenic acid, carnosic acid, ursolic acid. It becomes a report on constituents that may be in those botanicals, rather than the botanicals themselves.

As we go through this, we're thinking, okay, so the safety -- on many of these, because their GRAS ingredients, and they can be eaten in the ingestion isn't the concern. It's the irritation and sensitization. Is it something you look at as "Is it an irritant, is it a sensitizer, that cosmetic ingredient, as in formulation?"

So, as writers, we are also struggling with the best approach for these botanicals because of all these uncertainties.

DR. HILL: I take issue with what you just said. Just because something is GRAS, doesn't mean that that captures the toxicology if you smear it on your skin.

MS. FIUME: No, I agree.

DR. HILL: Because if you have a component that's present at relatively low levels -- I mean, our digestive tracts are engineered to respond to the -- "respond" is the wrong word, deal with the presence of some of these things.

Our skin may or may not be.

DR. SLAGA: It's one of the barriers.

DR. HILL: It's a barrier, and that's why the barrier is there. But there are some of these that can be extremely well dermally absorbed. I mean, we get poison ivy -- I mean, I can't even walk down the street from poison ivy, or I've got a problem. So that's just one example of the result of a constituent in a plant.

And what you said is exactly to the point. If somebody were going to study the toxicology of something that is fundamentally a complex mixture, we need to know, when we read across, even from things from the same plant, is that study, toxicologically relevant to the thing we're reading across to?

So, if you don't normalize to constituents of interest in terms of how much is there in the first place and, secondly, known biological effects, well, how do you base any read-across decisions?

I mean, you have to get at that issue. And I don't think it needs to be a needle in the haystack, because you're talking about things that are present at a high concentration, or are known to be sensitizers or allergens.

And that list is much shorter. That doesn't mean there couldn't come up something that we don't know, but odds are, you know, that will be found by people using something out there, and we're having a lot of incidences. And probably nobody dies from that. And so -- but we'll become aware of a new sensitizer, the more and more these botanicals get used.

But I think it's like any clinical study for a drug use of a botanical. You've got to standardize on something. One that's on my mind, for example, is echinacea. It's probable that people have been standardizing on the wrong thing or things. There's science going on, actually, at our institution that's showing that pretty nicely.

So, I mean, just because you're standardized on something doesn't mean you know what you're doing. But at least it has some -- if you capture those major things, and you capture the known bad actors, and you capture the known things that are doing something, then you can get a sense of if we study -- if we have a toxicological result on this particular extract, how relevant it is to those other things.

So, here we have a flower extract that's aqueous, that's clearly not going to be relevant to an oil extract. CO-2 extract, which we see in a couple of these is something different yet. We have to know.

You do a bit of toxicology results, is that relevant in the read-across? And how in the hell you should you get at that?

But in this particular case, if they're standardizing on that one component, I don't -- I think that suggests that there's at least thinking that that's important, and provide some way of getting some consistency with botanicals. That's probably about the best one can do until we are a little more sophisticated.

But the better mass-specs get, and the better we can do analytics that do pattern recognition, I think the better that will come.

I don't think "antioxidant" is a therapeutic claim, is it?

DR. SHANK: It could be a preservative --

DR. HILL: -- I mean, no, I don't think it is, you know.

DR. MARKS: So, let's get back to this report, and the specifics, whether or not we deal with, in this case, the botanical in a mixture as is, that we have -- you had suggested, Ron Shank, to take out -- we have some other acids. We talked about carnosic. There's also oleanolic, there's caffeic -- acids which Lillian Gill, the Director, mentioned in her memo to me. The counsel had concerns about that, and whether or not diterpene should be reviewed first.

So, I think the approach -- we have to make a decision, do we move ahead with botanicals mentioned in here, minus the acids, or do we do the acids separately? Do we do the acids first? The diterpene?

So, what -- team members, how would you like to proceed? Would you like to proceed with this as the botanical, remove the acid, and then we can save the acids for another day? Because I guess the question is, what needs -- if we remove the acid, what needs do we have for this mixture of ingredients, since that's not -- mixture of components in these rosemary ingredients?

DR. SLAGA: Well, I agree with Ron Shank. I think we should take it out, because there are other acids that are extremely important in this mixture. And all we're doing is highlighting one particular acid where there's other acids that could be more -- I'll pick out ursolic acid, just for comparison. And so, you know, we're dealing with botanical extracts. And I think we should deal with the total extract, regardless what's in them.

DR. BERGFELD: So you're really talking about only mixtures here.

DR. SLAGA: Right.

DR. MARKS: So, deal only with the extracts -- botanical extracts.

DR. SLAGA: Or we should highlight other acids, since --

DR. BERGFELD: We have oils, too, and they are considered -- extracts, and also powder?

DR. MARKS: Okay. So, remove the acid, deal only with the botanical extracts, the mixtures in this report. The acids would be in a separate report.

DR. SHANK: Just, as a --

DR. MARKS: Does that sound good to you, Ron Shank?

DR. SHANK: -- an aside, if you include specific acids, these are not GRAS ingredients necessarily. And that changes our focus.

If these are GRAS food additives, then our need for extensive systemic toxicology data -- right? -- goes away. All right? And we can focus on skin.

But now, if you add non-GRAS components, then we have to have a different data set.

So, I think it's a good idea to separate out acids which are known not to be components of the cosmetic extract.

DR. MARKS: Ron, do I understand -- they aren't "known" to be components? Of if they are, they're not enough to rise to a toxicologic level, since they're GRAS, in the mixture? Because they are components, are they not?

It's just they are --

DR. SHANK: They're components, okay. But to include a component of the plant, which is known not to be a component of the cosmetic ingredient that we're considering, toxicologically, it's easy to separate out those components which are -- plants components which are not components of the cosmetic ingredient.

DR. MARKS: So, so far, what I -- if I hear the team correctly, we will deal just with the mixtures, in this report. We'll remove rosmarinic acid. We'll deal with the acids in a separate report in the future.

And then, now the question is this -- do we need anything else from me?

The oil was okay. That's on page 18. But I wanted to see an HRIPT for leaf extract at 10 percent.

So I would issue an Insufficient Data Notice.

DR. HILL: So, what leapt out at me is, we have very little chronic toxicology on the leave oil. And it only is oral. And it only is three weeks' gavage in Swiss Albino mice. And there is no repro-tox. And in terms of possibility of getting something in by the dermal route, surely the things that are in the oil are much more likely than in these other extracts -- unless I'm missing something.

So, I wanted to see, really, repro-tox for the oil, delivered by a dermal route.

DR. MARKS: Ron Shank?

DR. HILL: Which is a big request, I realize.

DR. MARKS: Yes. Again, everything we say, at least at this stage, would be an Insufficient Data Notice.

But, Ron Shank, did you have -- I have "Question pregnancy" on page 19 of the report.

DR. SHANK: Under "human," I think we need to expand that, and know why the PDR says that rosemary preparations -- that's rather general -- shouldn't be used during pregnancy. I think that needs to be expanded, as to what they had in mind.

DR. MARKS: Monice, did you have anything more?

MS. FIUME: I'm sorry -- what? On the --

DR. SHANK: On page 19 -- no, 16, at the very bottom of the "Human" -- "Reproductive and Developmental Toxicolocy," it says "Human." And then, "According to the PDR...rosemary preparations should not be used as a drug during pregnancy." And then there's no mor information.

So I think we need to know why the PDR makes that recommendation.

DR. MARKS: That's Physician Drug Reference? PDR?

DR. SHANK: Yes.

DR. HILL: But for herbal medicines. It's not the standard PDR.

DR. MARKS: Right. Well, that's still --

DR. HILL: But it's still --

DR. MARKS: Herbal.

DR. HILL: Mm-hmm.

DR. SHANK: They had something in mind.

DR. MARKS: So that would be an "insufficient data" also, "Why is that?"

So, I think Ron Hill, it reinforces your concern about pregnancy.

DR. HILL: Well, I don't know if it does or it doesn't, I guess, in this. But I did notice that, and I didn't get a chance to consult with our in-house expert on that subject --

DR. BERGFELD: It says --

DR. HILL: -- before I came.

DR. BERGFELD: -- under "Toxicology," that in the rat model, it decreases fertility.

DR. HILL: That's there.

DR. SHANK: And there is a dose-response relationship there.

DR. BERGFELD: So, because there's no "human" on that --

DR. SHANK: Yes, that's rat data.

DR. BERGFELD: Yes.

DR. SHANK: But apparently there are human data.

DR. HILL: Something resulted in that --

DR. SHANK: Something caught to the attention of the committee that wrote that part of the PDR.

MS. FIUME: In reviewing this information -- and this is something that would be great to have guidance on from the panel -- is that the rosemary teas, or the very strong rosemary preparations, from what I found in reviewing botanical -- the folk medicine, the herbal guidelines -- is that it could be an abortifacient, and it's not recommended for pregnant women to drink rosemary teas.

Now, like I said, that is from herbal books. And that's the problem with the botanicals, it's -- you know, you have to be very careful as to what you're discerning. I took it from these two references that that's something that you would prefer not to have in the report? Because, they're looking at drinking the herbal tea, versus what you would be putting on the skin.

I'm happy to take it out. I didn't want to not put it in, and then have someone say "You haven't talked about this."

So I'd rather put it in, and then if the panel decides that they would just prefer not to have that in there because it really does not refer to the cosmetic use of the ingredient, I'd be happy with doing that.

DR. SHANK: I think you should leave it in. Good -- it's good that you put it in. I just think it needs to be expanded. And exactly what you say, is this would be at an exposure that would be not reached in cosmetic use.

DR. HILL: And I would question whether we know that for sure, because I'm looking at leave-on concentrations of 10 percent. And, again, I say there are components, especially in oils, that are probably going to get into the system better through the skin. I'm thinking of somebody smearing something all over their skin in a leave-on -- you know, large body surface area exposed, repeatedly, over some period of time. I'm not sure we're confident to say that the exposure would be less than drinking the strong tea, of whatever ingredients might be the cause of the abortifacient activity -- if, in fact, that's true.

DR. SLAGA: I guess I don't understand. Because it's an oil base, why it would be absorbed in the skin more than the intestine?

DR. HILL: Because oils diffuse through the skin. They're lipophilic, and they can reach the --

DR. SLAGA: Well, lipophilics can go through the digestive tract, too. I don't -- that's the point I'm getting at.

DR. HILL: But we have liver enzymes designed to --

DR. SLAGA: Or the respiratory tract.

DR. HILL: We have liver enzymes designed to take those things out, through millions of years, probably, of evolution in the digestive tract. Whereas I doubt that we've evolved to respond to things we might smear on at 10 percent, over a wide body surface area. And I just --

DR. SLAGA: If you look at all the portals of entry into the body, sure, they don't have the amount of enzymes you have in the liver, but they do have enzyme levels to help detoxify, just as the liver does.

DR. HILL: Of course they do, but it doesn't always get them. That's why transdermal delivery systems work. That's why we have numerous marketed products that make use of transdermal delivery, that really don't have anything magical in there to allow those things to penetrate the skin, it's just if you have enough potency.

And the bottom line is, we have first-pass effect in the gut, both microbial gut wall enzymes, liver enzymes, and even digestive enzymes, that we don't have in the skin.

DR. SLAGA: But if you look at, in the digestive tract, you would have a larger volume of things --

DR. HILL: But it all goes to --

DR. SLAGA: -- oil based, to what --

DR. HILL: -- but it all goes to the liver. So, unless you give whopping, huge doses, you don't swamp those systems.

DR. MARKS: Okay. So, let's come back a bit. I would suggest an Insufficient Data Notice. What I have right now are: Why rosemary should not be used in pregnancy, that's mentioned in the PDR Herbal. And let's try and clarify that.

We would remove rosmarinic acid, deal with only the botanical extracts, in this report. The acids would be in a separate report.

And the third thing is the HRIPT for the leaf extract at 10 percent.

DR. HILL: I have one more. Okay, that's why I wanted to summarize.

DR. MARKS: And then I also want to bring up -- so, go ahead, Ron Hill. What was the other? Is that -- team, do those three things, so far, sound good to you? Ron, Ron, and Tom -- those three things? Okay.

So, Ron Hill, what's the next thing that you --

DR. HILL: The other one was just a manufacturing question, and it goes to what things might be generated by the processes of deodorizing, which are not described. In other words, when they deodorized -- which is mentioned in at least two of these extracts -- what exactly is it that they're doing? What compounds might result, or -- if I know the process, then I can conjecture, based on what's present in the plant. But --

DR. MARKS: Interesting. Ron Shank --

DR. BRESLAWEC: I'm sorry, could you just repeat that?

DR. HILL: Yes. The question is, in the processes of preparing a couple of these abstracts -- I can give you the specific ones, but all you have to do is search on "deodorize" -- the question is, what is the chemistry involved? What are they actually doing to deodorize in those particular extracts?

And it goes to the issue are they generating any compounds of potential toxicological concern. You know, like when you whiten paper, for example, you're generated chlorinated biphenyls. And I'm not suggesting that's what happens here, but I'd like a little more information about what that process entails -- without somebody giving away what's in their patent, you know, roughly, what are they doing -- if we can get it.

DR. MARKS: So, what page is that?

DR. HILL: Probably in a couple of the tables. I can search it if you want to know.

DR. MARKS: So, Ron Shank, Tom, was this deodorizing step in the manufacturing a concern to you? Or is there enough in this section? Where is the manufacturing section? What page is that?

DR. HILL: I'm not even sure it shows up in the "manufacturing." I think it does. But it was in a couple of the tables that describe something about the processes by which these abstracts are prepared.

I'll just search "deod," and then I should be able to find that in just a second.

DR. MARKS: Do you remember --

MS. FIUME: I'm sorry, I'm in my WORD version. Let me look -- under "Preparation and extraction" --

DR. HILL: "Preparation and extraction," it shows up three times. And then --

DR. MARKS: What page is that?

DR. HILL: PDF page 10. PDF page 10.

DR. MARKS: Okay. So --

DR. HILL: It shows up again in the "Constituents/Impurities" in the -- one, two, three -- fourth paragraph down.

DR. MARKS: That's okay, let's go back to Ron Shank and Tom. Are you equally intrigued as to what does "deodorized" mean? "Deodorized, decolorized, and standardized using diluents and carriers that are permitted in foods," is the last sentence of that first paragraph under Preparation and Extraction."

DR. HILL: Table 6 is the other place, by the way, where this is mentioned a couple of times.

DR. EISENMANN: Those references to USP in the European Food Safety Authority. So it must be pretty standard methods.

DR. HILL: I'm assuming they're widely used processes. I have just -- I know nothing about it, and I'd like to know, in this particular case, if it's applied to these extracts, what sorts of things might be happening?

DR. SLAGA: I didn't have a concern with the deodorizing.

DR. MARKS: Okay. I'll just note that, then, under -- and, Ron Hill, I'll associate --

DR. HILL: That's fine. Put it out there.

DR. MARKS: -- your name. And I'll just put -- we'll find out what comes out of that. But that doesn't sound like that's a deal-breaker, as far as an Insufficient Data Notice, if we don't get that data.

DR. HILL: It's also in Table 7. I said Table 6, I also see it in Table 7 several times.

DR. MARKS: Okay. "What is 'deodorized'?"

DR. HILL: It sounds like a Jeopardy question.

DR. MARKS: Any other needs? So it's used in baby -- there's baby and inhalation exposure. Does that raise any concerns? Obviously, for inhalation, we'll just put the inhalation boilerplate, I presume.

Baby exposure? Any concerns about that? No -- other than what we've put.

So does it sound -- tomorrow, again, I'll repeat myself, our team would recommend an Insufficient Data Notice, and with the HRIPT of the leaf extract why is rosemary not recommended in pregnancy? Remove the rosmarinic acid. And then, potentially, clarify a bit on the manufacturing, what is "deodorize"?

Any other needs? Does that sound like a proper way to move forward?

DR. BERGFELD: Could I ask a question? The acid that will be deleted is mentioned all through the text.

DR. MARKS: Yes.

DR. BERGFELD: Are you taking it out, or leaving it in? Leaving it in, or taking it out?

DR. SLAGA: I would take it out.

DR. BERGFELD: And then there's mention of phototoxicity. How did you all feel about that? There were some photox testing -- the rat --

DR. SHANK: What page was that, please?

DR. HILL: I had a note that there wasn't any phototox done on the oil, but I wasn't sure, based on what's in it, that there was any need to do that. So --

DR. MARKS: Right -- which page are you, Wilma? I didn't pick out that.

DR. BERGFELD: I'm on 11, but I'm not sure how you're translating that. It has to do -- I think it's -- let me see if it's under this --

DR. SHANK: Oh, Report page 11?

DR. BERGFELD: Yes -- under the "Summary." I --

DR. MARKS: What is the PDF number? 11, for me, brings up the "steam distillation." Preparation extracts.

On the PDF, what page would that be? Let me see if I put it in --

DR. BERGFELD: It's also in the table.

DR. SHANK: It would be page 20.

MS. FIUME: 18 of the PDF. Page 18 on that is the first reference to phototoxicity (inaudible) extract.

I'm sorry -- PDF page 18.

DR. MARKS: It's the leaf -- "weak irritants," "phototoxicity" -- "None of the extracts were phototoxic." That was under was under -- that's the first study.

So I took that -- that's under 10 joules, which is a proper amount of UVA, 75 percent of the MED. So I thought that was okay. And I used that as the --

DR. BERGFELD: I saw that, too, but there was mention in the body of the document something about phototox, where it was positive -- or questionably positive.

I don't have it listed like you do.

DR. MARKS: Let me see here.

MS. FIUME: I believe it's Table 13.

DR. MARKS: And what page is that?

MS. FIUME: I'm looking.

DR. MARKS: Okay.

MS. FIUME: Is it that Adobe package you're using?

DR. MARKS: Yes.

DR. BERGFELD: Okay.

DR. MARKS: But it still should be the same page in the document. Yes, I'm using Adobe Pro, and they say --

So, which table did you say, Monice?

MS. FIUME: 13.

DR. MARKS: 13 -- so that -- let's see, where am I? Table 8 is the "Use."

DR. BERGFELD: So, you have pickled rosemary leaves. They had photo patch-testing reactions.

MS. FIUME: Page 49 of the PDF.

DR. MARKS: 49.

MS. FIUME: These are case studies.

DR. MARKS: Yes, that's --

MS. FIUME: Irritation, sensitization, and photo reactions.

DR. MARKS: Yes, I guess how I approach case studies is, if I see a cluster of a number of them, then I get really concerned. If I see one or two, it doesn't surprise me. I put much more weight on the photo-testing that was done in the body.

DR. BERGFELD: I just -- I don't know anything about the chemistry, specifically about the UV-spectra analysis of any of these. But you suspect them to have anything?

DR. MARKS: No.

DR. BERGFELD: Okay.

DR. MARKS: And it's not something that, in my mind, comes up as a phototoxic plant, in practice. So I wasn't concerned about it.

DR. BERGFELD: Okay.

DR. MARKS: From a phototoxic -- thanks.

DR. BERGFELD: It was questionable.

DR. MARKS: Thanks, Wilma. Any other comments? Okay. So we'll see, tomorrow, how the Belsito team --

So, Insufficient Data Notice. Okay. Let's see --

Safety Assessment of Rosmarinus Officinalis (Rosemary)-Derived Ingredients as Used in Cosmetics

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The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; 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 safety assessment was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer.

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ABSTRACT

*The Expert Panel assessed the safety of 10 Rosmarinus officinalis (rosemary)-derived ingredients and found [**to be added following the meeting]**. These ingredients are most frequently reported to function in cosmetics as skin conditioning agents or as fragrance ingredients. The Panel reviewed the available animal and clinical data to determine the safety of these ingredients. Because formulations may contain more than one botanical ingredient, caution was urged to avoid reaching levels of toxicity for constituents. Industry should use good manufacturing practices to limit impurities.*

INTRODUCTION

This report reviews the use and safety data of the following 10 *Rosmarinus officinalis* (rosemary)-derived ingredients as used in cosmetics:

Rosmarinus Officinalis (Rosemary) Extract
Rosmarinus Officinalis (Rosemary) Flower Extract
Rosmarinus Officinalis (Rosemary) Flower/Leaf Stem Extract
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Water
Rosmarinus Officinalis (Rosemary) Leaf
Rosmarinus Officinalis (Rosemary) Leaf Extract
Rosmarinus Officinalis (Rosemary) Leaf Oil
Rosmarinus Officinalis (Rosemary) Leaf Powder
Rosmarinus Officinalis (Rosemary) Leaf Water
Rosmarinus Officinalis (Rosemary) Water

Most of the ingredients included in this review are extracts, oils, powders, or solutions derived from a defined part of the *Rosmarinus officinalis* (rosemary) plant.

While *Rosmarinus officinalis* (rosemary)-derived ingredients are reported to have a number of functions, the most common functions in cosmetics are as a skin conditioning agent or use as a fragrance ingredient.[1] Two of the ingredients, i.e., rosmarinus officinalis (rosemary) flower extract and rosmarinus officinalis (rosemary) leaf extract, are reported to function as antioxidants. Rosmarinus officinalis (rosemary) leaf powder is reported to function only as a flavoring agent.

Normally, the CIR does not review ingredients that only function as fragrance ingredients because, as fragrances, the safety of these ingredients is evaluated by the Research Institute for Fragrance Materials (RIFM). Three of the *Rosmarinus officinallis* (rosemary)-derived ingredients, namely, rosmarinus officinalis (rosemary) flower/leaf/stem water, rosmarinus officinalis (rosemary) leaf water, and rosmarinus officinalis (rosemary) water, function only as fragrance ingredients, according to the *International Cosmetic Ingredient Dictionary and Handbook*. The CIR is in the process of confirming with the RIFM that these ingredients are fragrance ingredients; if confirmed, these ingredients will be deleted from this safety assessment.

CHEMISTRY

Definition

The definition and chemical class of each *Rosmarinus officinalis* (rosemary)-derived ingredient included in this report are provided in Table 1. The definition indicates what part(s) of the plant from which the ingredient is obtained. In some cases, the definition also gives insight as to the method of manufacture.

General Characterization

The *Rosmarinus officinalis* L. plant, from the botanical family Lamiaceae, is a scented, evergreen shrub with a very pungent odor that is native to the Mediterranean region and Portugal; the odor is sometimes defined as camphor-like.[2,3] It has a spicy, harsh, bitter, aromatic taste. Bluish labiate flowers grow on the upper green part of the branches. The oil is produced mostly in Spain, France, and Tunisia.[4]

Rosmarinus officinalis L. is generally recognized as safe (GRAS) as a spice and other natural seasoning and flavoring. (21CFR182.10) Rosemary has traditional or folk medicine uses, some with reported side effects.[2,5,6] The flowering dried twig tips, the dried leaves, the fresh leaves, the fresh aerial parts, and the flowering branches are considered to be the medicinal parts.[5]

Chemical and Physical Properties

Rosmarinus officinalis (rosemary)-derived ingredients are strongly aromatic. Chemical and physical property data are provided in Table 2.

Preparation/Extraction

Rosmarinus Officinalis (Rosemary) Leaf Extract

Food-grade rosmarinus officinalis (rosemary) extract is prepared by extraction from the leaves of *Rosmarinus officinalis*. Food-grade acetone, ethanol, hexane, or a combination of hexane and ethanol (in a two-step process) are used as extraction solvents; the extract can also be prepared from a deodorized or partially deodorized ethanol extract of rosemary.[7,8] Food-grade rosmarinus officinalis (rosemary) extract may also be extracted using supercritical carbon dioxide (CO_2). Subsequent

production steps include filtration, purification, solvent evaporation, drying, and sieving. The extract may be deodorized, decolorized, and standardized using diluents and carriers that are permitted in foods.

Supplier-provided data sheets report production of rosmarinus officinalis (rosemary) leaf extracts by supercritical fluid extraction with natural CO_2 and a small amount of ethanol as a solvent.[9-11] One supplier reported that the essential oil is removed by multistep separation.[11]

An additional method includes extraction with absolute ethanol (resulting in what has been called "an absolute") or a collection of the insoluble waxes (resulting in what has been called "a concrete").[12]

Rosmarinus Officinalis (Rosemary) Leaf Oil

Food-grade rosmarinus officinalis (rosemary) leaf oil is the volatile oil obtained by steam distillation from the fresh flowering tops or dried crushed aerial parts of *Rosmarinus officinalis* L.[13] The oil from *Rosmarinus officinalis* is also obtained by hydrodistillation of dried crushed aerial parts.[14]

One supplier reported their rosmarinus officinalis (rosemary) leaf oil is produced by supercritical fluid extraction with natural CO_2 and a small amount of ethanol.[15] This supplier adds a small amount (<4%) of sunflower oil to increase solubility when blending.

Constituents/Impurities

Rosmarinus officinalis L. is composed of an array of constituents, primarily phenolic acids, flavonoids, monoterpenes, diterpenes, diterpenoids, and triterpenes. Structures for some of the principal components according to chemical family are depicted in Figures 1-5.

A detailed list of chemical constituents by plant part is presented in Table 3, and a more focused listing of constituents of *Rosmarinus officinalis* is provided in Table 4. Table 5 provides composition data on three rosmarinus officinalis (rosemary) leaf extracts, based on certificates of analysis provided by suppliers of rosmarinus officinalis (rosemary) leaf extract; these certificates report a phenolic diterpenes content of 14 or 25%.[16-19]

According to the European Cosmetic Guideline 76/768/EEC, specific allergen compounds are subject to declaration on the label if the concentration of this substance exceeds 0.001% in leave-on and 0.01% in rinse-off products. One supplier reported, separately from the certificate of analysis, the following concentrations of allergen compounds in a rosmarinus officinalis (rosemary) leaf extract that needed to be declared: <0.1% linalool and <0.2% d-limonene.[20]

The principal antioxidative components of rosmarinus officinalis (rosemary) leaf extract are the phenolic diterpenes carnosol and carnosic acid.[8] The amount of carnosol and carnosic acid present in the extract varies with the method of extraction, with levels as low as 5-7% carnosol plus carnosic acid found in rosemary extract prepared from a partially deodorized ethanol extract of rosemary to as high as 30% carnosol plus carnosic acid in an extract prepared with supercritical carbon dioxide.[2,7]

Carnosol and carnosic acid are not the only constituents that vary with extraction method. Table 6 provides a sample of the differences in constituent profiles in rosemary leaves based on extraction method. Some of the studies summarized in this report provided information on the amount of constituents present in the test article; when this information was available, it is included.

In addition to extraction method, the actual amount of constituents present also varies according to the stage of development, variety of plant, season harvested, and origin of the leaves.[2,8,21,22] Water and light conditions also affect the amount of the constituents found in rosemary plants; for example, highly oxidized diterpenes increase in rosemary plants exposed to drought and high light stress.[23] Although it is generally accepted that the geographical region and stage of growth affects plant composition, some researchers reported that, within one country, the chemical composition of rosemary essential oil (plant parts not specified) did not vary with geographical region or harvest time.[24]

Food-grade rosmarinus officinalis (rosemary) leaf extract has acceptance criteria of not more than 3 mg/kg arsenic and 2 mg/kg lead, and not more than 8.0% loss on drying.[7] Food-grade rosemary leaf oil is to have not less than 8.0% borneol and not less than 1.5% esters, calculated as bornyl acetate.[13]

Table 7 provides toxicity and other information on some constituents of *Rosmarinus officinalis* (rosemary)-derived ingredients. Because formulations may contain more than one botanical ingredient, caution was urged to avoid reaching levels of toxicity for constituents. Industry should use good manufacturing practices to limit impurities.

USE

Cosmetic

The *Rosmarinus officinalis* (rosemary)-derived ingredients included in this safety assessment have a variety of functions in cosmetics. Most of the ingredients function as a skin conditioning agent and/or as a fragrance ingredient; rosmarinus officinalis (rosemary) leaf powder is reported to function only as a flavoring agent.[1] A listing of all the reported functions for each ingredient is provided in Table 1.

The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained from the FDA[25] and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council)[26,27] in 2013 indicate that nine of the ten ingredients included in this safety assessment are currently used in cosmetic formulations. Rosmarinus officinalis (rosemary) leaf extract has the greatest number of uses, 689, followed by rosmarinus officinalis (rosemary) leaf oil, 516. According to the results of the concentration of use survey, most cosmetic formulations contain very low concentrations of the *Rosmarinus officinalis* (rosemary)-derived ingredients, often much less than 0.1%. However, rosmarinus officinalis (rosemary) leaf extract is reported to be used at up to 10% in body and hand products and 3% in eye shadow formulations and bath soaps and detergents. Rosmarinus officinalis (rosemary) flower/leaf/stem water is the only ingredient not reported to be used.

Frequency and concentration of use data categorized by exposure and duration of use are provided in Table 8. In some cases, reports of uses were received in the VCRP, but concentration of use data are not available. For example, rosmarinus officinalis (rosemary) flower extract is reported to be used in 36 cosmetic formulations, but no use concentration data were reported. Additionally, for rosmarinus officinalis (rosemary) flower/leaf/stem extract, no reported uses were received in the VCRP, but a use concentration was provided in the industry survey; it should be presumed there is at least one use in a deodorant formulation, the category for which the concentration of use was reported

Products containing rosmarinus officinalis (rosemary)-derived ingredients may be applied to baby skin (e.g., 0.012% rosmarinus officinalis (rosemary) leaf extract in baby lotion, oils and creams), used in products that could be incidentally ingested (e.g., 0.012% rosmarinus officinalis (rosemary) leaf in lipstick formulations), or used near the eye area or mucous membranes (e.g., up to 3% rosmarinus officinalis (rosemary) leaf extract in eye shadow formulations and in bath soaps and detergents).[26] Additionally, *Rosmarinus officinalis* (rosemary)-derived ingredients are used in cosmetic sprays and powders; for example, rosmarinus officinalis (rosemary) leaf extract is used in other fragrance preparations at up to 0.5% and rosmarinus officinalis (rosemary) extract is used in face powders at up to 0.05%. These products could possibly be inhaled. In practice, 95 to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm.[28-31] 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.[28,31] Rosmarinus officinalis (rosemary) leaf extract is used in aerosol deodorants at concentrations up to 0.012%. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[28] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

All of the ingredients named in this safety assessment are listed in the European Union inventory of cosmetic ingredients.[32]

Non-Cosmetic

Rosmarinus officinalis L. is GRAS as a spice and other natural seasoning and flavoring when the intended use is for human consumption (21CFR182.10) and for animal drugs, feed, and related products (21CFR582.10). It is also GRAS as an essential oil, oleoresin (solvent-free), and natural extractive (including distillates) for human consumption (21CFR182.20) and for animal drugs, feed, and related products (21CFR582.20). Rosemary oil can be used in the formulation of denatured alcohol and rum (27CFR21.65).

In *The Official Journal of the European Union*, extracts of rosemary contain several anti-oxidant compounds, and although the European Food Safety Authority (EFSA) was not able to establish an acceptable daily intake due to insufficient toxicological data, the EFSA considered the margin of safety was high enough to conclude that dietary exposure was not a concern.[33] Extracts of rosemary are allowed in various food products at amounts of 30-1000 mg/kg, expressed as the sum of carnosol and carnosic acid.

Rosemary leaves are used as a seasoning in cooking.[34] Rosmarinus officinalis (rosemary) leaf oil is used as a condiment and flavoring agent in food; as an antioxidant in edible oils, meats, and other fat-containing foods; and as a dietary supplement. Rosemary oil is reported to have antimicrobial activities.[4]

Rosemary is reported to have use as an anti-inflammatory, antioxidant, and anti-microbial agent.[21,35-37] Rosemary has traditional or folk medicine uses, some with reported side effects.[2,5,6] Rosemary has been used as an antispasmodic in renal colic and dysmenorrhea, and it has been used for relieving respiratory disorders. The essential oil is used internally as a carminative and as an appetite stimulant; however, large amount of the oil are reported to cause gastroenteritis and nephritis. The essential oil is added to bath water as a circulation stimulant. As the oil or as an ointment, external application use is as an analgesic liniment for rheumatism. Rosemary is used as a poultice for poorly healing wounds and in the treatment of eczema. It is used in lotions to treat baldness,[14] and the leaves and branches have been used for treating headaches.[4]

TOXICOKINETICS

Penetration Enhancement

The effect of rosemary oil on the permeation of aminophylline was determined in human skin *in vivo* using attenuated total refection Fourier transform infrared (ATR-FTIR) spectroscopy.[38] Rosemary oil did enhance the permeation of aminophylline; however, the increase in permeation was less than that observed with 50% ethanol.

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Single-dose toxicity studies are summarized in Table 9. The acute toxicity of *Rosmarinus officinalis* (rosemary)-derived ingredients is not very remarkable. The dermal LD_{50} of rosmarinus officinalis (rosemary) leaf oil is > 10 ml/kg. The oral LD_{50} of rosmarinus officinalis (rosemary) leaves is >2 g/kg, of rosmarinus officinalis (rosemary) leaf extract is >8.5 g/kg, and of rosmarinus officinalis (rosemary) leaf oil is 5.5 g/kg bw.

Repeated Dose Toxicity

Repeated-dose toxicity studies are summarized in Table 10. A number of oral repeated-dose toxicity studies were performed in mice and in rats with rosmarinus officinalis (rosemary) leaves extracted in a number of solvents. Doses as high as 14.1 g/kg bw rosmarinus officinalis (rosemary) leaf extract were tested (5 days by gavage), and studies were performed for up to 3 mos (dietary). Increases in absolute and relative liver-to-body weights were observed in many of the studies, independent of the extraction method; these changes were shown to be reversible, and no other signs of toxicity were observed. Oral administration of rosmarinus officinalis (rosemary) leaf oil also affected liver weights.

Ocular Irritation

Rosemary oil is reported to be a moderate ocular irritant.[21] (Details not provided.)

Anti-Inflammatory Effects

Rosmarinus Officinalis (Rosemary) Leaf Extract

Rosmarinus officinalis (rosemary) leaf extract has been shown to inhibit formaldehyde-induced plantar edema and 12-tetradecanoylphorbol 13-acetate (TPA)-induced and arachidonic acid-induced ear edema.[39,40]

In the formaldehyde-induced plantar edema study, groups of six male Balb/C mice were given an injection of 20 µl of 3% formaldehyde into the sub-plantar region of both hind paws.[39] After 2 h, one hind paw was treated with 10 µl of 12 mg/ml of an ethanol extract of *Rosmarinus officinalis* (rosemary) leaves topically, as an injection, or both. The mice were killed after 24 h. Topical administration reduced edema by 80%, the injection reduced it by 22%, and the combined application reduced edema by 24%.

The TPA-induced ear edema study was conducted in groups of 10 male Balb/c mice.[39] The effect of pretreatment with 10-1000 µg/cm^2 of an ethanol extract of *Rosmarinus officinalis* (rosemary) leaves at 30 min prior to induction of inflammation with 25ng/cm^2 TPA was evaluated. The mice were killed after 4 h. Doses of 100, 250, 500, and 1000 µg/cm^2 of the extract resulted in a statistically significant reduction of inflammation by 38, 79, 84, and 99%, respectively.

In a TPA-induced mouse ear edema study conducted in groups of six to 10 female CD-1 mice, a single dose of 20 µl acetone, 0.5 nmol TPA, or TPA and 0.04, 0.12, or 0.36 mg of a methanol extract of *Rosmarinus officinalis* (rosemary) leaves in 20 µl acetone was applied to one ear of each mouse.[40] The mice were killed after 5 h, and rosmarinus officinalis (rosemary) leaf extract inhibited TPA-induced inflammation by 17, 75, and 92% respectively. The extract also inhibited TPA-induced erythema.

In the arachidonic acid-induced mouse ear edema study, 0.02, 0.09, or 0.45 mg of a methanol extract of *Rosmarinus officinalis* (rosemary) leaves in 20 µl acetone was applied to groups of 10 female CD-1 mice at 30 min prior to treatment with 0.3 mg arachidonic acid in 20 µl acetone. Inflammation was inhibited by 12, 28, and 54%, respectively.[40] The mice were killed after 1 h.

Effect on Epidermal Hyperplasia

The dorsal skin of three to four CD-1 mice per groups was treated with either 200 µl acetone, 1 nmol TPA, or 1 nmol TPA and 3.6 mg rosmarinus officinalis (rosemary) leaf extract in 200 µl acetone twice a day for 4 days.[40] Topical application of the extract with TPA inhibited a TPA-induced increase in the number of epidermal cell layers and epidermal thickness.

Immunologic Effects

An aq. extract of up to 2.5 mg/ml *Rosmarinus officinalis* (rosemary) leaves was found to inhibit ultraviolet (UV)-induced up-regulation of matrix metalloproteinase-1 (MMP-1) gene transcription in dermal human fibroblasts; the release of cytokines interleukin (IL)-1α and IL-6 was prevented by the extract.[41]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Non-Human

Rosmarinus Officinalis (Rosemary) Leaf Extract

Oral administration of rosmarinus officinalis (rosemary) leaf extract adversely affected fertility in male rats.[42] Groups of 10 male Sprague Dawley rats were fed a diet with 0, 250 or 500 mg/kg bw/day of an ethanol extract of *Rosmarinus officinalis* (rosemary) leaves in distilled water. After 53 days of dosing, each male rat was mated with two untreated female rats for 10 days; the female rats had been given a subcutaneous (s.c.) dose of 5.0 mg estradiol benzoate 54 h before and 0.5 mg progesterone 6 h before being placed with the males. The males were dosed during, and killed after, the 10-day mating period, and the reproductive organs were examined. The females were killed 1 wk after the mating period, and the reproductive tract of each female was examined to determine pregnancy and the number of implantation sites, viable fetuses, and fetal resorptions.

The body weights of male rats of the test groups were similar to those of controls. The absolute and relative organ to body weights of the testes, epididymides, seminal vesicles, ventral prostates, and vas deferens of the high dose animals were statistically significantly reduced compared to the controls. The sperm motility in cauda epididymides, sperm density, seminiferous tubule diameter, Leydig cell nuclear diameter, and epithelial height in epididymides and seminal vesicles were also statistically significantly reduced in the animals dosed with 500 mg/kg bw/day rosmarinus officinalis (rosemary) leaf extract. Also in the high-dose group rats, germinal cells (i.e., spermatogonia, primary and secondary spermatocytes, and spermatids) and interstitial cells (i.e., fibroblasts and immature and mature Leydig cells) were statistically significantly decreased, and degenerating cells were statistically significantly increased. Clinical chemistry parameters were also evaluated; testosterone, follicle-stimulating hormone, and luteinizing hormone levels were statistically significantly decreased in high-dose male rats. Exposure to 500 mg/kg bw rosmarinus officinalis (rosemary) leaf extract reduced fertility; the number of pregnant females was decreased in this group, there was a statistically significant decrease in the number of implantations and viable fetuses, and the total number of resorptions was statistically significantly increased. The same trends were generally found in the rats of the low-dose groups, but the changes did not reach statistical significance.

Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Extract

A group of 12 gravid female Wistar rats was dosed by gavage with 26 mg/day of a 30% aq. extract of rosmarinus officinalis (rosemary) flower/leaf/stem extract (13 mg/ml solids) on days 1-6 of gestation (preimplantation), and a group of 14 gravid rats was dosed with the extract on days 6-15 of gestation (organogenesis).[43] Negative control groups of 12 or 11 gravid rats were given saline by gavage on days 1-6 or 6-15 of gestation, respectively. All dams were killed on day 21 of gestation. No signs of maternal toxicity were observed, and maternal weight gains were similar for treated and control groups.

In the rats dosed on days 1-6 of gestation, a non-statistically significant increase in preimplantation loss was observed. No changes in post-implantation loss were seen as compared to controls, and no other reproductive parameters were affected. In the group treated on days 6-15 of gestation, a non-statistically significant increase in post-implantation loss rate (2.54%) was reported; analysis of the resorptions found that they occurred during the early post-implantation period. No other changes in reproductive parameters were observed when compared to the negative control group. Developmental effects were not observed in either group.

Human

According to the *PDR for Herbal Medicines*, rosemary preparations should not be used as a drug during pregnancy; very large quantities of the leaves reportedly can be misused as an abortifacient.[5] According to *Herbal Drugs and Phytopharmaceuticals*, toxic side effects may occur with components of the essential oil.[44]

Effects on Estrogenic Activity

Non-Human

Rosmarinus Officinalis (Rosemary) Leaf Extract

Groups of seven or eight 6-wk old ovariectomized CD-1 mice were fed a diet containing 2% of a methanol extract of *Rosmarinus officinalis* (rosemary) leaves or the basal diet.[45] After 3 wks, the animals were given an i.p. injection of 0, 45, or 100 ng/mouse estradiol or estrone in 50 µl corn oil, once daily for 3 days. Eighteen h after the last injection, the animals were killed and the uterus was removed. In the mice fed the basal diet, estradiol and estrone increased the uterine wet weight in a dose-dependent manner. Rosemary inhibited the uterine response in a statistically significant manner, with an inhibition of 35-50%.

Human

Rosmarinus Officinalis (Rosemary) Leaf Extract

In a study investigating the effects of a botanical supplement on sex steroid hormones and metabolic markers in premenopausal women, a few changes were found, however, the changes were not very remarkable.[46] A group of 15 premenopausal women were asked to take a supplement containing 100 mg *Rosmarinus officinalis* (rosemary) leaf 5:1 extract; 100 mg *Curcurma longa* (turmeric) root extract standardized to 95% curcumin; 100 mg *Cyanara scolymus* (artichoke) leaf 6:1 extract;

100 mg *Silybum marinum* (milk thistle) seed extracted standardized to 80% silybin, silichristin, silidianin, and silymarin; 100 mg *Taraxacum officinalis* (dandelion) root 4:1 extract; and 50 mg *Schidandra chinensis* (berry) 20:1 extract. Four capsules were to be taken twice a day with meals. Rice powder placebo capsules were given to a group of 15 premenopausal women using the same dosing regimen. Blood and urine samples were collected during the early-follicular and mid-luteal phases of study menstrual cycles 1 and 5.

On average, test subjects took 6.3 capsules/day, and controls took 7.1 capsules/day. Compared to the placebo group, the following changes from Cycle 1 to Cycle 5 in early-follicular phase serum hormone concentrations were statistically significant or borderline significant: decreases in serum dehydroepiandrosterone (-13.2%, p= 0.02); dehydroepiandrosterone sulfate (-14.6%, p=0.07); androstenedione (-8.6%, p=0.05); and estrone sulfate (-12.0%, p=0.08). No other statistically significant changes or trends were observed for other serum sex steroid hormones, serum metabolic markers, or urinary estrogen metabolites at either phase.

GENOTOXICITY

Genotoxicity studies are summarized in Table 11. Rosmarinus officinalis (rosemary) leaf extract was not genotoxic when tested *in vitro* in an Ames test, in a chromosomal aberration assay in human lymphocytes, or in a gene-locus mutation assay in human lymphocytes, and it was not genotoxic when tested *in vivo* in a chromosomal aberration assay or micronucleus test. Various extraction solvents were used. Rosmarinus officinalis (rosemary) leaf oil was not mutagenic *in vitro* in an Ames test. *In vivo*, however, oils that were extracted by hydrodistillation did induce statistically significant increases in chromosomal aberrations without gaps in a chromosomal aberration assay at 2000 mg/kg bw, increases in micronucleated polychromatic erythrocytes (MNPCEs) in several micronucleus tests at 1000 and 2000 mg/kg bw, and increases in DNA damage in a comet assay at ≥300 mg/kg bw; no genotoxic effects were seen in a micronucleus test at 1500 mg/kg bw/day with leaves extracted using absolute ethanol. A mixture containing 19% *Rosmarinus officinalis* (rosemary) leaves, 71.5% St. John's Wort, and 9.5% spirulina (algae) induced statistically significant increases in MNPCEs at 760 and 1520 mg/kg bw/day in a micronucleus test; in frequency of aneuploidy, percent polyploidy, and total percent aberrations with 760 and 1520 mg/kg bw/day in a chromosomal aberration assay; and in frequency of banana-shaped, swollen achrosome, and triangular head sperm abnormalities and percent total spermatozoa abnormalities at 1520 mg/kg bw/day in a spermatozoa abnormality assay. *In vitro*, rosmarinus officinalis (rosemary) leaf extract was shown to have anti-mutagenic potential. *In vivo*, in micronucleus assays, rosmarinus officinalis (rosemary) leaf extract did not decrease the number of MNPCEs induced by a genotoxic agent.

CARCINOGENICITY

Anti-Tumor Activity

Anti-tumor activity studies are summarized in Table 12. Topical application of methanol and double distilled water extracts of *Rosmarinus officinalis* (rosemary) leaves statistically significantly decreased skin tumors in mice; in these studies, 7,12-dimethylbenz[a]anthracene (DMBA) or benzo[a]pyrene (B(a)P)was used for initiation and TPA or croton oil was used for promotion. Dietary administration of rosmarinus officinalis (rosemary) leaf extract decreased the incidence of palpable mammary tumors in rats caused by DMBA.

IRRITATION AND SENSITIZATION

Skin Irritation/Sensitization

Non-Human

Rosmarinus Officinalis (Rosemary) Leaf Oil

An ointment containing 4.4% rosmarinus officinalis (rosemary) leaf oil (and other essential oils) was not irritating to rat skin.[47] The ointment was applied to the shaved skin of Lewis rats twice daily, for 14 days, at concentrations up to 40%. No gross or microscopic lesions were reported.

Rosmarinus officinalis (rosemary) leaf oil, applied undiluted to intact and abraded rabbit skin under occlusion, was moderately irritating.[48] No details were provided.

Human

Rosmarinus Officinalis (Rosemary) Leaf

The irritation potential of *Rosmarinus officinalis* (rosemary) leaves, tested undiluted with sufficient petrolatum for binding, was evaluated in a patch test in 234 patients with contact dermatitis or eczema.[49] Of the 234 subjects tested, 21 had +/- reactions, 18 had a + reaction, and 5 had a ++ reaction. No subjects had a +++ reaction.

Rosmarinus Officinalis (Rosemary) Leaf Extract

The dermal irritation potential of *Rosmarinus officinalis* (rosemary) leaves, extracted with supercritical CO_2, as a concrete (insoluble waxes) extracted in hexane, and as an absolute (soluble in hexane) and a concrete (insoluble waxes) extracted in hexane, was evaluated in epicutaneous tests.[12] Each test substance was applied undiluted in petrolatum on three sites using Finn chambers. The absolute was tested in 25 subjects, and the other two extracts were tested in 20 subjects. The super-

critical CO_2 extract of *Rosmarinus officinalis* (rosemary) leaves produced 1/20 positive reactions and the absolute produced 2/25 positive reactions; both were considered weak irritants. The concrete did not induce any irritation reactions.

A cream containing 0.2% rosmarinus officinalis (rosemary) leaf extract was not an irritant in a 24 h single insult occlusive patch test.[50] The test material was applied undiluted in 20 subjects. No reactions were observed, and the primary irritation index was 0.00.

Summary data submitted to the CIR reported that a hair spray containing 0.0013% rosmarinus officinalis (rosemary) leaf extract was not an irritant or sensitizer in a modified Draize human repeated insult patch test (HRIPT) in 102 subjects.[51] During induction, occlusive patches were applied for 24 h, and the sites were scored prior to the application of the next patch. Patches were applied three times per week for 3 wks. The material was allowed to volatilize and tested neat for 30 min prior to application. After a 2-wk non-treatment period, challenge patches were applied to a previously untreated site; the test sites were scored 24 and 72 h after application. Transient, barely perceptible to mild responses were observed in some subjects, but was not considered related to skin irritation or an allergic reaction.

A sunscreen cream containing 0.2% rosmarinus officinalis (rosemary) leaf extract was not a contact-sensitizer in a maximization study in 27 subjects.[52] During induction, an occlusive patch containing 0.1 ml of 0.25% aq. sodium lauryl sulfate (SLS) was applied to the upper out arm, volar forearm, or back of each subject for 24 h. The SLS patch was removed and an occlusive patch with 0.1 ml undiluted test material then applied for 48 or 72 h; the patch was then removed and the test site examined. A total of five SLS/test material patches were applied during induction. After a 10-day non-treatment period, an occlusive patch with 0.1 ml of a 5% aq. SLS solution was applied to a previously untreated site for 1 h; this patch was removed and an occlusive patch containing 0.1 ml undiluted test material was then applied for 48 h. The challenge site was graded 1 and 24 h after patch removal. No reactions were observed at either reading.

Rosmarinus Officinalis (Rosemary) Leaf Oil

Rosmarinus officinalis (rosemary) leaf oil, tested at a concentration of 10% in petrolatum, was not an irritant in a 48-h closed patch test (number of subjects not specified), and it was not a sensitizer in a maximization study in 25 subjects.[48] No other details were provided.

A leave-on massage oil containing 1.5% rosmarinus officinalis (rosemary) leaf oil did not induce allergic contact dermatitis in an HRIPT in 104 subjects.[53] An occlusive patch containing 50 µl of undiluted test material was applied for 48 h; the patches were then removed and a new patch applied. Nine induction patches were applied. Patches of 0.5% SLS were used as a positive control, and deionized water as a negative control. Challenge was performed 12-14 days after induction at the original test site and a previously untested site for 48 h. These sites were scored at 48 and 96 h. No reactions to the formulation containing 1.5% rosmarinus officinalis (rosemary) leaf oil were observed during induction or at challenge.

Phototoxicity

Rosmarinus Officinalis (Rosemary) Leaf Extract

The phototoxicity of rosmarinus officinalis (rosemary) leaf extract, extracted with supercritical CO_2, as a concrete extracted in hexane, and as an absolute and a concrete extracted in hexane, was evaluated as a part of the epicutaneous irritation test described above.[12] Photopatch tests were performed on two of the three test sites; one site was irradiated with 10 J/cm^2 UVA and the second site with 75% of the minimal erythema dose of UVB. The test sites were scored after 48 and 72 h, and were compared to the non-irradiated site. None of the extracts were phototoxic.

Case Reports

Several cases of allergic reactions to *Rosmarinus officinalis* (rosemary) have been reported, and are summarized in Table 13.[54-62] In some of the studies, follow-up patch testing included photopatch tests; generally, reactions were stronger in the photopatch tests, compared to standard testing.[58,59] Some of the follow-up patch testing included carnosol; testing with carnosol resulted in positive reactions.[55,59]

SUMMARY

This report addresses the safety of 10 *Rosmarinus officinalis* (rosemary)-derived ingredients as used in cosmetics. Most of the ingredients included in this review are extracts, oils, powders, or solutions derived from a defined part of the *Rosmarinus officinalis* (rosemary) plant. The *Rosmarinus officinalis* (rosemary)-derived ingredients are reported to have a number of functions, and the most common functions in cosmetics are as a skin conditioning agent or as a fragrance ingredient. According to VCRP data obtained from the FDA, rosmarinus officinalis (rosemary) leaf extract has the most uses, 689, followed by rosmarinus officinalis (rosemary) leaf oil, which has 516 uses. Most of the reported use concentrations for *Rosmarinus officinalis* (rosemary)-derived ingredients are well below 0.1%. However, rosmarinus officinalis (rosemary) leaf extract has higher concentrations of use reported, specifically, use at up to 10% in body and hand products and 3% in eye shadow formulations and bath soaps and detergents. Rosmarinus officinalis (rosemary) flower/leaf/stem water is the only ingredient not reported to be used.

Rosmarinus officinalis (rosemary) extract is prepared by extraction from the leaves of *Rosmarinus officinalis* with acetone, ethanol, hexane, a combination of hexane and ethanol (in a two-step process), or supercritical CO_2; it can also be prepared from a deodorized or partially deodorized ethanol extract of rosemary. Additional methods include extraction with absolute ethanol (resulting in an absolute) or a collection of the insoluble waxes (resulting in a concrete).

Rosmarinus officinalis L. is composed of an array of constituents, primarily phenolic acids, flavonoids, monoterpenes, diterpenes, diterpenoids, and triterpenes. The principal antioxidative components of rosmarinus officinalis (rosemary) leaf extract are the phenolic diterpenes carnosol and carnosic acid. The actual amount of constituents present varies according to the stage of development, variety of plant, season harvested, origin of the leaves, and extraction method.

Rosemary oil increased the permeation of aminophylline through human skin, but the increase was not as great as that seen with 50% ethanol.

The acute toxicity of *Rosmarinus officinalis* (rosemary)-derived ingredients is not very remarkable. The dermal LD_{50} of rosmarinus officinalis (rosemary) leaf oil is > 10 ml/kg. The oral LD_{50} of rosmarinus officinalis (rosemary) leaves is >2 g/kg, of rosmarinus officinalis (rosemary) leaf extract is >8.5 g/kg, and of rosmarinus officinalis (rosemary) leaf oil is 5.5 g/kg bw.

A number of oral repeated-dose toxicity studies were performed in mice and in rats with *Rosmarinus officinalis* (rosemary) leaves extracted in a various solvents. Doses as high as 14.1 g/kg bw rosmarinus officinalis (rosemary) leaf extract were tested (5 days by gavage), and studies were performed for up to 3 mos (dietary). Increases in absolute and relative liver-to-body weights were observed in many of the studies, independent of the extraction method; these changes were shown to be reversible, and no other signs of toxicity were observed. Oral administration of rosmarinus officinalis (rosemary) leaf oil also affected liver weights.

Rosmarinus officinalis (rosemary) leaf extract has been shown to have anti-inflammatory activity. Rosmarinus officinalis (rosemary) leaf extract inhibited a TPA-induced increase in the number of epidermal cell layers and epidermal thickness in mouse skin.

According to the *PDR for Herbal Medicines*, rosemary preparations should not be used as a drug during pregnancy. Dietary administration of an ethanol extract of *Rosmarinus officinalis* (rosemary) leaves adversely affected fertility in male rats. The absolute and relative organ to body weights of the testes, epididymides, seminal vesicles, ventral prostates, and vas deferens of rats dosed with 500 mg/kg bw/day of the extract were statistically significantly decreased compared to the vehicle controls. Also at that dose level, a reduction in fertility was observed; the number of pregnant females was decreased, there was a statistically significant decrease in the number of implantations and in viable fetuses, and the total number of resorptions was statistically significantly increased. The same trends were generally found in the rats of the low-dose groups, but the changes did not reach statistical significance. In a study in which gravid female Wistar rats was dosed by gavage with 26 mg/day of a 30% aq. extract of rosmarinus officinalis (rosemary) flower/leaf/stem extract during preimplantation or during organogenesis, no statistically significant changes were observed.

In a dietary study in ovariectomized CD-1 mice, 2% of a methanol extract of *Rosmarinus officinalis* (rosemary) leaves inhibited the uterine response in a statistically significant manner.

In a clinical study investigating the effects on sex steroid hormones and metabolic markers of a botanical supplement containing 100 mg *Rosmarinus officinalis* (rosemary) leaf 5:1 extract (and other botanical ingredients) in premenopausal women, a few changes were found. Overall, the changes were not remarkable.

Rosmarinus officinalis (rosemary) leaf extract was not genotoxic when tested *in vitro* in an Ames test, in a chromosomal aberration assay in human lymphocytes, or in a gene-locus mutation assay in human lymphocytes, and it was not genotoxic when tested *in vivo* in a chromosomal aberration assay or micronucleus test. Various extraction solvents were used. Rosmarinus officinalis (rosemary) leaf oil was not mutagenic *in vitro* in an Ames test. However, *in vivo*, oils that were extracted by hydrodistillation did induce statistically significant increases in chromosomal aberrations without gaps in a chromosomal aberration assay at 2000 mg/kg bw, increases in MNPCEs in several micronucleus tests at 1000 and 2000 mg/kg bw, and increases in DNA damage in a comet assay at ≥300 mg/kg bw; no genotoxic effects were seen in a micronucleus test at 1500 mg/kg bw/day with an oil that was extracted using absolute ethanol. A mixture containing 19% rosmarinus officinalis (rosemary) leaves, 71.5% St. John's Wort, and 9.5% spirulina (algae) induced statistically significant increases in MNPCEs at 760 and 1520 mg/kg bw/day in a micronucleus test; in frequency of aneuploidy, percent polyploidy, and total percent aberrations with 760 and 1520 mg/kg bw/day in a chromosomal aberration assay; and in frequency of banana-shaped, swollen achrosome, and triangular head sperm abnormalities and percent total spermatozoa abnormalities at 1520 mg/kg bw/day in a spermatozoa abnormality assay. *In vitro*, rosmarinus officinalis (rosemary) leaf extract was shown to have anti-mutagenic potential. *In vivo* in micronucleus assays, rosmarinus officinalis (rosemary) leaf extract did not decrease the number of MNPCEs induced by a genotoxic agent.

Topical application of methanol and double distilled water extracts of rosmarinus officinalis (rosemary) leaves statistically significantly decreased skin tumors in mice; in these studies, DMBA or benzo[a]pyrene was used for initiation and TPA or

croton oil was used for promotion. Dietary administration of rosmarinus officinalis (rosemary) leaf extract decreased the incidence of palpable mammary tumors in rats caused by DMBA.

An ointment containing 4.4% rosmarinus officinalis (rosemary) leaf oil (and other essential oils), applied at concentrations up to 40%, was not irritating to rat skin. However, in a rabbit study, occlusive application to intact and abraded skin produced moderate irritation.

In clinical testing, rosmarinus officinalis (rosemary) leaves produced irritation (scores of +/-, +, or ++) in 44/234 patients with contact dermatitis or eczema. A supercritical extract and the absolute of *Rosmarinus officinalis* (rosemary) leaves were considered weak irritants in a small study with test populations of 20-25 subjects; the extracts were not phototoxic. Formulations containing up to 0.2% rosmarinus officinalis (rosemary) leaf extract were not irritants or sensitizers. Rosmarinus officinalis (rosemary) leaf oil, 10% in petrolatum, was not an irritant in a 48-h closed patch test, or a sensitizer in a maximization study; a formulation containing 1.5% rosmarinus officinalis (rosemary) leaf oil was not an irritant or a sensitizer in an HRIPT.

Several cases of allergic reactions to *Rosmarinus officinalis* (rosemary) have been reported. In some of the studies, follow-up patch testing included photopatch tests; generally, reactions were stronger in the photopatch tests, compared to standard testing. Some also evaluated the effect of carnosol; testing with carnosol resulted in positive reactions.

DRAFT DISCUSSION

The discussion for the report will be developed at the meeting. Some of the following discussion items might be included. Additional discussion points may be added; some that are included below may be deleted or changed.

Upon initial review of the safety assessment of *Rosmarinus officinalis* (rosemary)-derived ingredients, the Panel issued an Insufficient Data Announcement requesting the following:

1. Dermal sensitization data for 10% rosmarinus officinalis (rosemary) leaf extract (i.e., a human repeated-insult patch test in a sufficient number of subjects at concentration of use);
2. Chemical characterization of the flower, if available;
3. Additional information on the deodorizing process performed during preparation of some of the ingredients, including information on what by-products may form; and
4. Information as to why the *PDR of Herbal Medicines* states that rosemary preparations should not be used during pregnancy.

The majority of these data were not received. **[The Panel response to not receiving dermal sensitization data on the leaf extract at concentration of use will be developed at the meeting.]**

Rosmarinus officinalis is GRAS as a spice and other natural seasoning and flavoring. The plant itself is well-defined in the published literature, but the chemical characterization of the individual components of the plant was not as well-defined. The Panel considered this, and concluded that the information on the plant was sufficient in determining the safety of all the ingredients, noting that cosmetic use of these ingredients would have oral exposures well below food exposure.

The Panel did note that because botanical ingredients, derived from natural plant sources, are complex mixtures, there is concern that multiple botanical ingredients may each contribute to the final concentration of a single constituent. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse effects. Specific examples of constituents that could possibly induce sensitization or adverse effects are caffeic acid, thujone, and terpenes, especially linalool, linolyl acetate, limonene, and methyleugenol.

The Expert Panel expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

At high concentrations, there is the potential for *Rosmarinus officinalis* (rosemary)-derived ingredients to cause irritation. The Panel specified that products containing these ingredients must be formulated to be non-irritating.

According to the *PDR for Herbal Medicines*, rosemary preparations should not be used as a drug during pregnancy, and mixed results were obtained in reproductive and development toxicity studies in rats. The Panel discussed these facts, stating that effects were observed only at exposure concentrations well above those used in cosmetic products, and therefore reproductive and developmental toxicity is not a concern with cosmetic use of *Rosmarinus officinalis* (rosemary)-derived ingredients.

Finally, the Panel discussed the issue of incidental inhalation exposure to *Rosmarinus officinalis* (rosemary)-derived ingredients. The Panel stated that although there were no inhalation data available, the *Rosmarinus officinalis* (rosemary)-derived ingredients are used at very low concentrations in products that could incidentally be inhaled, e.g., rosmarinus officinalis (rosemary) leaf extract is used in other fragrance preparations at up to 0.5% and rosmarinus officinalis (rosemary) extract is

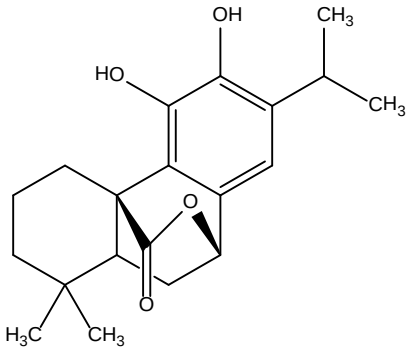
used in face powders at up to 0.05%. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the 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

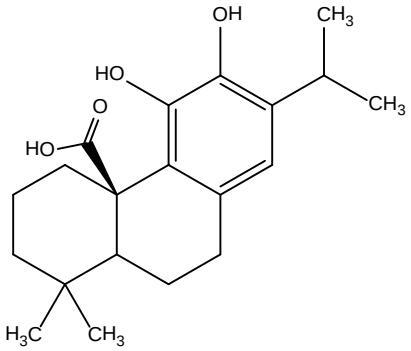
To be determined.

FIGURES

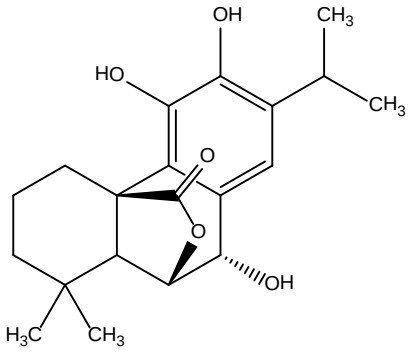
Figure 1. Principal diterpenes



1a. Carnosol

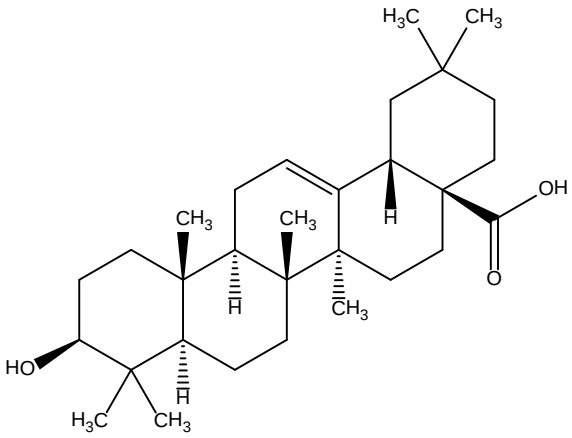


1b. Carnosic acid

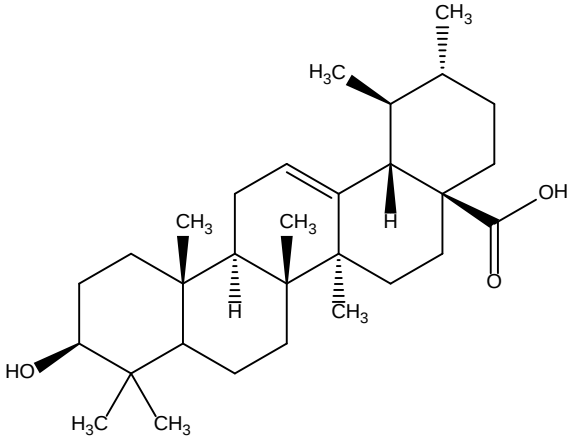


1c. Rosmanol

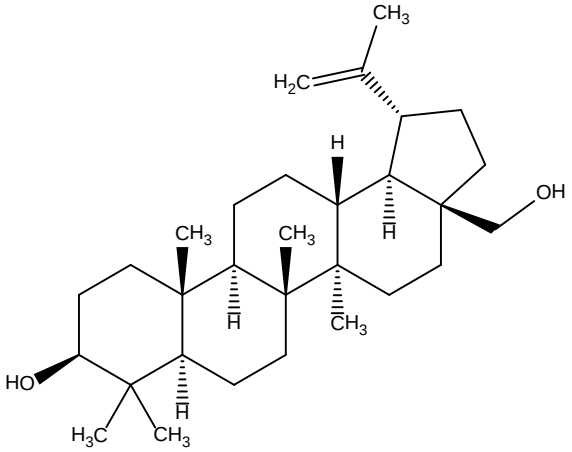
Figure 2. Principal triterpenes



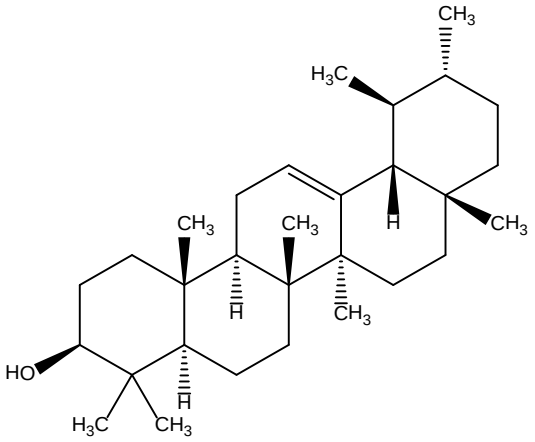
2a. Oleanolic acid



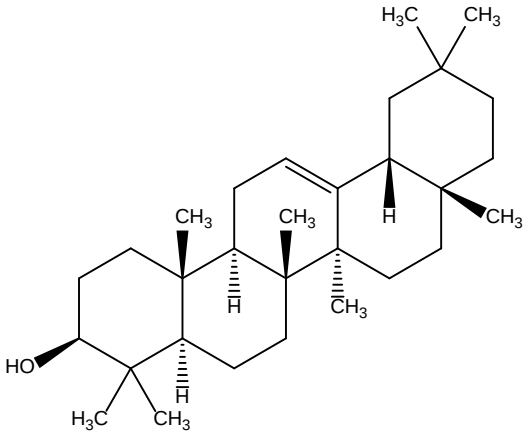
2b. Ursolic acid



2c. Betulin

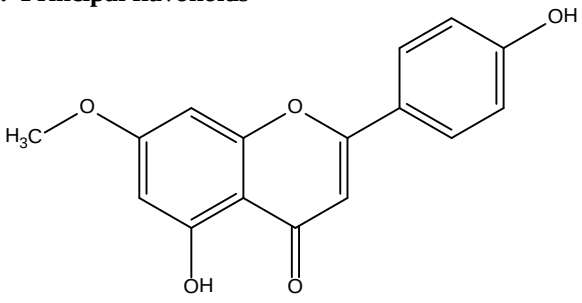


2d. α-Amyrin

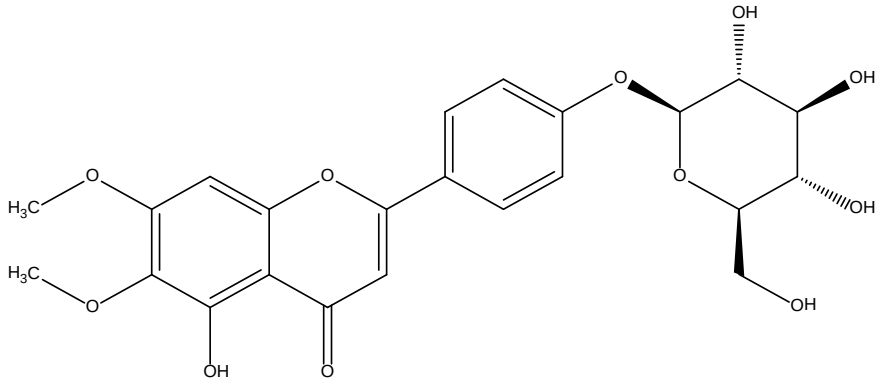


2e. β-Amyrin

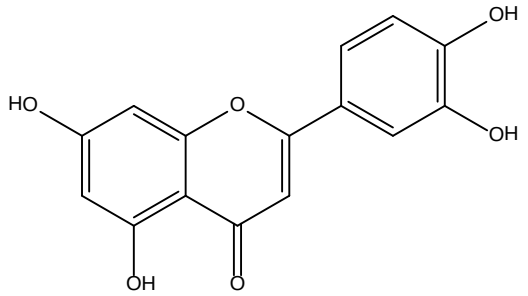
Figure 3. Principal flavonoids



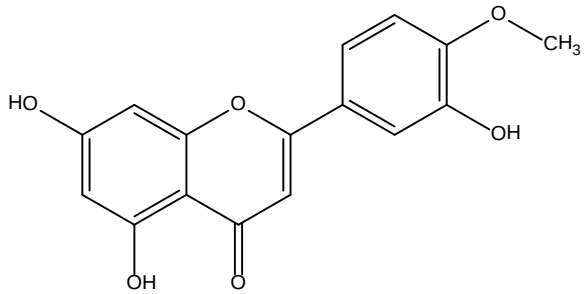
3a. Genkwanin



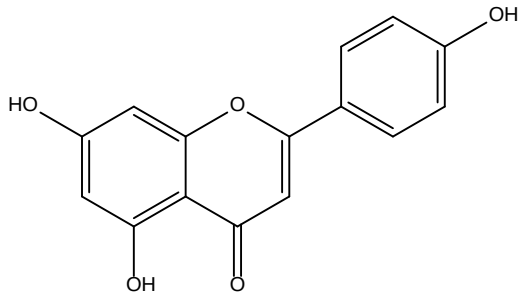
3b. Cirsimarin



3c. Luteolin

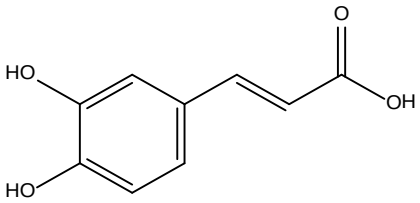


3d. Diosmetin

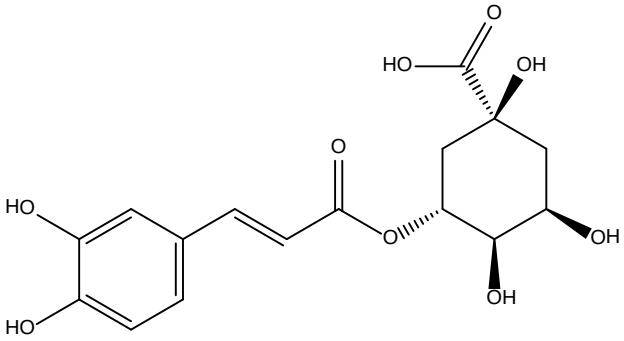


3e. Apigenin

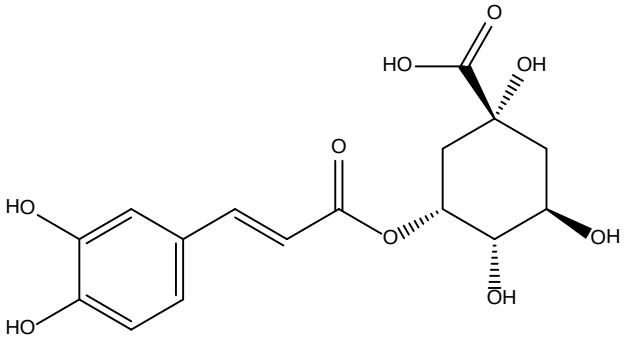
Figure 4. Phenolic acids



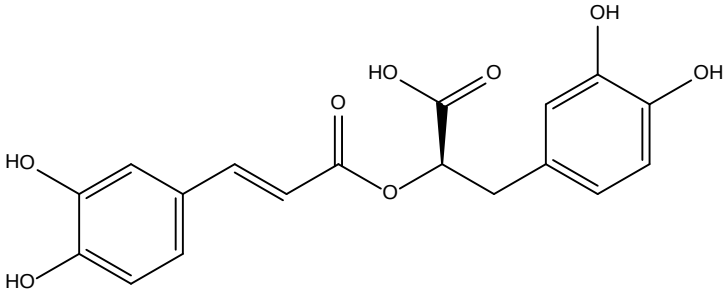
4a. Caffeic acid



4b. Chlorogenic acid

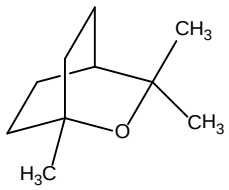


4c. Neochlorogenic acid

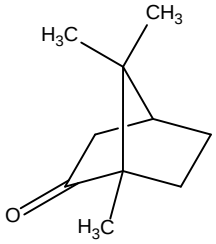


4d. Labiatic acid

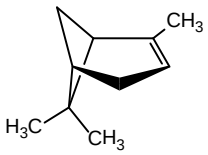
Figure 5. Principal Volatiles



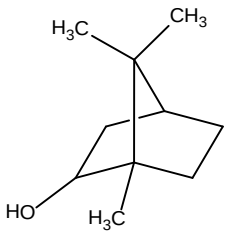
5a. 1,8-Cineole



5b. Camphor



5c. α-Pinene



5d. Borneol

TABLES

Table 1. Definitions and reported functions

Ingredient (CAS No.)	Definition[1]	Reported Function(s)[1]
Rosmarinus Officinalis (Rosemary) Extract (84604-14-8)	the extract of the whole plant *Rosmarinus officinalis*	skin-conditioning agent – misc
Rosmarinus Officinalis (Rosemary) Flower Extract	the extract of the flowers of *Rosmarinus officinalis*	antioxidant; deodorant agents; skin-conditioning agents – misc
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Extract	the extract of the flowers, leaves and stems of *Rosmarinus officinalis*	fragrance ingredients; skin-conditioning agents - misc
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Water	the aqueous solution of the steam distillates obtained from the flowers, leaves and stems of *Rosmarinus officinalis*	fragrance ingredient
Rosmarinus Officinalis (Rosemary) Leaf	the leaf of *Rosmarinus officinalis*	skin-conditioning agents – misc
Rosmarinus Officinalis (Rosemary) Leaf Extract (84604-14-8)	the extract of the leaves of *Rosmarinus officinalis*	antimicrobial agents; antioxidant; fragrance ingredients; skin-conditioning agents - miscellaneous; skin-conditioning agents – occlusive
Rosmarinus Officinalis (Rosemary) Leaf Oil (8000-25-7)	the essential oil obtained from the flowering tops and leaves of *Rosmarinus officinalis*	fragrance ingredients; skin-conditioning agents – misc
Rosmarinus Officinalis (Rosemary) Leaf Powder	the powder derived from the dried, ground leaves of *Rosmarinus officinalis*	flavoring agents
Rosmarinus Officinalis (Rosemary) Leaf Water	an aqueous solution of the steam distillate obtained from the leaves of *Rosmarinus officinalis*	fragrance ingredient
Rosmarinus Officinalis (Rosemary) Water	an aqueous solution of the steam distillate obtained from *Rosmarinus officinalis*	fragrance ingredient

Table 2. Chemical and physical properties

Property	Description	Reference
	Rosmarinus Officinalis (Rosemary) Leaf	
odor	strongly aromatic	35
	Rosmarinus Officinalis (Rosemary) Leaf Extract	
physical state and appearance	powder or liquid	7
	colorless, volatile oil	8
	dark brown viscous liquid with a characteristic smell and taste (as the extract (and) Helianthus Annuus Seed Oil)	9,10
solubility	insoluble in water	7
refractive index	1.4710 - 1.4740	17
density	0.9165 - 0.9220	17
	Rosmarinus Officinalis (Rosemary) Leaf Oil	
physical state and appearance	colorless or pale yellow liquid with characteristic odor and a warm, camphoraceous taste	13,34
	colorless, pale yellow, or pale green liquid with a camphorous odor	63
solubility	almost insoluble in water	34
	soluble in most vegetable oils; insoluble in alcohol and in propylene glycol	13
density (d^{25}_{25})	0.894-0.912	34
	0.907-0.920	63
index of refraction (n_D^{20})	1.464-1.476	34
	Rosmarinus Officinalis (Rosemary) Leaf Powder	
physical state and appearance	greyish-green to yellowish-green powder	35

Table 3. Chemical constituents by plant part (ppm) [64]

Constituent*	Plant	Leaf	Flower	Shoot	Resin, Exudate, Sap	Essential Oil	Tissue Culture
carbohydrates	640,600-704,660	-	-	-	-	-	-
fiber	165,420-206,338	-	-	-	-	-	-
fat	134,020-187,418	-	-	-	-	-	-
water	77,900-108,300	-	-	-	-	-	-
ash	61,900-75,570	-	-	-	-	-	-
protein	40,700-62,568	-	-	-	-	-	-
ursolic acid	28,000-41,000	-	-	20	-	-	-
rosmarinic acid	25,000	3500	-	13,500	-	-	38,957
EO	3300-25,000	-	-	-	-	-	-
calcium	10,919-16,150	-	-	-	-	-	-
potassium	8842-11,284	-	-	-	-	-	-
oleanolic acid	10,500	-	-	20	-	-	-
carnosol	-	530-9803					
cineole	168-9728	-	-	-	-	-	-
1,8-cineole	8125	-	-	-	-	-	-
camphor	60-5800	-	-	-	-	-	-
myrcene	25-5605	-	-	-	-	-	-
bornyl acetate	5054	-	-	-	-	-	-
α –pinene	235-4750	-	-	-	-	-	-
borneol	12-4237	-	-	-	-	-	-
magnesium	2142-2483	-	-	-	-	-	-
rosmaric acid	3000-3500	-	-	-	-	-	-
camphene	23-2350	-	-	-	-	-	-
β-caryophyllene	12-2075	-	-	70-2075			
toluene	436-2071	-	-	-	-	-	-
limonene	1950	-	-	-	-	-	-
α –terpineol	24-1555	-	-	-	-	-	-
β-pinene	17-1425	-	-	-	-	-	-
phosphorus	490-1000	-	-	-	-	-	-
p-cymene	25-950	-	-	-	-	-	-
carvone	16-760	-	-	-	-	-	-
α-humulene	-	-	-	725			
salicylates	-	70-680	-	-	-	-	-
ascorbic acid	612-673	-	-	-	-	-	-
α-amorphene	70-665	-	-	-	-	-	-
γ-muurolene	70-665	1	-	-	-	-	-
phytosterols	580-640	-	-	-	-	-	-
sodium	462-592	-	-	-	-	-	-
linalool	585	-	-	-	-	-	-
α –terpinene	4-555	-	-	-	-	-	-
terpinen-4-ol	4-521	-	-	-	-	-	-
α –thujene	1-475	-	-	-	-	-	-
δ-terpineol	7-418	-	-	-	-	-	-
iron	220-400	-	-	-	-	-	-
α –thujone	84-399	-	-	-	-	-	-
(E)-β-ocimene	-	-	-	380			
verbenone	10-375	-	-	-	-	-	-
geraniol	50-370	-	-	-	-	-	-
3-hexanone	74-351	-	-	-	-	-	-
terpinolene	12-350	-	-	-	-	-	-
caryophyllene	16-340	-	-	-	-	-	-
δ-3-carene	330	-	-	-	-	-	-
fenchone	250	-	-	-	-	-	-
β-thujone	11-209	-	-	-	-	-	-
β-elemene	-	-	-	3-200			
sabinene	190	-	-	-	-	-	-
mesityl alcohol	40-190	-	-	-	-	-	-
linalool acetate	32-152	-	-	-	-	-	-
α –phellandrene	133	-	-	-	-	-	-
α- fenchyl alcohol	28-133	-	-	-	-	-	-
p-menth-3-en-1-ol	28-133	-	-	-	-	-	-
3,5,5-trimethylhexan-1-ol	28-133	-	-	-	-	-	-
trans-ocimene	4-130	-	-	-	-	-	-
cis-pinan-3-one	-	17-110	-	-	-	-	-
4-terpinenyl-acetate	-	12-110	-	-	-	-	-
safrole	32-95	-	-	-	-	-	-
cis-β-terpineol	20-95	-	-	-	-	-	-

Table 3. Chemical constituents by plant part (ppm) [64]

Constituent*	Plant	Leaf	Flower	Shoot	Resin, Exudate, Sap	Essential Oil	Tissue Culture
α- fenchyl acetate	20-95	-	-	-	-	-	-
longifolene	20-95	-	-	-	-	-	-
isoborneol	7-95	-	-	-	-	-	-
rosmanol	-	92	-	-	-	-	-
(+)-limonene	16-76	-	-	-	-	-	-
δ-cadinene	75	-	-	-	-	-	-
caryophyllene oxide	75	-	-	-	-	-	-
(Z)-β-ocimene	-	-	-	75	-	-	-
trans-pinocarveol	-	32-42	-	-	-	-	-
3-octanone	20-40	-	-	-	-	-	-
boron	22-39	-	-	-	-	-	-
zinc	30-38	-	-	-	-	-	-
AR-curcumene	8-38	-	-	-	-	-	-
methyl heptenone	8-38	-	-	-	-	-	-
myrtenol	8-38	-	-	-	-	-	-
lavandulol	7-34	-	-	-	-	-	-
trans-β-terpineol	7-34	-	-	-	-	-	-
trans-myrtenol	-	32	-	-	-	-	-
benzyl alcohol	7-32	-	-	-	-	-	-
elemol	7-32	-	-	-	-	-	-
γ-eudesmol	7-32	-	-	-	-	-	-
rosmadial	-	30	-	-	-	-	-
α-amyrenone	-	-	-	30	-	-	-
β-amyrenone	-	-	-	30	-	-	-
epirosmanol	-	26	-	-	-	-	-
β-carotene	19-21	-	-	-	-	-	-
rofficerone	-	-	-	20	-	-	-
trans-sabinene hydrate	19	-	-	-	-	-	-
manganese	18-19	-	-	-	-	-	-
cis-α-bisabolene	4-19	-	-	-	-	-	-
isopinocarveol	4-19	-	-	-	-	-	-
isopulegol	4-19	-	-	-	-	-	-
3-octanol	4-19	-	-	-	-	-	-
dimethyl styrene	1-19	-	-	-	-	-	-
7-methoxy-rosmanol	-	-	-	18			
isorosmanol	-	-	17	-	-	-	-
cis-myrtenol	-	11-17	-	-	-	-	-
cisimaritrin	-	-	-	16	-	-	-
α-amyrin	NS	-	-	13	-	-	-
β-amyrin	NS	-	-	13	-	-	-
botulin	-	-	-	12.1	-	-	-
α –muurolene	NS	2-12	-	-	-	-	-
3-o-acetyloleanolic acid	-	-	-	11	-	-	-
3-o-acetylursolic acid	-	-	-	11	-	-	-
niacin	10-11	-	-	-	-	-	-
peperitenone	-	4-8	-	-	-	-	-
eugenol methyl ether	-	5-7	-	-	-	-	-
copper	5-6	-	-	-	-	-	-
thiamin	5-6	-	-	-	-	-	-
carvacrol	NS	5-6	-	-	-	-	-
α -terpinenyl acetate	-	5-6	-	-	-	-	-
allo-aromadendrene	-	4-5	-	-	-	-	-
neo-thujol	-	1.5-5	-	-	-	-	-
calamenene	1-5	-	-	-	-	-	-
trans-carveol	1-5	-	-	-	-	-	-
p-cymen-8-ol	1-5	-	-	-	-	-	-
nopol	1-5	-	-	-	-	-	-
γ-candinene	NS	1-5	-	-	-	-	-
α-copaene	-	2-4	-	-	NS	-	-
epi- α -bisabolol	-	3	-	-	-	-	-
sabinyl acetate	-	1.5	-	-	-	-	-
β-gurjunene	-	0.5	-	-	-	-	-
cis-sabinene hydrate	NS	0.4	-	-	-	-	-
β-phellandrene	trace	-	-	-	-	-	-
tricyclene	trace	-	-	-	-	-	-
α-fenchol	-	trace	-	-	-	-	-
p-menth-cis-en-1-ol	-	trace	-	-	-	-	-

Table 3. Chemical constituents by plant part (ppm) [64]

Constituent*	Plant	Leaf	Flower	Shoot	Resin, Exudate, Sap	Essential Oil	Tissue Culture
p-menth-trans-en-1-ol	-	trace	-	-	-	-	-
trans-anethole	NS	-	-	-	-	-	-
apigen-7-glucoside	NS	-	-	-	-	-	-
betulin	NS	-	-	-	-	-	-
bornylene	NS	-	-	-	-	-	-
cadalene	NS	-	-	-	-	-	-
caffeic acid	NS	-	-	-	-	-	-
calacorene	NS	-	-	-	-	-	-
carnosic acid	NS	-	-	-	-	-	-
chlorogenic acid	NS	-	-	-	-	-	-
cirsilion	NS	-	-	-	-	-	-
cubenene	NS	-	-	-	-	-	-
diosmetin	NS	-	-	-	-	-	-
epi- α -amyrin	NS	-	-	-	-	-	-
eriodictiol	NS	-	-	-	-	-	-
ethanol	NS	-	-	-	-	-	-
α-fenchene	NS	-	-	-	-	-	-
β-fenchene	NS	-	-	-	-	-	-
genkwanin-4'-methyl ether	NS	-	-	-	-	-	-
glycolic acid	NS	-	-	-	-	-	-
genkwanin	NS	-	-	-	-	-	-
hesperidin	NS	-	-	-	-	-	-
hispidulin	NS	-	-	-	-	-	-
hispiduloside	NS	-	-	-	-	-	-
humulene epoxide I	NS	-	-	-	-	-	-
humulene epoxide II	NS	-	-	-	-	-	-
5-hydroxy-4',7-dimethoxyflavone	NS	-	-	-	-	-	-
hydroxybenzoic acid-4- β -D-glucoside	NS	-	-	-	-	-	-
4-hydroxybenzoyl glucoside	NS	-	-	-	-	-	-
α-hydroxyhydrocaffeic acid	NS	-	-	-	-	-	-
2- β -hydroxyoleanolic acid	NS	-	-	-	-	-	-
3-β-hydroxyurea-12,20(30)-dien-17-on acid	NS	-	-	-	-	-	-
19- α -hydroxyursolic acid	NS	-	-	-	-	-	-
isobornyl acetate	NS	-	-	-	-	-	-
isobutyl acetate	NS	-	-	-	-	-	-
isorosmaricine	NS	-	-	-	-	-	-
labiatic acid	NS	-	-	-	-	-	-
ledene	NS	-	-	-	-	-	-
luteolin	NS	NS	-	-	-	-	-
luteolin-7-glucoside	NS	-	-	-	-	-	-
6-methoxy-genkwanin	NS	-	-	-	-	-	-
6-methoxy-luteolin	NS	-	-	-	-	-	-
6-methoxy-luteolin-7-glucoside	NS	-	-	-	-	-	-
6-methoxyluteolin-7-methyl ether	NS	-	-	-	-	-	-
methyl ether	NS	-	-	-	-	-	-
methyl eugenol	NS	-	-	-	-	-	-
N-methyl rosmaricine	NS	-	-	-	-	-	-
neo-chlorogenic acid	NS	-	-	-	-	-	-
nepetin	NS	-	-	-	-	-	-
nepetrin	NS	-	-	-	-	-	-
1-octen-3-ol	NS	-	-	-	-	-	-
picrosalvin	NS	-	-	-	-	-	-
rosmadiol	NS	-	-	-	-	-	-
rosmaricine	NS	-	-	-	-	-	-
rosmaridiphenol	NS	-	-	-	-	-	-
rosmarinol	NS	-	-	-	-	-	-
rosmariquinone	NS	-	-	-	-	-	-
salvigenin	NS	-	-	-	-	-	-
santene	NS	-	-	-	-	-	-
salicylic-acid-2-β-D-glucoside	NS	-	-	-	-	-	-
α –selinene	NS	-	-	-	-	-	-
sinensetin	NS	-	-	-	-	-	-
β-sitosterol	NS	-	-	-	-	-	-

Table 3. Chemical constituents by plant part (ppm) [64]

Constituent*	Plant	Leaf	Flower	Shoot	Resin, Exudate, Sap	Essential Oil	Tissue Culture
squalene	NS	-	-	-	-	-	-
syringic-acid-4-β-D-glucoside	NS	-	-	-	-	-	-
tannin	NS	-	-	-	-	-	-
thymol	NS	-	-	-	-	-	-
trimethylalkane	NS	-	-	-	-	-	-
o-o-N-trimethylrosmaricine	NS	-	-	-	-	-	-
vanillic-acid-4-β-D-glucoside	NS	-	-	-	-	-	-
verbenol	NS	-	-	-	-	-	-
betulinic acid	-	NS	-	-	-	-	-
δ-4-carene	-	NS	-	-	-	-	-
diosmin	-	NS	-	-	-	-	-
7-ethoxy-rosmanol	-	NS	-	-	-	-	-
luteolin-3'-o-(3"-o-acetyl)- β -D-glucuronide	-	NS	-	-	-	-	-
luteolin-3'-o-(4"-o-acetyl)- β -D-glucuronide	-	NS	-	-	-	-	-
luteolin-3'-o- β -D-glucuronide	-	NS	-	-	-	-	-
monomethyl alkane	-	NS	-	-	-	-	-
pristane	-	NS	-	-	-	-	-
protocatechuic-acid-4-β-D-glucoside	-	NS	-	-	-	-	-
pectin	-	-	-	NS	-	-	-
acetic acid	-	-	-	-	NS	-	-
butan-2-ol	-	-	-	-	NS	-	-
caproic acid	-	-	-	-	NS	-	-
deca-trans-2,trans-4-dien-1-al	-	-	-	-	NS	-	-
hept-trans-2-en-1-al	-	-	-	-	NS	-	-
heptan-1-al	-	-	-	-	NS	-	-
heptan-2-ol	-	-	-	-	NS	-	-
heptanoic acid	-	-	-	-	NS	-	-
hexan-1-al	-	-	-	-	NS	-	-
hexan-1-ol	-	-	-	-	NS	-	-
3-methyl-butan-1-ol	-	-	-	-	NS	-	-
β-ocimene	-	-	-	-	NS	-	-
octan-1-ol	-	-	-	-	NS	-	-
octane-2,3-dione	-	-	-	-	NS	-	-
octanoic acid	-	-	-	-	NS	-	-
pentan-1-al	-	-	-	-	NS	-	-
pentan-1-ol	-	-	-	-	NS	-	-
pentan-2-ol	-	-	-	-	NS	-	-
zingiberene	-	-	-	-	NS	-	-
dipentene	-	-	-	-	-	NS	-

*constituents reported in ppm
NS – amount not specified
" – " means not reported

Table 4. Constituent data by plant part

	Reference
Plant part not specified	
- volatile oil (0.5-2.5%): 1,8-cineole (20-50%); camphor (10-25%); α-pinene (up to 25%); other monoterpenes (including borneol and limonene)	2,4,5
- rosmarinic acid	
- diterpene bitter substances: carnosol; carnosolic acid (picrosalvin); isorosmanol; rosmanol; rosmadiol; rosmaridiphenol rosmariquinone	
- triterpene acids: ursolic acid; oleanolic acids; rosmanol; 7-ethoxyrosmanol; betulic acid; carnosol; traces of 19 α-hydroxyursolic, 2 β-hydroxyoleanolic, and 3 β-hydroxyurea-12,20(30)-dien-17-oic acids	
- triterpene alcohols: α-amyrin; β-amyrin; betulin	
- flavonoids: luteolin; genkwanin (7-*O*-methlylapigenin); diosmetin; diosmin; genkwanin-4'-methyl ether; 6-methoxygenkwanin; 6-methyoxyluteolin; 6-methoxyluteolin-7-glucoside; 6-methoxyluteolin-7-methylether; hispidulin; apigenin	
- corresponding glycosides	
Leaf	
- volatile oil (1.0-2.5%): 1,8-cineole (15-55%); camphor (5-25%); α-pinene (9-26%); camphene (2.5-12%); β-pinene (2-9%); borneol (1.5-6%); limonene (1.5-5%); bornyl acetate (1-5%); isobutyl acetate; β-caryophyllene; p-cymene; linalool; myrcene; α-terpineol (12-24%); verbenol	5,22,34,35,65
- diterpenes (up to 4.6%): carnosic acid; carnosol; isorosmanol; rosmadiol; rosmaridiphenol; rosmanol; rosmariquinone; triacetylrosmanol; dimethylrosmanol	
- triterpenes: oleanolic acid (10%); ursolic acid (2-5%); α-amyrin; β-amyrin; epi-α-amyrin; 19-α-ursolic acid; 2-β-hydroxy oleanolic acid; betulin	
- phenolic acids (2-3%): rosmarinic acid (3.5%); chlorogenic acid; neo-chlorogenic acid; caffeic acid; labiatic acid	
- flavonoids: genkwanin; cirsimarin; diosmetin; apigenin; luteolin; nepetin; nepitrin; diosmin; hesperidin; homoplantiginin; phegopolin	
- alkaloids: rosmaricin; isorosmaricine	
- tannins	
- saponins	
- glycolic acid and glyceric acid	
- vitamin C; vitamin P	
- choline	
Leaf Oil	
- α-pinene (8-25%), β-pinene (7.6%); eucalyptol (20-50%), camphor (10-27.6%), borneol (20%), 1,8-cineole (15.8%); β-myrcene (10%); camphene (5.2-5.8%), limonene (5.9%); *p*-cymene (4.8%); β-caryophyllene (3.1%); verbenone (2.6%); linalool	34,63,66-68
- From one sample (concentration in the oil):	66
- monoterpenoid esters (24.76%): bornyl acetate (20.86%); linolyl acetate (2.90%); terpinyl acetate (1.0%)	
- monoterpenoid alcohols (23.78%): borneol (8.25%); linalool (5%); isoborneol (4.13%); γ-terpineol (2.94%); α-terpineol (1.9%); terpinene 4-ol (1.43%); carveol (0.13%)	
- monoterpenoid ketones (18.67%): L-camphor (14.06%); verbenone (2.56%); carvone (1.9%); α-thujone (0.15%)	
- monoterpenoid ethers (10.86%): methyl eugenol (5.46%); 1,8-cineole (5.05%); linalool oxide (0.35%)	
- sesquiterpenes (8.96%): β-caryophellene (4.31%); caryophellene oxide (3.19%); spathulenol (1.27%); α-copene (0.19%)	
- phenols (4.06%): thymole (3.06%); carvacrol (0.91%); methyl chavicol (0.19%)	
- monoterpenes (3.4%): p-cymene (1.15%); α-pinene (0.95%); camphene (0.81%); myrcene (0.22%); limonene (0.15%)	
Seed	
- 560.5 µg/g α-tocotrienol; 300.3 µg/g β-tocotrienol; 109.4 µg/g γ-tocotrienol	69
Essential Oil	
- mainly monoterpenes: α-pinene (20.1-21.7%), β-pinene; camphene; limonene; 1,8-cineole (23.5-26.5%); eucalyptol (4.5%); and borneol	4,70,71
- camphor (7.2%); berbonone (7.6%); linalool; verbenol; terpineol; 3-octanone; isobornyl acetate	

Table 5. Rosmarinus Officinalis (Rosemary) Leaf Extracts (CO_2 extract) – Certificates of Analysis

Analytical Detail	Specifications (%)	Results (%)
Rosmarinus Officinalis (Rosemary) Extract (CO_2) [17]		
Essential Oil Content	78-88	78
Volatile components:		
α -pinene	8-12	11.4
camphene	n.s.	4.0
β -pinene	n.s.	3.7
myrcene	n.s.	2.7
p-cymene	n.s.	1.2
limonene	2-4	2.4
1,8-cineole	>40	41.3
linalool	n.s.	0.83
camphor	6-13	13.0
borneol	n.s.	3.8
α -terpineol	n.s.	3.9
verbenone	n.s.	0.45
bornyl acetate	n.s.	0.94
carophyllene	3-10	4.7
Rosmarinus Officinalis (Rosemary) Leaf Extract (CO_2; 14% diterpene phenols) (and) Helianthus Annuus Seed Oil [18]		
Essential Oil Content	<2	1.9
Phenolic diterpenes:		
rosmanol	n.s.	0.07
7-methyl-rosmanol	n.s.	0.09
carnosol	n.s.	1.2
carnosolic acid	n.s.	10.5
12-methyl-carnosolic acid	n.s.	2.4
sum of phenolic diterpenes	13-15	14.3
Reference antioxidant compounds (carnesol + carnosic acid, calculated as carnosic acid)	n.s.	9.5
Ursolic Acid	n.s,	0.43
Oleanolic Acid	n.s.	0.62
residual ethanol	<2	0.71
water content	<1	0.30
Rosmarinus Officinalis (Rosemary) Leaf Extract (CO_2; 25% diterpene phenols) (and) Helianthus Annuus Seed Oil [19]		
Essential Oil Content	<4	3.0
Phenolic diterpenes:		
rosmanol	n.s.	0.13
7-methyl-rosmanol	n.s.	0.18
carnosol	n.s.	1.4
carnosolic acid	n.s.	18.7
12-methyl-carnosolic acid	n.s.	4.5
sum of phenolic diterpenes	24-26	24.9
Ursolic Acid	n.s.	0.29
Oleanolic Acid	n.s.	0.51
residual ethanol	<2	0.39
water content	<1	0.91
Rosmarinus Officinalis (Rosemary) Leaf Extract (CO_2; 25% diterpene phenols) (and) Helianthus Annuus Seed Oil [16]		
Essential Oil Content	<4	1.7
Phenolic diterpenes:		
rosmanol	n.s.	0.t3
7-methyl-rosmanol	n.s.	0.32
carnosol	n.s	2.9
carnosic acid	> t6	20.6
12-methyl-carnosic acid	n.s.	1.0
sum of phenolic diterpenes	24-26	25.0
Ursolic Acid	n.s.	0.42
Oleanolic Acid	n.s.	0.52
residual ethanol	<2	0.33
water content	<1	0.15

n.s. – not specified

Table 6. Differences in constituent profiles in Rosmarinus officinalis (rosemary) Leaf Extract based on extraction method *[8]

		Extraction Method				
Constituent (ppm)	**dried leaves**	**supercritical CO_2**	**acetone**	**ethanol extract, partially deodorized**	**ethanol extract, deodorized**	**decolorized and deodorized using hexane and ethanol**
Triterpenes						
betulin	<4760	6000	5600	8450	9460	6790
amyrin	<500	34	200	160	230	360
oleanic+ursolic acid	148,100	48,500	100,500	119,800	164,500	60,000
Flavonoids						
genkwanin	2.9	0.65	1.60	2.30	3.66	2.1
Volatiles						
1,8-cineole	56,100	80	1700	1320	53	30
camphor	25,200	220	2360	2080	120	20
borneol	10,000	90	960	840	40	10
Heavy Metals						
lead	2.90	0.09	0.03	0.13	0.15	0.18
arsenic	1.14	<0.034	0.05	0.25	0.25	0.32

* standardized to 10% carnosic acid + carnosol content

Table 7. Toxicity information on constituents of Rosmarinus officinalis (rosemary)

Component	Toxicity information
Phenol Acids	
Caffeic Acid	- in a MMC-induced SCE assay in human lymphocytes, 100 µM caffeic acid enhanced MMC-induced SCEs by 55%; 100 µM caffeic acid alone enhanced MMC-induced SCEs by 26%[72] - caffeic acid is reported to penetrate skin and have UV photoprotective activity[73] - humans and animals metabolize caffeic acid to the same metabolites and hydrolyze chlorogenic acid to caffeic acid; IARC concluded that there is sufficient evidence for carcinogenicity in animal; no data were available on the carcinogenicity in humans, and IARC concluded that caffeic acid is possibly carcinogenic to humans[74] - the carcinogenic potency of caffeic acid, estimated based on an average human intake of 1 mg/kg bw/day, was less than 1000 cancer cases per 1,000,000 individuals; in rats 1 or 2% (10,000 or 20,000 ppm) caffeic acid in the diet for 51 wks to 2 yrs induced papillomas of the forestomach and renal adenomas; one study, in which rats were exposed to 2% (20,000 ppm) caffeic acid in the diet for 2 yrs, showed treatment-induced carcinomas of the forestomach, whereas two studies with shorter exposure durations showed no such effect; caffeic acid was shown to exert strong promotion activity for forestomach carcinogenesis; chronic exposure to caffeic acid in the diet induced hyperplasia of the forestomach (mice, rats, and hamsters), hyperplasia of the kidney (mice and rats), and increased liver and kidney wts (rats); few toxic effects resulted from acute exposure; subchronic dietary exposures did not induce clinical symptoms of toxicity, however, hyperplasia of the forestomach was observed; some genotoxic effects seen in vitro but not in vivo[75]
Chlorogenic Acid	-an antioxidant that inhibited tumor promotion by phorbol esters in mice; some controversy exists over allergic reactions in green coffee beans, but it was accepted that chlorogenic acid was not the allergen[73] -in mice, 2% (20,000 ppm) chlorogenic acid in the diet for 96 weeks induced papillomas and carcinomas of the forestomach, alveolar type II-cell tumors of the lung, and renal cell adenomas; few toxic effects resulted from acute exposure; subchronic dietary exposures did not induce clinical symptoms of toxicity, however, reduced kidney and adrenal wts and hyperplasia of the forestomach were observed; some genotoxic effects seen in vitro but not in vivo[75]
Flavonoids	epidemiological studies implicated high dietary intake levels of flavonoids in heart disease, but a study of cancer risk failed to find a link; some evidence of genotoxicity in bacterial assays, but a European Organization of Cosmetic Ingredients Industries and Services (UNITIS) report stated that flavonoids do not appear to be genotoxic to mammals in vivo; flavonoids are not considered allergens[73]
Diterpenes	
Carnosic Acid	- is a known antioxidant;[76] in a toxicokinetic study in male Sprague-Dawley rats, carnosic acid was absorbed into the blood stream after oral administration and was bioavailable, traces of the acid were found in the intestinal content, liver, and muscle tissue of the abdomen and legs, carnosic acid was present in its free form, and the main rout of elimination was the feces;[76] not mutagenic in an Ames test, with or without metabolic activation, at doses equivalent of the concentration present in up to 6000 µg/plate of a decolorized and deodorized rosemary leaf extract[8]
Carnosol	- topical application of carnosol isolated from rosemary inhibited TPA-induced ear inflammation and tumor promotion in mice;[40] not mutagenic in an Ames test, with or without metabolic activation, at doses equivalent of the concentration present in up to 6000 µg/plate of a decolorized and deodorized rosemary leaf extract[8]

Table 7. Toxicity information on constituents of Rosmarinus officinalis (rosemary)

Component	Toxicity information
Monoterpenes	these chemicals may be skin sensitizers[73]
d- Limonene	- d-limonene consumption has been estimated as 0.2 -2 mg/kg bw/day; in men, oral intake induced transient proteinuria[74] - developmental toxicity in the form of delayed prenatal growth has been observed in mice, rats and rabbits exposed to *d*-limonene during gestation, and skeletal anomalies have also been observed in the fetuses of exposed mice and rabbits;[77] - the few genotoxicity studies available indicated that *d*-limonene and its 1,2-epoxide metabolite are not genotoxic[77] - in a mouse study, administration by gavage did not result in any treatment-related tumors; in a rat study, administration by gavage significantly increased the combined incidence of renal tubular adenomas and carcinomas and induced renal tubular hyperplasia in male rats, but no increases were seen in female rats;[77] oral treatment with *d*-limonene after administration of N-nitrosoethylhydroxy-ethylamine enhanced the development of renal adenomas and renal tubular hyperplasia in male Fischer 344 rats but not in male NBR rats;[74] - IARC found there are sufficient evidence for carcinogenicity in animals, concluding that *d*-limonene produces renal tubular tumors in male rats by a non-DNA-reactive mechanism, through an α_{2u}-globulin-associated response, and therefore, the mechanism by which *d*-limonene increases the incidence of renal tubular tumors in male rats is not relevant to humans; no data were available on the carcinogenicity in humans, and IARC concluded that d-limonene is not classifiable as to its carcinogenicity in humans[77]
α-Pinene	negative in the Ames assay and a mouse micronucleus test[78]
1,8-Cineole	positive in a sister chromatid exchange assay; negative in a chromosomal aberration assay; negative in an Ames test[79]
β-Myrcene	has been reported to cause dermatitis and conjunctivitis in humans; in Wistar rats, the NOAEL for embryotoxicity was 0.5 g/kg bw/day and the NOAEL for peri- and post-natal developmental toxicity was 0.25 g/kg bw/day; was not genotoxic *in vitro* in SCE and chromosomal aberration assays in Chinese hamster cells or human lymphocytes, but it did induce a slight increase is SCEs in cultured hepatic tumor cells; was not genotoxic *in vivo* in rat bone marrow cells[80]
Linalool	safe at up to 4.3% (20% in consumer fragrance); listed as a fragrance allergen by the European Commission[73]
α,β-Thujone	α,β-thujone was not mutagenic in the Ames test; in the micronucleus test, negative in male and positive in female mice; β-thujone: *some evidence of carcinogenicity in male rats* – significant incidence of cancers of the preputial gland in male rats given 25 mg/kg by gavage, and an increase in adrenal gland tumors in male rats may have been due to β-thujone; no increase in in cancer incidence in female rats (dosed with up to 50 mg/kg by gavage) or male or female mice (dosed with up to 25 mg/kg by gavage); all rats dosed with 50 mg/kg and all female mice dosed with 25 mg/kg died[81]
Methyleugenol	- IARC concluded that there is sufficient evidence in experimental animals for carcinogenicity; no data were available on the carcinogenicity in humans, and IARC concluded that methyleugenol is possibly carcinogenic to humans[82]
Terpene Alcohols	
α-Terpineol	- oral LD50 in mice, 2830 mg/kg; 1000 mg/kg bw/day for 2 wks caused reduced body wt gains and an increase in serum cholesterol; not mutagenic in an Ames test or mouse lymphoma assay; did not induce pulmonary tumors in mice given i.p. injections; a derma irritant in animals studies, but not a dermal irritant in a 4-h clinical study; not a sensitizer in guinea pigs; in clinical patch tests, 5% in pet. had 1/1606 positive and 11/1606 questionable reactions in one study and 2/1200 positive reactions in another[83]
Ursolic acid	topical application of carnosol isolated from rosemary inhibited TPA-induced ear inflammation and tumor promotion in mice[40]
Triterpene Alcohols	hepatoprotective and anti-carcinogenic activity has been suggested for lupeol; no toxicity data were available; triterpene alcohols were considered to have intermediate risk[73]

Table 8. Frequency and concentration of use according to duration and type of exposure

	# of Uses[25]	*Max. Conc. of Use (%)*[26]	*# of Uses*[25]	*Max. Conc. of Use (%)*[26]	*# of Uses*[25]	*Max. Conc. of Use (%)*[26]
	Rosmarinus Officinalis (Rosemary) Extract		**Rosmarinus Officinalis (Rosemary) Flower Extract**		**Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Extract**	
Totals*	**387**	**0.00004-0.16**	**36**	**NR**	**NR**	**0.0024**
Duration of Use						
Leave-On	*234*	*0.00096 – 0.051*	*11*	*NR*	*NR*	*0.0024*
Rinse Off	*150*	*0.00004 -0.16*	*25*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*3*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	18	0.01-0.05	2	NR	NR	NR
Incidental Ingestion	7	0.011	NR	NR	NR	NR
Incidental Inhalation-Spray	6[a]	0.00096-0.01[a]	1	NR	NR	NR
Incidental Inhalation-Powder	NR	0.05	NR	NR	NR	NR
Dermal Contact	265	0.00096-0.16	11	NR	NR	0.0024
Deodorant (underarm)	NR	not spray: 0.0098 aerosol: 0.0098-0.012	NR	NR	NR	0.0024
Hair - Non-Coloring	112	0.00004-0.003	25	NR	NR	NR
Hair-Coloring	1	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	27	0.0005-0.16	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 8. Frequency and concentration of use according to duration and type of exposure

	# of Uses[25]	*Max. Conc. of Use (%)*[26]	*# of Uses*[25]	*Max. Conc. of Use (%)*[26]	*# of Uses*[25]	*Max. Conc. of Use (%)*[26]
	Rosmarinus Officinalis (Rosemary) Leaf		**Rosmarinus Officinalis (Rosemary) Leaf Extract**		**Rosmarinus Officinalis (Rosemary) Leaf Oil**	
Totals*	**16**	**0.002**	**689**	**0.00001-10**	**516**	**0.00001-1.5**
Duration of Use						
Leave-On	*1*	*0.002*	*422*	*0.00001-10*	*342*	*0.0003-1.5*
Rinse Off	*14*	*NR*	*263*	*0.00001-3*	*149*	*0.00001-0.12*
Diluted for (Bath) Use	*1*	*NR*	*4*	*0.0002-0.04*	*25*	*0.5-0.97*
Exposure Type						
Eye Area	NR	NR	36	0.002-3	8	*NA*
Incidental Ingestion	NR	NR	25	0.00001-0.002	3	0.008
Incidental Inhalation-Spray	NR	NR	9[a]	0.001-0.5 aerosol: 0.0016 pump spray: 0.0001-0.005	32	0.011-1.5 aerosol: 0.007
Incidental Inhalation-Powder	NR	NR	8	0.0002	3	0.0003
Dermal Contact	4	NR	416	0.00001-10	425	0.0003-1.5
Deodorant (underarm)	NR	NR	NR	NR	1	NA
Hair - Non-Coloring	12	0.002	225	0.00001-0.5	87	0.00001-1.5
Hair-Coloring	NR	NR	22	0.04	1	NA
Nail	NR	NR	1	0.005-0.053	NR	NA
Mucous Membrane	1	NR	74	0.00001-3	66	0.002-0.97
Baby Products	NR	NR	7	0.012	4	NA
	Rosmarinus Officinalis (Rosemary) Leaf Powder		**Rosmarinus Officinalis (Rosemary) Leaf Water**		**Rosmarinus Officinalis (Rosemary) Water**	
Totals*	**1**	**0.05**	**22**	**0.000069-1**	**1**	---
Duration of Use						
Leave-On	*1*	*NR*	*7*	*0.000069-1*	*1*	*NR*
Rinse Off	*NR*	*0.05*	*15*	*0.00015-0.25*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	0.000069-0.00016	NR	NR
Incidental Ingestion	NR	NR	NR	0.005	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	7	0.00009-0.36	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.05	15	0.00019-1	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	0.005	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Rosemary [#]					
Totals*	**12**	---				
Duration of Use						
Leave-On	*4*	---				
Rinse Off	*7*	---				
Diluted for (Bath) Use	*1*	---				
Exposure Type						
Eye Area	NR	---				
Incidental Ingestion	NR	---				
Incidental Inhalation-Spray	NR	---				
Incidental Inhalation-Powder	1	---				
Dermal Contact	8	---				
Deodorant (underarm)	NR	---				
Hair - Non-Coloring	4	---				
Hair-Coloring	NR	---				
Nail	NR	---				
Mucous Membrane	2	---				
Baby Products	NR	---				

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses
NR – not reported
[a] Includes suntan preparations, and it t is not known whether or not those product are sprays
[#]Plant part and method of extraction not known

Table 9. Single-dose toxicity studies

Test Article	Extraction Solvent/Method	Species	No./Group	Vehicle	Conc/Dose Range	LD_{50}/Results	Reference
DERMAL							
Rosmarinus Officinalis (Rosemary) Leaf Oil	-----	rabbits	not stated	not stated	not stated	>10 ml/kg	[48]
Rosmarinus Officinalis (Rosemary) Leaf Oil	-----	rabbits	not stated	not stated	not stated	>10 g/kg	[67]
ORAL							
Rosmarinus Officinalis (Rosemary) Leaves – 2 samples; one harvested in autumn (112.7, 477.8, 700.1 µg/mg extract carnosol, carnosic acid, total diterpenes, respectively) and one in spring (45.9, 245.9, 343.1 µg/mg extract carnosol, carnosic acid, total diterpenes, respectively)	supercritical CO_2	Wistar rats	6 M/6F	corn oil	2 g/kg bw (gavage)	>2 g/kg	[22]
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	ethanol extract, partially deodorized	mice	not stated	none stated	8.5 g/kg bw (males) 10 g/kg bw (females)	>8.5 g/kg bw (males) >10 g/kg bw (females)	[8]
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	ethanol extract, deodorized	mice	not stated	none stated	24 g/kg bw (males) 28.5 g/kg bw (females)	>24 g/kg bw (males) >28.5 g/kg bw (females)	[8]
Rosmarinus Officinalis (Rosemary) Leaf Oil (see Table 4 for composition)	hydrodistillation	Swiss albino rats	20/group	-----	2-9 g/kg bw (gavage)	LD_{50} = 5.50 g/kg bw LD_{10} = 1.10 g/kg bw LD_{100} = 9 g/kg bw	[66]
Rosmarinus Officinalis (Rosemary) Leaf Oil (see Table 5 for composition)	-----	rats	not stated	none stated	not stated	5 ml/kg bw	[48]

Table 10. Repeated-Dose Toxicity Studies

Test Article	Extraction Solvent/Method	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
				ORAL			
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	ethanol extract, partially deodorized	mice; no./group not stated	5 days (gavage)	none stated	4300 mg/kg bw (males) 5000 mg/kg bw (females)	- no mortality - body wt increased slightly in males, but no changes were seen in females; "marked increase" in fatty liver was observed in males after repeated administration	8
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table for composition)	ethanol extract, deodorized	mice; no./group not stated	5 days (gavage)	none stated	11,800 mg/kg bw (males) 14,100 mg/kg bw (females)	- no changes in body wts; liver wts of females were slightly increased; fatty livers were observed in test animals at necropsy.	8
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	acetone	rats; no./group not stated	14 day (diet)	-----	up to 3800 mg/kg diet	- no treatment-related signs of toxicity, mortality, or changes in body wts or feed consumption	8
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	supercritical CO_2	rats; no./group not stated	14 days (diet)	-----	up to 2400 mg/kg diet	- no treatment-related signs of toxicity, mortality, or changes in body wts or feed consumption	8
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	acetone	20 rats/group	13 wks (diet)	-----	300, 600, 2400, or 3800 mg/kg diet	- variations in clinical chemistry parameters at times were stat sig, but the researchers stated that because the changes were inconsistent, they were not considered dose-related - stat. sig, decrease in alkaline phosphate in the 3800 mg/kg group - NOAEL was 3800 mg/kg diet	8
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	supercritical CO_2	20 rats/group	13 wks (diet)	-----	300, 600, or 2400 mg/kg diet	- variations in clinical chemistry parameters at times were stat sig; the researchers stated that because the changes were inconsistent, they were not considered dose-related - a marginal reduction in body weights and feed consumption in the animals of the 2400 mg/kg diet groups were attributed to a lack of palatability of the feed - changes were more notable in females - NOAEL was 2400 mg/kg diet (equiv. to 180 and 200 mg/kg bw/day for males and females, respectively)	8
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	supercritical CO_2	female rats; no./ group not stated	91 days (diet); 28-day recovery period	-----	0 or 2400 mg/kg diet (equiv. to 0 or 195 mg/kg bw/day)	- slight increase in liver wts after 91-days of dosing, but not in those killed after the 28-day recovery period - an increase in microsomal protein concentration observed after 91 days of dosing was also reversible - no notable effects on the activity of selected enzymes	8
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	ethanol extract, partially deodorized	Sprague-Dawley rats; no./group not stated	90 days (diet)	-----	0, 500, 1500,or 5000 mg/kg diet (equiv. to 0, 40, 120, or 400 mg/kg bw/day)	- a dose-response relationship was observed for relative liver-to-body wt; extracts; a slight but stat sig increase was observed - no microscopic changes in the liver were reported	8
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	ethanol extract, deodorized	Sprague-Dawley rats; no./group not stated	90 days (diet)	-----	0, 500, 1500,or 5000 mg/kg diet (equiv. to 0, 40, 120, or 400 mg/kg bw/day)	- a dose-response relationship was observed for relative liver-to-body wt; extracts; a slight but stat sig increase was observed - no microscopic changes in the liver were reported	8

Table 10. Repeated-Dose Toxicity Studies

Test Article	Extraction Solvent/Method	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
Rosmarinus Officinalis (Rosemary) Leaf Extract (see Table 5 for composition)	hexane and ethanol (2-step extraction)	Sprague-Dawley rats; no./group not stated	3 mos (diet); 28-day interim group; 1-mo recovery period	-----	0, 1000, 2500, or 5000 mg/kg diet (equiv. to 0, 65, 164, or 320 mg/kg bw/day)	- no signs of toxicity, no mortality and no gross lesions at necropsy - reversible dose-dependent increases in absolute liver wts and relative liver-to-body wts; stat sig in the high dose group only - treatment-related increase in bile duct hyperplasia at the interim necropsy; the incidence was decreased at the end of dosing and not seen after recovery - in females, a decrease in pancreas wt was observed at the interim necropsy - no stat sig changes in hematology parameters, and no microscopic changes - the NOAEL was at least 320 mg/kg bw/day	8
Rosmarinus Officinalis (Rosemary) Leaf Extract (after the volatile oil [1.1%] was removed)	absolute ethanol	Swiss albino mice; 6M/group	3 wks (gavage)	olive oil	1500 mg/kg extract controls – olive oil	no stat sig changes in relative liver, spleen, heart, or lung wt to body wt compared to controls; there were no stat sig changes in clinical chemistry parameters	66
			single dose CCl_4 (gavage), then 3 wks extract (gavage)	olive oil	3.3% CCl_4 (100 mg/kg bw) 1500 mg/kg extract	- with CCl_4 only, stat sig increases in relative liver to body wt (18%) and spleen to body wt (45.6%) compared to olive oil controls; CCl_4 affected all measured clinical chemistry parameters - with the extract, the increase in relative spleen to body wt was stat sig, but not as great as with CCl_4 alone (34.9%); there was no stat sig increase in relative liver to body wt; many of the changes in clinical chemistry values were reduced or were non-stat sig	
Rosmarinus Officinalis (Rosemary) Leaf Oil (see Table 4 for composition)	hydrodistillation	Swiss albino mice; 6M/group	3 wks (gavage)	-----	1100 mg/kg bw controls – olive oil	no stat sig changes in relative liver, spleen, heart, or lung wt to body wt compared to controls; there were no stat sig changes in clinical chemistry parameters	66
			single dose CCl_4 (gavage), then 3 wks oil (gavage)	olive oil (for CCl_4)	3.3% CCl_4 (100 mg/kg bw) 1100 mg/kg extract	- (effects of CCl_4 only are described above) - with the oil, the increases in relative liver to body wt (9.8%) and spleen to body wt (38.8%) were stat sig, but not as great as with CCl_4 alone; many of the changes in clinical chemistry values were reduced but were still stat sig	

Abbreviations: CCl_4: - carbon tetrachloride; conc – concentration; equiv. – equivalent; NOAEL – no-observable adverse effect level; stat sig – statistically significant

Table 11. Genotoxicity studies

Test Article	Extraction Solvent/Method	Conc./Vehicle	Procedure	Test System	Results	Reference
			IN VITRO			
Rosemary Extract (not defined; water-soluble; contained 17% rosmarinic acid)	-----	50, 100, or 200 µg/plate	Ames test, with and without metabolic activation	*S. typhimurium* TA98	not mutagenic	84
as above	-----	50 µg/ml (highest non-cytotoxic dose)	comet assay	human hepatoma cell line (HepG2)	not genotoxic	84
Rosemary Extract (not defined; oil-soluble; contained 50.27% carnosic acid and 5.65% carnosol)	-----	50, 100, or 200 µg/plate	Ames test, with and without metabolic activation	*S. typhimurium* TA98	not mutagenic	84
as above	-----	5 µg/ml (highest non-cytotoxic dose)	comet assay	human hepatoma cell line (HepG2)	not genotoxic	84
Rosmarinus Officinalis (Rosemary) Leaf Extract	supercritical CO_2	up to 5000 µg/plate	bacterial assay, with and without metabolic activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA102	not mutagenic - in TA102 only, toxicity at the highest dose with metabolic activation	8
Rosmarinus Officinalis (Rosemary) Leaf Extract	ethanol extract,, partially deodorized	up to 20,000 µg/plate	bacterial assay, with and without metabolic activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA102	not mutagenic - some bactericidal effects in all strains; effects were reduced with metabolic activation	8
Rosmarinus Officinalis (Rosemary) Leaf Extract	ethanol extract, deodorized	up to 20,000 µg/plate	bacterial assay, with and without metabolic activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA102	not mutagenic - some bactericidal effects in all strains; effects were reduced with metabolic activation	8
Rosmarinus Officinalis (Rosemary) Leaf Extract	hexane and ethanol (2-step extraction)	up to 6000 µg/plate	Ames test, with and without metabolic activation	*S. typhimurium* TA97, TA98, TA100, TA102	-mutagenic in TA102 in one set of trials; not reproducible with less cytotoxic conc -not mutagenic in the other strains - without metabolic activation: bactericidal for all strains at 3000-6000 µg/plate; bactericidal to TA102 at almost all dose levels -with metabolic activation, bactericidal only at the highest dose level, if at all	8
Rosmarinus Officinalis (Rosemary) Leaf Extract	ethanol extract, partially deodorized	up to 100 mg/ml	chromosomal aberration assay, with and without metabolic activation	human lymphocytes	not genotoxic	8
Rosmarinus Officinalis (Rosemary) Leaf Extract	hexane and ethanol (2-step extraction)	not clearly specified but at least up to 50 µg/ml without and 35 µg/ml with metabolic activation	gene-locus mutation assay, with and without metabolic activation	thymidine kinase (tk) and hgprt loci of a human lymphoblastoid cell line (TK6)	-not genotoxic without metabolic activation at up to 50 µg/ml - 35 µg/ml increased mutations in the tk, but not the hgprt, locus with activation; the increase was stat sig when compared to solvent control, but not when compared to untreated cells; determined to be not mutagenic under the conditions used because of a lack of a dose-dependent increase in mutation frequency and a lack of a stat sig increase of mutation frequency compared to controls	8
Rosmarinus Officinalis (Rosemary) Leaf Oil	-----	not stated	Ames test	not stated	negative	85

Table 11. Genotoxicity studies

Test Article	Extraction Solvent/Method	Conc./Vehicle	Procedure	Test System	Results	Reference
			IN VIVO			
Rosmarinus Officinalis	hydro-alcoholic	6.43, 100, and 200 mg/kg bw	chromosomal aberration assay	Wistar rats; 6/group	not genotoxic	86
Rosmarinus Officinalis	hydro-alcoholic	6.43, 100, and 200 mg/kg bw	micronucleus assay	Wistar rats; 6/group	not genotoxic	86
Rosmarinus Officinalis (Rosemary) Leaf Extract (after the volatile oil [1.1%] was removed)	absolute ethanol	1500 mg/kg bw/day in olive oil	micronucleus test; dosed by gavage for 7 days; negative controls were given olive oil; positive controls were given a single i.p. dose of 100 mg/kg bw CPA; bone marrow cells collected 24 h after dosing	Swiss albino mice	not genotoxic; no stat sig change in the number of MNPCE or NCE or in PCE/NCE	66
Rosmarinus Officinalis (Rosemary) Leaf Oil (see Table 4 for composition)	hydrodistillation	1100 mg/kg bw/day	same protocol	Swiss albino mice	no stat sig change in no. of MNPCE no. of NCE was stat sig decreased ($p<0.05$) PCE/NCE was stat sig increased ($p<0.01$)	66
Rosmarinus Officinalis (Rosemary) Leaf Oil	hydrodistillation	300, 1000, or 2000 mg/kg bw (by gavage)	chromosome aberration assay; single 0.5 ml dose; negative controls were given distilled water; positive controls were dosed with 50 mg CPA/kg; bone marrow cells collected 24 h after dosing	Wistar rats; 3M/3F per group	- chromosomal aberrations without gaps were stat sig increased at 2000 mg/kg bw - mitotic index was stat sig increased with 300 mg/kg, but not with other doses or the positive control	14
Rosmarinus Officinalis (Rosemary) Leaf Oil	hydrodistillation	300, 1000, or 2000 mg/kg bw (by gavage)	micronucleus test; single 0.5 ml dose; negative controls were given distilled water; positive controls were dosed with 50 mg CPA/kg; bone marrow cells collected 24 h after dosing	Swiss mice; 3M/3F per group	- stat sig increase in MNPCEs with 1000 and 2000 mg/kg bw - PCE/NCE was not stat sig different from controls	14
Rosmarinus Officinalis (Rosemary) Leaf Oil	hydrodistillation	300, 1000, or 2000 mg/kg bw (by gavage)	micronucleus test; protocol as above; bone marrow cells collected 24 h after dosing	Wistar rats; 3M/3F per group	stat sig increase in MNPCEs with 2000 mg/kg bw	14
Rosmarinus Officinalis (Rosemary) Leaf Oil	hydrodistillation	300, 1000, or 2000 mg/kg bw (by gavage)	comet assay; single 0.5 ml dose; negative controls were given distilled water; positive controls were dosed with 50 mg cyclophosphamide/kg; liver and peripheral blood cells collected 24 h after dosing	Swiss mice; 3M/3F per group	all 3 doses induced stat sig increases in DNA damage in peripheral blood cells and liver cells; most of the damaged cells showed minor damage, very few had a large amount of damage	14
mixture containing 19% Rosmarinus officinalis (rosemary) leaves, 71..5% St. John's Wort; 9.5% spirulina (algae)	-----	0, 380, 760, or 1520 mg/ kg bw/day in water (gavage)	micronucleus test; mice were dosed for 7 days; femoral bone marrow cells were used	male Swiss albino mice; 30/group	- stat. sig. increase in MNPCEs with 760 and 1520 mg/kg bw/day - PCE/NCE was not stat sig different from controls	87
mixture defined above	-----	0, 380, 760, or 1520 mg/ kg bw/day in water (gavage)	chromosomal aberration assay; mice were dosed for 7 days and killed 19 days after last dose	male Swiss albino mice; 30/group	- stat sig increased in frequency of aneuploidy with 760 and 1520 mg/kg bw/day - % polyploids and total % aberrations were stat sig increased at these doses	87

Table 11. Genotoxicity studies

Test Article	Extraction Solvent/Method	Conc./Vehicle	Procedure	Test System	Results	Reference
mixture defined above	-----	0, 380, 760, or 1520 mg/ kg bw/day in water (gavage)	assay for spermatozoa abnormality; mice were dosed for 7 days and killed 5 wks after last dose	male Swiss albino mice; 30/group	- stat sig increase in frequency of banana-shaped, swollen achrosome, and triangular head sperm abnormalities with 1520 mg/kg bw/day - % total spermatozoa abnormalities stat sig increased with 1520 mg/kg bw/day	[87]
ANTI-MUTAGENIC EFFECTS						
			IN VITRO			
Rosemary Extract (not defined; contained 8.8-10.6% carnosic acid and 1.2-1.4% carnosol) + tBOOH	-----	≤0.8 mg/ml in medium-chain triglycerides; only the carnosic acid and carnosol were soluble	Ames test; 0.5 ml rosemary extract was incubated with 0.5 ml tBOOH	*S. typhimurium* TA102	stat sig reduced tBOOH-induced mutagenicity	[88]
Rosemary Extract (not defined; water-soluble; contained 17% rosmarinic acid) + IQ	-----	50, 100, or 200 µg/ plate extract 10 ng/plate IQ	Ames test, with metabolic activation	*S. typhimurium* TA98	a stat sig reduction in IQ-induced genotoxicity was observed only at the highest dose	[84]
as above + NQNO	-----	0, 50, 100, or 200 µg/ plate extract 500 ng/plate NQNO	Ames test, without metabolic activation	*S. typhimurium* TA98	no stat sig effect on NQNO-induced genotoxicity	[84]
as above + tBOOH	-----	0, 0.05, 0.5, 5, or 50 µg/ml extract; 0.05 mM tBOOH	Comet assay; pretreatment with extract for 21 h, followed by 20 min exposure to tBOOH	human hepatoma cell line (HepG2)	stat sig reduction in tBOOH-induced DNA damage at all doses; the reduction was not dose-dependent – 0.05 µg/ml caused a greater reduction than 0.5 µg/ml	[84]
as above + tBOOH	-----	0, 0.05, 0.5, 5, or 50 µg/ml extract; 0.05 mM tBOOH	Comet assay; co-treatment with extract and tBOOH for 20 min	human hepatoma cell line (HepG2)	no stat sig effect on tBOOH-induced DNA damage	[84]
as above + tBOOH	-----	0, 0.05, 0.5, 5, or 50 µg/ml extract; 0.05 mM tBOOH	Comet assay; pretreatment with extract for 21 h, followed by co-treatment with extract and tBOOH for 20 min	human hepatoma cell line (HepG2)	stat sig reduction in tBOOH-induced DNA damage at all except the lowest dose	[84]
as above + BaP	-----	0, 0.05, 0.5, 5, or 50 µg/ml extract; 40 µM BaP	by co-treatment with extract and BaP for 21 h	human hepatoma cell line (HepG2)	stat sig reduction in BaP-induced DNA damage only at the highest dose	[84]
as above + PhIP	-----	0, 0.05, 0.5, 5, or 50 µg/ml extract; 80 µM PhIP	Comet assay; by co-treatment with extract and PhIP for 21 h	human hepatoma cell line (HepG2)	stat sig reduction in PhIP-induced DNA damage only at the highest dose	[84]
Rosemary Extract (not defined; oil-soluble; contained 50.27% carnosic acid and 5.65% carnosol) + IQ	-----	50, 100, or 200 µg/ plate extract 10 ng/plate IQ	Ames test, with metabolic activation	*S. typhimurium* TA98	suppressed IQ-induced mutations in a stat sig, dose-dependent, manner	[84]
as above + NQNO	-----	50, 100, or 200 µg/ plate extract 500 ng/plate NQNO	Ames test, without metabolic activation	*S. typhimurium* TA98	suppressed NQNO-induced mutations in a stat sig, dose-dependent, manner	[84]
as above + tBOOH	-----	0, 0.05, 0.5, or 5 µg/ml extract; 0.05 mM tBOOH	comet assay; pretreatment with extract for 21 h, followed by 20 min exposure to tBOOH	human hepatoma cell line (HepG2)	stat sig reduction in tBOOH-induced DNA damage at all doses	[84]

Table 11. Genotoxicity studies

Test Article	Extraction Solvent/Method	Conc./Vehicle	Procedure	Test System	Results	Reference
as above + tBOOH	-----	0, 0.05, 0.5, or 5 µg/ml extract; 0.05 mM tBOOH	comet assay; co-treatment with extract and tBOOH for 20 min	human hepatoma cell line (HepG2)	no stat sig effect on tBOOH-induced DNA damage	[84]
as above + tBOOH	-----	0, 0.05, 0.5, or 5 µg/ml extract; 0.05 mM tBOOH	comet assay; pretreatment with extract for 21 h, followed by co-treatment with extract and tBOOH for 20 min	human hepatoma cell line (HepG2)	stat sig reduction in tBOOH-induced DNA damage at all doses; the reduction was not dose-dependent`	[84]
as above + BaP	-----	0, 0.05, 0.5, or 5 µg/ml extract; 40 µM BaP	by co-treatment with extract and BaP for 21 h	human hepatoma cell line (HepG2)	stat sig reduction in BaP-induced DNA damage at the two highest doses	[84]
as above + PhIP	-----	0, 0.05, 0.5, or 5 µg/ml extract; 80 µM PhIP	by co-treatment with extract and PhIP for 21 h	human hepatoma cell line (HepG2)	stat sig reduction in PhIP-induced DNA damage at the two highest doses	[84]
			IN VIVO			
Rosmarinus Officinalis (Rosemary) Leaf Extract (after the volatile oil [1.1%] was removed) + CPA	absolute ethanol	1500 mg/kg bw/day in olive oil	micronucleus test; dosed by gavage with the extract for 7 days, then given a single i.p. dose of 100 mg/kg bw CPA; bone marrow cells collected 24 h after dosing; olive oil was used as a negative control	Swiss albino mice	stat sig increase in the number of MNPCE and NCE compared to olive oil only; no stat sig change in PCE/NCE	[66]
Rosmarinus Officinalis (Rosemary) Leaf Oil (contained 20.86% bornyl acetate; 16.24% L-camphor, and 8.25% borneol) + CPA	hydrodistillation	1100 mg/kg bw/day	micronucleus test; dosed by gavage with the oil for 7 days, then given a single i.p. dose of 100 mg/kg bw CPA; bone marrow cells collected 24 h after dosing; olive oil was used as a negative control	Swiss albino mice	stat sig increase in the number of MNPCE and NCE, and a stat sig decrease in PCE/NCE, compared to olive oil only	[66]

Abbreviations: BaP – benzo(*a*)pyrene; conc – concentration; CPA - cyclophosphamide: IQ – 2-amino-3-methyl-3H-imidao[4,5-F]quinoline; MMS – methyl methanesulfonate; MNPCE – micronucleated polychromatic erythrocytes; NCE – normochromatic erythrocytes; NQNO – 4-nitroquinoline-N-oxide; PCE/NCE – ratio of polychromatic erythrocytes to normochromatic erythrocytes; PhIP – 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; stat sig – statistically significant; tBOOH - t-butyl hydroperoxide

Table 12. Anti-tumor activity

Test Article	Extraction Solvent/Method	Dose/Exposure Route	Species No./Group	Tumor Type	Carcinogenicity Model	Results	Reference
Rosmarinus Officinalis (Rosemary) Leaf Extract (contained 16.5-19.2% urosolic acid; 3.8-4.6% carnosol; 0.1-0.5% carnosic acid; trace-0.1% miltirone)	methanol	1.2 or 3.6 mg; dermal	CD-1 mice; 30F/grp	skin	- initiation: topical treatment with 200 nmol DMBA in 200 µl acetone - promotion: after 1 wk, topical treatment with 200 µl acetone (controls), 5 nmol TPA in 200 µl acetone (carc grp), or 5 nmol TPA and extract in 200 µl acetone (RE grp), 2x/wk, for 20 wks	1.2 mg: decreased tumor/mouse by 48, 27, and 28% after 7, 11, and 15 wks TPA promotion 3.6 mg: decreased tumor/mouse by 84, 37, and 48% after 7, 11, and 15 wks TPA promotion	[40]
as above	methanol	1.2 or 3.6 mg; 5 min prior to B(a)P; dermal	CD-1 mice; 30F/grp	skin	- initiation: topical treatment with 200 µl acetone (controls) or with extract in 200 µl acetone (RE grp) 5 min prior to each 20 nmol application of B(a)P or 2 nmol DMBA, 1x/wk, for 10 wks - promotion: after 1 wk, promotion with 15 nmol TPA in 200 µl acetone, 2x/wk, for 20 wks	1.2 mg: decreased tumor/mouse by 15, 42, and 54% after 9, 13, or 21 wks TPA promotion 3.6 mg: decreased tumor/mouse by 62, 63, and 64% after 9, 13, or 21 wks TPA promotion	[40]
as above	methanol	3.6 mg; dermal	CD-1 mice; 30F/grp	skin	- initiation: topical treatment with 200 µl acetone (controls) or 3.6 mg extract in 200 µl acetone (RE grp) at 120, 60, and 5 min before topical application of 200 nmol B(a)P in 200 µl acetone - promotion: after 1 wk, 15 nmol in 200 µl acetone, 2x/wk, for 20 wks	decreased tumor/mouse by 83, 81, and 58% after 9, 13, or 21 wks TPA promotion	[40]
Rosmarinus Officinalis (Rosemary) Leaf Extract	DDW	500 mg/kg bw; gavage	Swiss albino mice; 12M/grp	skin	DMBA-initiated and croton oil-promoted skin tumorigenesis Grp 1: controls – topical treatment with 100 µl acetone; DDW by gavage for 15 wks Grp 2: 500 mg/kg bw/day RE in 100 µl DDW for 15 wks Grp 3: single topical dose 100 µg DMBA in 100 µl acetone; 2 wks later, 1% croton oil in acetone, 3 x/wk; also, 100 µl by gavage for 15 wks Grp 4: single topical dose 100 µg DMBA in 100 µl acetone; 500 mg/kg bw RE by gavage 7 days before, during, and 7 days after DMBA; 2 wks after DMBA, 1% croton oil in acetone, 3x/wk Grp 5: single topical dose 100 µg DMBA in 100 µl acetone; after 2 wks, 500 mg/kg bw RE extract by gavage for 15 days and 1% croton oil in acetone 3x/wk Grp 6: single topical dose 100 µg DMBA in 100 µl acetone; 500 mg/kg bw RE by gavage 7 days before DMBA until study end; 2 wks after DMBA, 1% croton oil in acetone, 3x/wk	-a stat sig decrease in tumor number, diameter, and weight and a stat sig increase in the avg. latency period was observed in grps given RE compared to Grp 3 (the carcinogen-control grp) - blood serum and liver lipid peroxidation level was stat sig decreased in all RE grps compared to grp 3 - Grp 6 had the greatest changes for all the above parameters - no tumors were found in animals given RE only - RE had no effect on body weight gains	[89]
Rosmarinus Officinalis (Rosemary) Leaf Extract	DDW	1000 mg/kg bw in DDW; gavage	Swiss albino mice; 12M/grp	skin	DMBA-initiated and croton oil-promoted skin tumorigenesis -same protocol as above (Grps 1-6), except 1000 mg/kg bw RE was used	- stat sig decrease in tumor burden and tumor yield, and a stat sig increase in avg. latency period, in grps given RE compared to Grp 3 (the carcinogen-control grp); tumor incidence was decreased - blood serum lipid peroxidation level was stat sig decreased in all RE grps, and the liver glutathione levels stat sig increased, compared to grp 3 - RE did not cause any adverse effects; no tumors were seen in the RE-only grp.	[90]

Table 12. Anti-tumor activity

Test Article	Extraction Solvent/Method	Dose/Exposure Route	Species No./Group	Tumor Type	Carcinogenicity Model	Results	Reference
Rosmarinus Officinalis (Rosemary) Extract	not specified	1.0%, in diet	Sprague-Dawley rats; 20F/grp	mammary	- rats were fed untreated or RE-supplemented diet throughout the study (16 wks post-DMBA) - after 27 days of the test diet, each rat was dosed with 30.9 mg/kg bw DMBA in corn oil by gavage	- the incidence of palpable mammary tumors was less in the RE-fed rats than the controls; at study termination, the tumor incidence was 47% less; this difference was stat sig - the difference in tumors per tumor-bearing rat was not stat sig btwn the two grps - at study termination, 94% and 90% of tumor-bearing rats of the control and RE groups, respectively, possessed mammary adenocarcinomas - RE had no effect on body wt	[91]

Abbreviations: B(a)P – benzo[a]pyrene; DDW – double-distilled water; DMBA – 7,12-dimethylbenz[a]anthracene; grp – group; GR – glutathione reductase; GSH – reduced glutathione; GST – glutathione-s-transferase; RE – Rosmarinus officinalis (rosemary) leaf extract; stat sig – statistically significant; TPA – 12-*O*-tetradecanoylphorbol-13-acetate

Table 13. Case reports with *Rosmarinus officinalis* (rosemary)

Mode of Contact	Indication	Patch Testing	Reference
cosmetics and cleansing gel containing 0.1% Rosmarinus officinalis (rosemary) leaf extract	itchy erythema of the face; red papules around the eyes and on the nose and cheeks	patch test with cosmetics and 1% aq. cleansing gel gave positive result (+) to gel only on D3 - patch tested gel ingredients, only positive reaction (+) was to 0.1% aq. Rosmarinus officinalis (rosemary) leaf extract on D3	[54]
occupational exposure to a Rosmarinus officinalis (rosemary) leaf extract	severe hand, forearm, and face dermatitis	patch tested with 5 and 10% extract in petrolatum; + reaction to 5 and 10% on D2 and D5; 1 control was negative - patch tested with carnosol in ethanol; ?+ reaction to 0.1% at 3 and D7, + reaction to 1% on D3 and D7; controls were negative to 0.1 (n=110) and 1% (n=116) carnosol	[55]
occupational use of essential aromatherapy oils (5 cases)	hand eczema in all; other involvement seen	- patch testing with the European baseline series, fragrance series, and 2% of each essential oil in petrolatum; ++ reaction to rosemary oil in 2 subjects, + in one, among other positive reactions	[56]
history of eating foods spiced with rosemary	severe cheilitis	patch tested with 41 antigens, 21 flavoring agents and dyes, and medications; ++ on D2 and + on D5 to rosemary (also + to nickel on D2 and D5; + to wood tars on D2)	[57]
picked rosemary leaves	developed hand, forearm, and face dermatitis within hours	prick-by-prick testing was negative at 15 min and positive (++) at D2 - patch testing gave positive reactions with rosemary (++) and thyme (+) on D2 and D4 - a photopatch test (10 J/cm) with rosemary and thyme showed stronger reactions (+++ and ++, respectively, on D4) - 5 controls were negative	[58]
walked near, and touched, odorous plants	cutaneous lesions on the hand and face; developed edema and eczematous lesions on her hands, eyelids, and face	patch and photopatch test with 1% rosemary extract was positive (+++) - patch and photopatch test with rosemary leaves was positive; more intense with photopatch (++/+++) - hydrophilic and lipophilic rosemary extracts 10%, patch and photopatch tests were positive - patch test with 0.1% carnosol in alcohol was positive - patch test with sage and oregano were negative -5 controls were negative with all	[59]
rosemary leaf plasters applied to knee	after 3 days, acute dermatitis in the application area	positive (++ on D2; +++ on D4) reactions in a patch test with rosemary leaves, but not thyme, origanum, or mint - 10 controls did not react to rosemary leaves	[60]
applied a poultice containing rosemary and thyme	after 24 h, acute, cutaneous, eczematous lesion on right thigh, with vesicles and blisters	positive patch test results with the poultice (++ on D2 and D4); rosemary (++ on D2 and D4); thyme (- on D2, ++ on D4); and colophony (+ on D2 and D4); negative results with arnica, chamomile, and horsetails - 12 controls were negative with rosemary and thyme	[61]
rosemary alcohol applied to chest	swelling of face, chest, and dorsal aspect of arms, followed by peeling	positive reactions were found in patch test with fresh Rosmarinus officinalis (rosemary) leaves (+++ on D2, D3, D4), dry rosemary leaves (+ reaction on D2, D3, D3), dry leaves wetted with water (+ reaction on D2, D3, D3), the flower (++ reaction on D2, D3, D3), and rosemary alcohol ((+ reaction on D2, D3, D3) - negative reactions to 50% aq. rosemary alcohol - positive reactions were also found with sage and lavender	[62]

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ROSEMARY	02A - Bath Oils, Tablets, and Salts	1
ROSEMARY	04C - Powders (dusting and talcum, excluding aftershave talc	1
ROSEMARY	04E - Other Fragrance Preparation	1
ROSEMARY	05A - Hair Conditioner	2
ROSEMARY	05F - Shampoos (non-coloring)	2
ROSEMARY	10A - Bath Soaps and Detergents	1
ROSEMARY	12A - Cleansing	2
ROSEMARY	12C - Face and Neck (exc shave)	2

ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	02A - Bath Oils, Tablets, and Salts	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	02B - Bubble Baths	2
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	03D - Eye Lotion	11
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	03F - Mascara	2
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	03G - Other Eye Makeup Preparations	5
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05A - Hair Conditioner	35
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05C - Hair Straighteners	2
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05E - Rinses (non-coloring)	2
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05F - Shampoos (non-coloring)	46
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05G - Tonics, Dressings, and Other Hair Grooming Aids	17
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05H - Wave Sets	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	05I - Other Hair Preparations	9
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	06D - Hair Shampoos (coloring)	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	07A - Blushers (all types)	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	07C - Foundations	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	07E - Lipstick	7
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	07F - Makeup Bases	3
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	07I - Other Makeup Preparations	4
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	10A - Bath Soaps and Detergents	16
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	10E - Other Personal Cleanliness Products	1
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12A - Cleansing	30
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12C - Face and Neck (exc shave)	42
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12D - Body and Hand (exc shave)	17
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12F - Moisturizing	58
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12G - Night	12
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12H - Paste Masks (mud packs)	16
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12I - Skin Fresheners	12
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	12J - Other Skin Care Preps	27
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	13A - Suntan Gels, Creams, and Liquids	2
ROSMARINUS OFFICINALIS (ROSEMARY) EXTRACT	13B - Indoor Tanning Preparations	4

ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	03B - Eyeliner	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	03G - Other Eye Makeup Preparations	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05A - Hair Conditioner	6
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05B - Hair Spray (aerosol fixatives)	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05C - Hair Straighteners	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05F - Shampoos (non-coloring)	8
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05H - Wave Sets	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	05I - Other Hair Preparations	7
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	11A - Aftershave Lotion	4
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	12C - Face and Neck (exc shave)	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	12F - Moisturizing	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	12G - Night	1
ROSMARINUS OFFICINALIS (ROSEMARY) FLOWER EXTRACT	12H - Paste Masks (mud packs)	2

ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	02A - Bath Oils, Tablets, and Salts	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	05A - Hair Conditioner	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	05F - Shampoos (non-coloring)	10
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	10E - Other Personal Cleanliness Products	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	12A - Cleansing	1

ROSMARINUS OFFICINALIS (ROSEMARY) LEAF	12F - Moisturizing	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	01A - Baby Shampoos	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	01B - Baby Lotions, Oils, Powders, and Creams	6
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	02A - Bath Oils, Tablets, and Salts	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	02B - Bubble Baths	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	03B - Eyeliner	12
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	03C - Eye Shadow	6
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	03D - Eye Lotion	11
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	03G - Other Eye Makeup Preparations	7
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	04E - Other Fragrance Preparation	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05A - Hair Conditioner	72
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05B - Hair Spray (aerosol fixatives)	4
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05C - Hair Straighteners	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05D - Permanent Waves	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05E - Rinses (non-coloring)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05F - Shampoos (non-coloring)	64
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05G - Tonics, Dressings, and Other Hair Grooming Aids	56
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05H - Wave Sets	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	05I - Other Hair Preparations	19
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	06B - Hair Tints	22
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07B - Face Powders	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07C - Foundations	5
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07D - Leg and Body Paints	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07E - Lipstick	24
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07F - Makeup Bases	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	07I - Other Makeup Preparations	6
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	08A - Basecoats and Undercoats	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	09B - Mouthwashes and Breath Fresheners	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	10A - Bath Soaps and Detergents	38
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	10E - Other Personal Cleanliness Products	7
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	11A - Aftershave Lotion	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	11E - Shaving Cream	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12A - Cleansing	36
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12B - Depilatories	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12C - Face and Neck (exc shave)	73
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12D - Body and Hand (exc shave)	29
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12F - Moisturizing	108
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12G - Night	16
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12H - Paste Masks (mud packs)	11
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12I - Skin Fresheners	8
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	12J - Other Skin Care Preps	18
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF EXTRACT	13A - Suntan Gels, Creams, and Liquids	5
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	01A - Baby Shampoos	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	01B - Baby Lotions, Oils, Powders, and Creams	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	01C - Other Baby Products	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	02A - Bath Oils, Tablets, and Salts	18
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	02B - Bubble Baths	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	02D - Other Bath Preparations	5
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	03D - Eye Lotion	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	03G - Other Eye Makeup Preparations	5
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	04A - Cologne and Toilet waters	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	04B - Perfumes	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	04C - Powders (dusting and talcum, excluding aftershave talc	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	04E - Other Fragrance Preparation	19
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05A - Hair Conditioner	18
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05B - Hair Spray (aerosol fixatives)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05E - Rinses (non-coloring)	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05F - Shampoos (non-coloring)	42
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05G - Tonics, Dressings, and Other Hair Grooming Aids	13

ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	05I - Other Hair Preparations	10
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	06D - Hair Shampoos (coloring)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	07B - Face Powders	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	07D - Leg and Body Paints	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	07I - Other Makeup Preparations	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	09B - Mouthwashes and Breath Fresheners	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	09C - Other Oral Hygiene Products	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	10A - Bath Soaps and Detergents	32
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	10B - Deodorants (underarm)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	10E - Other Personal Cleanliness Products	6
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	11A - Aftershave Lotion	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	11D - Preshave Lotions (all types)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	11E - Shaving Cream	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	11G - Other Shaving Preparation Products	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12A - Cleansing	26
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12C - Face and Neck (exc shave)	66
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12D - Body and Hand (exc shave)	61
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12E - Foot Powders and Sprays	4
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12F - Moisturizing	56
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12G - Night	4
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12H - Paste Masks (mud packs)	14
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12I - Skin Fresheners	15
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	12J - Other Skin Care Preps	66
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	13A - Suntan Gels, Creams, and Liquids	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF OIL	13B - Indoor Tanning Preparations	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF POWDER	12C - Face and Neck (exc shave)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	05A - Hair Conditioner	3
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	05F - Shampoos (non-coloring)	10
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	05G - Tonics, Dressings, and Other Hair Grooming Aids	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	07C - Foundations	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	07H - Makeup Fixatives	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	12F - Moisturizing	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	12H - Paste Masks (mud packs)	1
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	12I - Skin Fresheners	2
ROSMARINUS OFFICINALIS (ROSEMARY) LEAF WATER	12J - Other Skin Care Preps	1
ROSMARINUS OFFICINALIS (ROSEMARY) WATER	12C - Face and Neck (exc shave)	1

Personal Care Products Council
Committed to Safety, Quality & Innovation
1101 17th Street, N.W., Suite 300
Washington, D.C. 20036-4702

Memorandum

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

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

DATE: September 10, 2013

SUBJECT: Studies on a Product Containing 0.2% Rosmarinus Officinalis (Rosemary) Leaf Extract

KGL, Inc. (Ivy Laboratories). 1998. An evaluation of the contact-sensitization potential of a topical coaded product in human skin by means of the maximization assay (product contains 0.2% Rosmarinus Officinalis (Rosemary) Leaf Extract).

Anonymous. 1998. Human patch test of a product containing 0.2% Rosmarinus Officinalis (Rosemary) Leaf Extract.

FINAL REPORT November 13, 1998

KGL Protocol: #4384

Sample: Sunscreen Cream [redacted]

University City Science Center
3401 Market Street - Suite 226
Philadelphia, PA 19104-3355 (USA)

Telephone: [215] 387-8400
FAX: [215] 387-1046

IR 43844

Title: An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

[redacted]

Contains 0.2% Rosmarinus officinalis (Rosemary) Leaf Extract

Principal Investigator: Kays Kajdbey, M.D. (Board Certified Dermatologist)

Testing Facility: Ivy Laboratories (KGL, INC.)
University City Science Center
3401 Market Street
Suite 226 and Suite 232
Philadelphia, PA 19104-3355
(Phone: 215-387-8400)

Protocol: KGL Protocol #4384

Final Report Date: November 13, 1998

Kays Kajdbey, M.D.
Investigator

November 13, 1998
Date

FINAL REPORT

PROTOCOL:

Ivy Laboratories - KGL Protocol #4384

[redacted]

SPONSOR STUDY:

Letter Dated: September 28, 1998

TITLE:

Evaluation of the contact-sensitizing potential of a test agent.

OBJECTIVE:

The objective of this study is to assess the skin sensitizing potential of any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

TEST MATERIAL:

The test sample, supplied by the sponsor, was a product labeled Sunscreen Cream [redacted] and tested as supplied viz., neat.

TEST PRODUCT ACCOUNTABILITY:

All test samples and materials were received in good condition by our Quality Assurance Department. The test materials and quantities were checked for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory director and the investigator (physician). All test materials were stored under ambient conditions in an inaccessible location under the supervision of the investigator.

PRINCIPAL INVESTIGATOR:

Kays Kaidbey, M.D. (Board Certified Dermatologist)

Medical Director, KGL, INC.

KGL TECHNICIANS:

Angelit Barnes (Patcher)

John B. Chicchi (Expert Grader)

STUDY LOCATION:

Ivy Laboratories (KGL, INC.)

3401 Market Street - Suite 226

Philadelphia, PA 19104

CONDUCTION DATES:

This study was conducted from October 5, 1998 through November 6, 1998

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics. The criteria for exclusion were:

1 - History of sun hypersensitivity and photosensitive dermatoses

2 - History of drug hypersensitivity or recurrent dermatological diseases

3 - Pregnancy or mothers who are breastfeeding

4 - Scars, moles or other blemishes over the test site which can interfere with the study

5 - Recent sunburn

6 - Subjects receiving systemic or topical drugs or medications, including potential sensitizers within the previous 4 weeks

7 - Other medical conditions considered by the investigator as sound reasons for disqualification from enrollment into the study.

INFORMED CONSENT:

After the protocol, reasons for the study, possible associated risks and potential benefits or risks of the treatment had been completely explained, signed, informed

subject consent was obtained from each volunteer prior to the start of the study. Copies of all consent forms are on file at Ivy Laboratories (KGL, INC.). Each subject was assigned a permanent identification number and completed a Medical History Form. These forms are also on file at Ivy Laboratories.

METHOD:

Patches were applied to the upper outer arm, volar forearm or the back of each subject. The entire test was composed of two distinct phases: (1) an Induction phase and (2) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.1ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.1ml of the test material coded [redacted] (Sunscreen Cream) was applied to the same site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Challenge Phase**:

After a ten day rest period which follows the last induction patch application, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm or side of back in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.1ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and the test material was applied to the same site. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded one hour later and again 24 hours later for any reaction.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	GRADES:	CLASSIFICATION:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

RESULTS:

Twenty-eight healthy, adult volunteers of both sexes who satisfied the inclusion criteria were enrolled into this study. There were 7 males and 21 females ranging in age from 18 to 54 years. One subject (#04, initials H.J.K., a female) was dropped from the study because she failed to return for the challenge phase and was lost to follow-up. The remaining 27 subjects completed this investigation as outlined in the protocol. The demographic data are shown in Table 1. No other adverse or unexpected reactions were seen in any of the panelists during the induction phase. The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Sunscreen Cream coded [redacted] does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	S.B.B.	42	M	B
02	D.K.I.	23	F	A
03	E.V.R.	54	M	B
04	H.J.K.	21	F	A
05	C. - R.	33	F	B
06	L. - T.	41	F	C
07	A.M.S.	31	F	C
08	A.L.W.	19	F	C
09	K.D.R.	18	F	C
10	J. - S.	33	F	B
11	E.R.M.	18	F	C
12	D. - C.	25	F	B
13	R.N.B.	34	F	B
14	D.N.N.	47	M	C
15	M.D.M.	34	F	C
16	J.E.L.	21	F	C
17	J.M.B.	26	F	C
18	D.A.C.	45	F	C
19	E. - G.	21	M	C
20	M.S.B.	19	M	C
21	R.C.C.	21	F	C
22	A.E.MCC.	19	F	C
23	M.E.W.	20	M	C
24	N.M.R.	19	F	B
25	K.A.F.	42	M	B
26	R. - P.	19	F	C
27	K.T.C.	21	F	C
28	J.T.MCN.	32	F	B

A = Asian
B = Black
C = Caucasian

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Sunscreen Cream coded [redacted]

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	0	0
03	0	0
04	Dropped from study	Dropped from study
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0
26	0	0
27	0	0
28	0	0

Challenge Readings:

48-Hour Reading - November 5, 1998
72-Hour Reading - November 6, 1998

[redacted]

RESEARCH AND DEVELOPMENT
CLINICAL EVALUATION DEPARTMENT

CLINICAL EVALUATION REPORT: HUMAN PATCH TEST

This test follows the procedure described in SOP, HPT.1

[redacted]

PRODUCT PROFILE NO: [redacted] DATE: May 15, 1998 NOTEBOOK REF.: APTC-1153-98
NB# 7465-02

1. TEST MATERIAL: [redacted] Cream contains 0.2 % Rosmarinus Officinalis Leaf Extract.

2. CONTROL MATERIAL: [redacted] Cream.

3. TEST PROCEDURE:

Single-Insult (24hr.) X Occlusive (Blenderm) Patch X Semi-Occlusive Patch_____.

4. CONCENTRATION:

Full-Strength X Aqueous _____% Solution _____ Dispersion_____ Aqueous Paste_____.
Other:_____.

__ Volatiles were allowed to evaporate on the patch _____. Patch was hydrated just prior to application to skin_____.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
		0	±	1	1+	2	2+	3	3+	4	PII
[redacted] Cream [redacted]	20	20	0	0	0	0	0	0	0	0	0.00
[redacted] Cream [redacted]	20	20	0	0	0	0	0	0	0	0	0.00

_ Skin staining noted. Erythematous response were read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). X.

B. _____.

Data Submitted By: [redacted] **Read/Understood By:** [redacted]

Approved By: _____
Norman B. Kanof, M.D.
Consulting Dermatologist

* SCORE
0 = No evidence of any effect.
± (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by adding the Irritation Score and dividing by the total number of test subjects.

[redacted]

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: October 8, 2013

SUBJECT: HRIPT on a Product Containing Rosmarinus Officinalis (Rosemary) Leaf Oil

Clinical Research Services. 2007. Human repeat insult patch test of a massage oil containing 1.5% Rosmarinus Officinalis (Rosemary) Leaf Oil.

Clinical Research Services
Clinical & Biomedical Testing

Human Repeat Insult Patch Test
Study C07-0006
[redacted] 07-258-CRS)

Leave-on massage oil
Contains
1.5%
Rosmarinus
Officinalis
Leaf
Oil in finished
product.

Sample
07-258-CRS
[redacted]

October 31, 2007

Prepared for:

[redacted]

U.W. Parkside - Tallent Hall - Kenosha, WI 53141 - Phone (262) 595-2185 - Fax (262) 595-2555

Human Repeat Insult Patch Test
Study Number C07-0006
September 10 - October 19, 2007

Abstract

One-hundred-four (104) healthy male and female subjects between the ages of 18 and 70 completed a six-week repeat insult patch test.

During the 'Induction Phase' no irritation was observed to the test agent. A modified Berger/Bowman cumulative score is shown below for comparison to distilled water and sodium lauryl sulfate (SLS) controls.[5]

Sample	Concentration	Cumulative Score	Interpretation
07-258-CRS [redacted]	Neat	0	Mild Test Agent. No irritation anticipated with normal use.
Deionized Water	-	0	Control
SLS	0.5%	2511	Cumulative Irritant

During the 'Challenge Phase' no irritation was observed.

Conclusion

Based on the results of the present study, there is no indication of allergic contact dermatitis to sample '07-258-CRS'.

Purpose:

This study evaluated the potential of the Sponsor's test materials to induce irritant and allergic contact dermatitis.

Materials:

The Sponsor provided the following sample:

07-258-CRS ([redacted])

A *Test Material Identification Form* describes the sample received by Clinical Research (Appendix I). The Sponsor was responsible for the stability, purity and characterization of the test materials.

Subject Selection:

One-hundred-four (104) male and female subjects completed the study. Subjects were admitted to the study at the discretion of the Principal Investigator based on the medical history, study criteria and pre-study interview and examination.

Inclusion Criteria

1. Age: 18-70

2. Gender: Males and Females

3. Subjects who were in good health as determined by the health questionnaire. (Appendix II)

4. Subjects who met all eligibility requirements. (Appendix III)

5. Subjects who would not use other treatments on the skin (i.e., soaps, lotions, ointments, etc.) that would interfere with the test.

6. Subjects who were willing to comply with the study directions.

7. Subject who could comprehend and complete an Informed Consent Agreement. (Appendix IV).

Exclusion Criteria

1. Anyone with an uncontrolled metabolic disorder (e.g., diabetes, hyperthyroidism, etc.), active psoriasis, active eczema, acne or tattoos (on test areas), skin infection, skin cancer, or with active, or a history of atopic dermatitis.

2. Subjects who were taking medications that the investigator knew would interfere with the study (e.g., steroids, anti-cancer, immunosuppressive or anti-inflammatory drugs, etc.).

3. Female subjects who were pregnant, nursing, or planning a pregnancy within six months.

4. Subjects with suntans and/or sunburns.

5. Subjects with excessive hair on the back or arms that might interfere with the placement of patches.

6. Subjects who were in, or had participated in, other patch tests within the past 30 days.

7. Subjects who were taking retinoid preparations (e.g., Retin-A, Accutane, Tegison, etc.)

Subject Numbering

Each subject admitted to the study was assigned a unique three digit number. This number remained with the subject throughout the study. Subjects 013, 014, 063 and 103 withdrew from the study for reasons unrelated to testing (Appendix V). Their data was removed from the final analysis. Only the study number and subject number are used in all references to a specific subject.

Methods:[1, 2, 3, 4, 5]

Induction Phase:

An occlusive patch was used for the present study. It consisted of a 1 cm^2 Novanette® patch held on all sides with 3M Micropore® tape. Blenderm® covertape was used for occlusion. The test agent was applied neat at a dose of approximately 50μl per patch.

Subjects were instructed to wear the patch for approximately 48 hours. They were asked to remove their patches at home. Patches were reapplied to the subjects' back approximately every 48 hours for a total of nine (9) exposures. Scoring of each test area was done by a clinical grader. (Appendix VI) Subsequent patches in the induction series were returned to the original location, provided it was clear of reactions. A patch was relocated if there was a score of 2 or greater for erythema with or without edema, papules, vesicles, bullae, or spreading of the reaction. There were two alternate locations for each sample. If the original and both alternate areas had residual reaction, the test sample was stopped until the Challenge Phase. A positive control patch,

(0.5% sodium lauryl sulfate), and a negative control patch, (distilled water) were also applied. The positive control patch was stopped when the score reached a 3 or greater for erythema, or edema or papules with erythema, or vesicles, bullae, or spreading with or without erythema.

Subjects were provided written instructions for the patch test (Appendix VII). Subjects were asked not to get the patches wet. They were allowed to shower, but bathing, swimming and suntanning was prohibited.

Rest Phase

There was a rest phase of approximately 12 to 14 days between the Induction and the Challenge Phase. No patches were applied.

Challenge Phase

A challenge patch was returned to the original site on the back. In addition, an alternate patch was placed on the upper arm. The alternate patch system helps to reduce the incidence of false positive scores. Both patches were worn for approximately 48 hours. The patches were removed by the subjects at home. The test areas were scored at 48 hours and again at 96 hours. Subjects were under the same constraints as in the Induction Phase.

Statistical Methods:

Induction Phase statistics are reported by 'Day' and as the 'Cumulative Response'. The frequency, percent of the total, a cumulative frequency and cumulative percent is given.

In addition, a standardized system of interpretation has been adopted from the 14-day cumulative irritant study described by Berger and Bowman.[5] A single 'Cumulative Score' is reported for each sample. A Berger/Bowman category is then assigned to each test agent (Appendix VIII).

Challenge Phase scores are reported at 48 and 96 hours. The frequency, percent of the total, a cumulative frequency and cumulative percent is given.

Results

One-hundred-four (104) healthy male and female subjects between the ages of 18 and 70 completed the six-week repeat insult patch test. Cumulative and daily scores are shown in the tabbed sections labeled 'Induction Phase' and 'Challenge Phase'. In addition, a single cumulative score for the sample is shown in table 1. A standardized system of interpretation had been adopted from the 14-day cumulative irritant study described by Berger/Bowman.[5] The total score for each sample is normalized to a base 100. This is done by multiplying the total score by (100/number of participants). A Berger/Bowman category is then assigned to each test agent.

During the 'Induction Phase' no irritation was observed.

Table 1

Sample	Concentration	Exposure	Patch	Score	Interpretation
07-258-CRS [redacted]	Neat	48 hours	Occlusive	0	Mild Test Agent. No irritation anticipated with normal use.
Deionized Water	-	48 hours	Occlusive	0	Control
SLS	0.5%	48 hours	Occlusive	2511	Cumulative Irritant

During the 'Challenge Phase' no irritation was observed.

Conclusion

Based on the results of the present study, there is no indication of allergic contact dermatitis to sample '07-258-CRS'.

John Seitz PA-C Date 11/12/07
Clinical Research Services, Inc.

Ken Pechman, M.D., Ph.D. Date 11/16/07
Medical Investigator/Dermatologist

References:

[1]S Fregert and DH Bandmann, **Patch Testing**, Springer-Verlag Publ., New York, 1975.

[2]J Serup and GB Jemec (eds.) **Non-Invasive Methods and the Skin**, Chapters 29.2 and 31.2, CRC Press, Boca Raton, FL, 1995.

[3]American Academy of Dermatology, **Diagnostic Patch Test Technique**, Hermal Pharmaceutical Video Series, Oak Hill, New York, 1990.

[4]Food and Drug Administration, **Good Clinical Practices**, Federal Register: Volume 62, Number 90, pages 25691-25709, May 9, 1997.

[5]RS Berger and JP Bowman. **A Reappraisal of the 21-day Cumulative Irritation Test**, J. Toxicol - Cutaneous & Ocular Toxicol., 1(2):109-115, 1982.

HRIPT Study C07-0006
Induction Phase - Cumulative Scores
Sample 07-258-CRS
September 10 - October 19, 2007

The FREQ Procedure

sample	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	931	99.47	931	99.47
N9G	5	0.53	936	100.00

water	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	931	99.47	931	99.47
N9G	5	0.53	936	100.00

sls	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	46	4.91	46	4.91
0.5	1	0.11	47	5.02
1	17	1.82	64	6.84
2	2	0.21	66	7.05
2e	48	5.13	114	12.18
3	44	4.70	158	16.88
3e	12	1.28	170	18.16
N9G	5	0.53	175	18.70
X	761	81.30	936	100.00

HRIPT Study C07-0006
Induction Phase - Daily Scores
Sample 07-258-CRS
September 10 - October 19, 2007

---------- day=2 ----------

The FREQ Procedure

sample	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	104	100.00	104	100.00

water	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	104	100.00	104	100.00

sls	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	8	7.69	8	7.69
0.5	1	0.96	9	8.65
1	3	2.88	12	11.54
2	2	1.92	14	13.46
2e	11	10.58	25	24.04
3	19	18.27	44	42.31
3e	5	4.81	49	47.12
X	55	52.88	104	100.00

HRIPT Study C07-0006
Induction Phase - Daily Scores
Sample 07-258-CRS
September 10 - October 19, 2007

---------- day=4 ----------

The FREQ Procedure

sample	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	104	100.00	104	100.00

water	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	104	100.00	104	100.00

sls	Frequency	Percent	Cumulative Frequency	Cumulative Percent
2e	3	2.88	3	2.88
X	101	97.12	104	100.00

HRIPT Study C07-0006
Induction Phase - Daily Scores
Sample 07-258-CRS
September 10 - October 19, 2007

---------- day=6 ----------

The FREQ Procedure

sample	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	104	100.00	104	100.00

water	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	104	100.00	104	100.00

sls	Frequency	Percent	Cumulative Frequency	Cumulative Percent
X	104	100.00	104	100.00

HRIPT Study C07-0006
Induction Phase - Daily Scores
Sample 07-258-CRS
September 10 - October 19, 2007

---------- day=8 ----------

The FREQ Procedure

sample	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	104	100.00	104	100.00

water	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	104	100.00	104	100.00

sls	Frequency	Percent	Cumulative Frequency	Cumulative Percent
X	104	100.00	104	100.00

HRIPT Study C07-0006
Induction Phase
Sample 07-258-CRS
September 10 - October 19, 2007

	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
2	1	1	0	0	3
3	1	2	0	0	X
4	1	3	0	0	X
5	1	4	0	0	X
6	1	5	0	0	X
7	1	6	0	0	X
8	1	7	0	0	X
9	1	8	0	0	X
10	1	9	0	0	X
11					
12	2	1	0	0	0
13	2	2	0	0	0
14	2	3	0	0	0
15	2	4	0	0	2e
16	2	5	0	0	X
17	2	6	0	0	X
18	2	7	0	0	X
19	2	8	0	0	X
20	2	9	0	0	X
21					
22	3	1	0	0	2e
23	3	2	0	0	X
24	3	3	0	0	X
25	3	4	0	0	X
26	3	5	0	0	X
27	3	6	0	0	X
28	3	7	0	0	X
29	3	8	0	0	X
30	3	9	0	0	X
31					
32	4	1	0	0	0
33	4	2	0	0	3e
34	4	3	0	0	X
35	4	4	0	0	X
36	4	5	0	0	X
37	4	6	0	0	X
38	4	7	0	0	X
39	4	8	0	0	X
40	4	9	0	0	X
41					
42	5	1	0	0	3
43	5	2	0	0	X
44	5	3	0	0	X
45	5	4	0	0	X
46	5	5	0	0	X
47	5	6	0	0	X
48	5	7	0	0	X
49	5	8	0	0	X
50	5	9	0	0	X
51					

HRIPT Study C07-0006
Induction Phase
Sample 07-258-CRS
September 10 - October 19, 2007

	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
102	11	1	0	0	2e
103	11	2	0	0	X
104	11	3	0	0	X
105	11	4	0	0	X
106	11	5	0	0	X
107	11	6	0	0	X
108	11	7	0	0	X
109	11	8	0	0	X
110	11	9	0	0	X
111					
112	12	1	0	0	3
113	12	2	0	0	X
114	12	3	0	0	X
115	12	4	0	0	X
116	12	5	0	0	X
117	12	6	0	0	X
118	12	7	0	0	X
119	12	8	0	0	X
120	12	9	0	0	X
121					
122	15	1	0	0	3
123	15	2	0	0	X
124	15	3	0	0	X
125	15	4	0	0	X
126	15	5	0	0	X
127	15	6	0	0	X
128	15	7	0	0	X
129	15	8	0	0	X
130	15	9	0	0	X
131					
132	16	1	0	0	0
133	16	2	0	0	0
134	16	3	0	0	3
135	16	4	0	0	X
136	16	5	0	0	X
137	16	6	0	0	X
138	16	7	0	0	X
139	16	8	0	0	X
140	16	9	0	0	X
141					
142	17	1	0	0	2e
143	17	2	0	0	X
144	17	3	0	0	X
145	17	4	0	0	X
146	17	5	0	0	X
147	17	6	0	0	X
148	17	7	0	0	X
149	17	8	0	0	X
150	17	9	0	0	X
151					

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	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
202	23	1	0	0	3
203	23	2	0	0	X
204	23	3	0	0	X
205	23	4	0	0	X
206	23	5	0	0	X
207	23	6	0	0	X
208	23	7	0	0	X
209	23	8	0	0	X
210	23	9	0	0	X
211					
212	24	1	0	0	0
213	24	2	0	0	3e
214	24	3	0	0	X
215	24	4	0	0	X
216	24	5	0	0	X
217	24	6	0	0	X
218	24	7	0	0	X
219	24	8	0	0	X
220	24	9	0	0	X
221					
222	25	1	0	0	3
223	25	2	0	0	X
224	25	3	0	0	X
225	25	4	0	0	X
226	25	5	0	0	X
227	25	6	0	0	X
228	25	7	0	0	X
229	25	8	0	0	X
230	25	9	0	0	X
231					
232	26	1	0	0	0
233	26	2	0	0	3
234	26	3	0	0	X
235	26	4	0	0	X
236	26	5	0	0	X
237	26	6	0	0	X
238	26	7	0	0	X
239	26	8	0	0	X
240	26	9	0	0	X
241					
242	27	1	0	0	1
243	27	2	0	0	2e
244	27	3	0	0	X
245	27	4	0	0	X
246	27	5	0	0	X
247	27	6	0	0	X
248	27	7	0	0	X
249	27	8	0	0	X
250	27	9	N9G	N9G	N9G
251					

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Induction Phase
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	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
302	33	1	0	0	3
303	33	2	0	0	X
304	33	3	0	0	X
305	33	4	0	0	X
306	33	5	0	0	X
307	33	6	0	0	X
308	33	7	0	0	X
309	33	8	0	0	X
310	33	9	0	0	X
311					
312	34	1	0	0	3
313	34	2	0	0	X
314	34	3	0	0	X
315	34	4	0	0	X
316	34	5	0	0	X
317	34	6	0	0	X
318	34	7	0	0	X
319	34	8	0	0	X
320	34	9	0	0	X
321					
322	35	1	0	0	0
323	35	2	0	0	3
324	35	3	0	0	X
325	35	4	0	0	X
326	35	5	0	0	X
327	35	6	0	0	X
328	35	7	0	0	X
329	35	8	0	0	X
330	35	9	0	0	X
331					
332	36	1	0	0	0
333	36	2	0	0	2e
334	36	3	0	0	X
335	36	4	0	0	X
336	36	5	0	0	X
337	36	6	0	0	X
338	36	7	0	0	X
339	36	8	0	0	X
340	36	9	0	0	X
341					
342	37	1	0	0	0
343	37	2	0	0	0.5
344	37	3	0	0	2e
345	37	4	0	0	X
346	37	5	0	0	X
347	37	6	0	0	X
348	37	7	0	0	X
349	37	8	0	0	X
350	37	9	0	0	X
351					

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	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
402	43	1	0	0	2e
403	43	2	0	0	X
404	43	3	0	0	X
405	43	4	0	0	X
406	43	5	0	0	X
407	43	6	0	0	X
408	43	7	0	0	X
409	43	8	0	0	X
410	43	9	0	0	X
411					
412	44	1	0	0	3e
413	44	2	0	0	X
414	44	3	0	0	X
415	44	4	0	0	X
416	44	5	0	0	X
417	44	6	0	0	X
418	44	7	0	0	X
419	44	8	0	0	X
420	44	9	0	0	X
421					
422	45	1	0	0	2e
423	45	2	0	0	X
424	45	3	0	0	X
425	45	4	0	0	X
426	45	5	0	0	X
427	45	6	0	0	X
428	45	7	0	0	X
429	45	8	0	0	X
430	45	9	0	0	X
431					
432	46	1	0	0	2e
433	46	2	0	0	X
434	46	3	0	0	X
435	46	4	0	0	X
436	46	5	0	0	X
437	46	6	0	0	X
438	46	7	0	0	X
439	46	8	0	0	X
440	46	9	0	0	X
441					
442	47	1	0	0	0
443	47	2	0	0	3
444	47	3	0	0	X
445	47	4	0	0	X
446	47	5	0	0	X
447	47	6	0	0	X
448	47	7	0	0	X
449	47	8	0	0	X
450	47	9	0	0	X
451					

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	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
502	53	1	0	0	2e
503	53	2	0	0	X
504	53	3	0	0	X
505	53	4	0	0	X
506	53	5	0	0	X
507	53	6	0	0	X
508	53	7	0	0	X
509	53	8	0	0	X
510	53	9	0	0	X
511					
512	54	1	0	0	0
513	54	2	0	0	3e
514	54	3	0	0	X
515	54	4	0	0	X
516	54	5	0	0	X
517	54	6	0	0	X
518	54	7	0	0	X
519	54	8	0	0	X
520	54	9	N9G	N9G	N9G
521					
522	55	1	0	0	1
523	55	2	0	0	0
524	55	3	0	0	2e
525	55	4	0	0	X
526	55	5	0	0	X
527	55	6	0	0	X
528	55	7	0	0	X
529	55	8	0	0	X
530	55	9	0	0	X
531					
532	56	1	0	0	0
533	56	2	0	0	2
534	56	3	0	0	3
535	56	4	0	0	X
536	56	5	0	0	X
537	56	6	0	0	X
538	56	7	0	0	X
539	56	8	0	0	X
540	56	9	0	0	X
541					
542	57	1	0	0	0
543	57	2	0	0	2e
544	57	3	0	0	X
545	57	4	0	0	X
546	57	5	0	0	X
547	57	6	0	0	X
548	57	7	0	0	X
549	57	8	0	0	X
550	57	9	0	0	X
551					

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	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
602	64	1	0	0	3
603	64	2	0	0	X
604	64	3	0	0	X
605	64	4	0	0	X
606	64	5	0	0	X
607	64	6	0	0	X
608	64	7	0	0	X
609	64	8	0	0	X
610	64	9	0	0	X
611					
612	65	1	0	0	3e
613	65	2	0	0	X
614	65	3	0	0	X
615	65	4	0	0	X
616	65	5	0	0	X
617	65	6	0	0	X
618	65	7	0	0	X
619	65	8	0	0	X
620	65	9	0	0	X
621					
622	66	1	0	0	1
623	66	2	0	0	3
624	66	3	0	0	X
625	66	4	0	0	X
626	66	5	0	0	X
627	66	6	0	0	X
628	66	7	0	0	X
629	66	8	0	0	X
630	66	9	0	0	X
631					
632	67	1	0	0	2e
633	67	2	0	0	X
634	67	3	0	0	X
635	67	4	0	0	X
636	67	5	0	0	X
637	67	6	0	0	X
638	67	7	0	0	X
639	67	8	0	0	X
640	67	9	0	0	X
641					
642	68	1	0	0	2e
643	68	2	0	0	X
644	68	3	0	0	X
645	68	4	0	0	X
646	68	5	0	0	X
647	68	6	0	0	X
648	68	7	0	0	X
649	68	8	0	0	X
650	68	9	0	0	X
651					

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	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
702	74	1	0	0	2e
703	74	2	0	0	X
704	74	3	0	0	X
705	74	4	0	0	X
706	74	5	0	0	X
707	74	6	0	0	X
708	74	7	0	0	X
709	74	8	0	0	X
710	74	9	0	0	X
711					
712	75	1	0	0	1
713	75	2	0	0	3
714	75	3	0	0	X
715	75	4	0	0	X
716	75	5	0	0	X
717	75	6	0	0	X
718	75	7	0	0	X
719	75	8	0	0	X
720	75	9	0	0	X
721					
722	76	1	0	0	0
723	76	2	0	0	2e
724	76	3	0	0	X
725	76	4	0	0	X
726	76	5	0	0	X
727	76	6	0	0	X
728	76	7	0	0	X
729	76	8	0	0	X
730	76	9	0	0	X
731					
732	77	1	0	0	2e
733	77	2	0	0	X
734	77	3	0	0	X
735	77	4	0	0	X
736	77	5	0	0	X
737	77	6	0	0	X
738	77	7	0	0	X
739	77	8	0	0	X
740	77	9	0	0	X
741					
742	78	1	0	0	0
743	78	2	0	0	2e
744	78	3	0	0	X
745	78	4	0	0	X
746	78	5	0	0	X
747	78	6	0	0	X
748	78	7	0	0	X
749	78	8	0	0	X
750	78	9	0	0	X
751					

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	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
802	84	1	0	0	0
803	84	2	0	0	3
804	84	3	0	0	X
805	84	4	0	0	X
806	84	5	0	0	X
807	84	6	0	0	X
808	84	7	0	0	X
809	84	8	0	0	X
810	84	9	0	0	X
811					
812	85	1	0	0	3
813	85	2	0	0	X
814	85	3	0	0	X
815	85	4	0	0	X
816	85	5	0	0	X
817	85	6	0	0	X
818	85	7	0	0	X
819	85	8	0	0	X
820	85	9	0	0	X
821					
822	86	1	0	0	2e
823	86	2	0	0	X
824	86	3	0	0	X
825	86	4	0	0	X
826	86	5	0	0	X
827	86	6	0	0	X
828	86	7	0	0	X
829	86	8	0	0	X
830	86	9	0	0	X
831					
832	87	1	0	0	0
833	87	2	0	0	2e
834	87	3	0	0	X
835	87	4	0	0	X
836	87	5	0	0	X
837	87	6	0	0	X
838	87	7	0	0	X
839	87	8	0	0	X
840	87	9	0	0	X
841					
842	88	1	0	0	3
843	88	2	0	0	X
844	88	3	0	0	X
845	88	4	0	0	X
846	88	5	0	0	X
847	88	6	0	0	X
848	88	7	0	0	X
849	88	8	0	0	X
850	88	9	0	0	X
851					

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	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
902	94	1	0	0	0
903	94	2	0	0	0
904	94	3	0	0	1
905	94	4	0	0	2e
906	94	5	0	0	X
907	94	6	0	0	X
908	94	7	0	0	X
909	94	8	0	0	X
910	94	9	0	0	X
911					
912	95	1	0	0	3
913	95	2	0	0	X
914	95	3	0	0	X
915	95	4	0	0	X
916	95	5	0	0	X
917	95	6	0	0	X
918	95	7	0	0	X
919	95	8	0	0	X
920	95	9	0	0	X
921					
922	96	1	0	0	2e
923	96	2	0	0	X
924	96	3	0	0	X
925	96	4	0	0	X
926	96	5	0	0	X
927	96	6	0	0	X
928	96	7	0	0	X
929	96	8	0	0	X
930	96	9	0	0	X
931					
932	97	1	0	0	0
933	97	2	0	0	1
934	97	3	0	0	2e
935	97	4	0	0	X
936	97	5	0	0	X
937	97	6	0	0	X
938	97	7	0	0	X
939	97	8	0	0	X
940	97	9	0	0	X
941					
942	98	1	0	0	3e
943	98	2	0	0	X
944	98	3	0	0	X
945	98	4	0	0	X
946	98	5	0	0	X
947	98	6	0	0	X
948	98	7	0	0	X
949	98	8	0	0	X
950	98	9	0	0	X
951					

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	A	B	C	D	E
1	Subject	Day	Sample	Water	SLS
1002	105	1	0	0	3e
1003	105	2	0	0	X
1004	105	3	0	0	X
1005	105	4	0	0	X
1006	105	5	0	0	X
1007	105	6	0	0	X
1008	105	7	0	0	X
1009	105	8	0	0	X
1010	105	9	0	0	X
1011					
1012	106	1	0	0	2e
1013	106	2	0	0	X
1014	106	3	0	0	X
1015	106	4	0	0	X
1016	106	5	0	0	X
1017	106	6	0	0	X
1018	106	7	0	0	X
1019	106	8	0	0	X
1020	106	9	0	0	X
1021					
1022	107	1	0	0	3
1023	107	2	0	0	X
1024	107	3	0	0	X
1025	107	4	0	0	X
1026	107	5	0	0	X
1027	107	6	0	0	X
1028	107	7	0	0	X
1029	107	8	0	0	X
1030	107	9	0	0	X
1031					
1032	108	1	0	0	0
1033	108	2	0	0	3
1034	108	3	0	0	X
1035	108	4	0	0	X
1036	108	5	0	0	X
1037	108	6	0	0	X
1038	108	7	0	0	X
1039	108	8	0	0	X
1040	108	9	0	0	X

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Sample - 07-258-CRS
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---------- site=Original time=48Hours ----------

The FREQ Procedure

sample	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	104	100.00	104	100.00

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---------- site=Original time=96Hours ----------

The FREQ Procedure

sample	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	104	100.00	104	100.00

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	A	B	C	D
1	Subject	Site	Time	Sample
2	1	Original	48Hours	0
3	1	Alternate	48Hours	0
4	1	Original	96Hours	0
5	1	Alternate	96Hours	0
6				
7	2	Original	48Hours	0
8	2	Alternate	48Hours	0
9	2	Original	96Hours	0
10	2	Alternate	96Hours	0
11				
12	3	Original	48Hours	0
13	3	Alternate	48Hours	0
14	3	Original	96Hours	0
15	3	Alternate	96Hours	0
16				
17	4	Original	48Hours	0
18	4	Alternate	48Hours	0
19	4	Original	96Hours	0
20	4	Alternate	96Hours	0
21				
22	5	Original	48Hours	0
23	5	Alternate	48Hours	0
24	5	Original	96Hours	0
25	5	Alternate	96Hours	0
26				
27	6	Original	48Hours	0
28	6	Alternate	48Hours	0
29	6	Original	96Hours	0
30	6	Alternate	96Hours	0
31				
32	7	Original	48Hours	0
33	7	Alternate	48Hours	0
34	7	Original	96Hours	0
35	7	Alternate	96Hours	0
36				
37	8	Original	48Hours	0
38	8	Alternate	48Hours	0
39	8	Original	96Hours	0
40	8	Alternate	96Hours	0
41				
42	9	Original	48Hours	0
43	9	Alternate	48Hours	0
44	9	Original	96Hours	0
45	9	Alternate	96Hours	0
46				
47	10	Original	48Hours	0
48	10	Alternate	48Hours	0
49	10	Original	96Hours	0
50	10	Alternate	96Hours	0
51				

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	A	B	C	D
1	Subject	Site	Time	Sample
102	23	Original	48Hours	0
103	23	Alternate	48Hours	0
104	23	Original	96Hours	0
105	23	Alternate	96Hours	0
106				
107	24	Original	48Hours	0
108	24	Alternate	48Hours	0
109	24	Original	96Hours	0
110	24	Alternate	96Hours	0
111				
112	25	Original	48Hours	0
113	25	Alternate	48Hours	0
114	25	Original	96Hours	0
115	25	Alternate	96Hours	0
116				
117	26	Original	48Hours	0
118	26	Alternate	48Hours	0
119	26	Original	96Hours	0
120	26	Alternate	96Hours	0
121				
122	27	Original	48Hours	0
123	27	Alternate	48Hours	0
124	27	Original	96Hours	0
125	27	Alternate	96Hours	0
126				
127	28	Original	48Hours	0
128	28	Alternate	48Hours	0
129	28	Original	96Hours	0
130	28	Alternate	96Hours	0
131				
132	29	Original	48Hours	0
133	29	Alternate	48Hours	0
134	29	Original	96Hours	0
135	29	Alternate	96Hours	0
136				
137	30	Original	48Hours	0
138	30	Alternate	48Hours	0
139	30	Original	96Hours	0
140	30	Alternate	96Hours	0
141				
142	31	Original	48Hours	0
143	31	Alternate	48Hours	0
144	31	Original	96Hours	0
145	31	Alternate	96Hours	0
146				
147	32	Original	48Hours	0
148	32	Alternate	48Hours	0
149	32	Original	96Hours	0
150	32	Alternate	96Hours	0
151				

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	A	B	C	D
1	Subject	Site	Time	Sample
202	43	Original	48Hours	0
203	43	Alternate	48Hours	0
204	43	Original	96Hours	0
205	43	Alternate	96Hours	0
206				
207	44	Original	48Hours	0
208	44	Alternate	48Hours	0
209	44	Original	96Hours	0
210	44	Alternate	96Hours	0
211				
212	45	Original	48Hours	0
213	45	Alternate	48Hours	0
214	45	Original	96Hours	0
215	45	Alternate	96Hours	0
216				
217	46	Original	48Hours	0
218	46	Alternate	48Hours	0
219	46	Original	96Hours	0
220	46	Alternate	96Hours	0
221				
222	47	Original	48Hours	0
223	47	Alternate	48Hours	0
224	47	Original	96Hours	0
225	47	Alternate	96Hours	0
226				
227	48	Original	48Hours	0
228	48	Alternate	48Hours	0
229	48	Original	96Hours	0
230	48	Alternate	96Hours	0
231				
232	49	Original	48Hours	0
233	49	Alternate	48Hours	0
234	49	Original	96Hours	0
235	49	Alternate	96Hours	0
236				
237	50	Original	48Hours	0
238	50	Alternate	48Hours	0
239	50	Original	96Hours	0
240	50	Alternate	96Hours	0
241				
242	51	Original	48Hours	0
243	51	Alternate	48Hours	0
244	51	Original	96Hours	0
245	51	Alternate	96Hours	0
246				
247	52	Original	48Hours	0
248	52	Alternate	48Hours	0
249	52	Original	96Hours	0
250	52	Alternate	96Hours	0
251				

HRIPT Study C07-0006
Challenge Phase
Sample 07-258-CRS
October 15-19, 2007

	A	B	C	D
1	Subject	Site	Time	Sample
302	64	Original	48Hours	0
303	64	Alternate	48Hours	0
304	64	Original	96Hours	0
305	64	Alternate	96Hours	0
306				
307	65	Original	48Hours	0
308	65	Alternate	48Hours	0
309	65	Original	96Hours	0
310	65	Alternate	96Hours	0
311				
312	66	Original	48Hours	0
313	66	Alternate	48Hours	0
314	66	Original	96Hours	0
315	66	Alternate	96Hours	0
316				
317	67	Original	48Hours	0
318	67	Alternate	48Hours	0
319	67	Original	96Hours	0
320	67	Alternate	96Hours	0
321				
322	68	Original	48Hours	0
323	68	Alternate	48Hours	0
324	68	Original	96Hours	0
325	68	Alternate	96Hours	0
326				
327	69	Original	48Hours	0
328	69	Alternate	48Hours	0
329	69	Original	96Hours	0
330	69	Alternate	96Hours	0
331				
332	70	Original	48Hours	0
333	70	Alternate	48Hours	0
334	70	Original	96Hours	0
335	70	Alternate	96Hours	0
336				
337	71	Original	48Hours	0
338	71	Alternate	48Hours	0
339	71	Original	96Hours	0
340	71	Alternate	96Hours	0
341				
342	72	Original	48Hours	0
343	72	Alternate	48Hours	0
344	72	Original	96Hours	0
345	72	Alternate	96Hours	0
346				
347	73	Original	48Hours	0
348	73	Alternate	48Hours	0
349	73	Original	96Hours	0
350	73	Alternate	96Hours	0
351				

HRIPT Study C07-0006
Challenge Phase
Sample 07-258-CRS
October 15-19, 2007

	A	B	C	D
1	Subject	Site	Time	Sample
402	84	Original	48Hours	0
403	84	Alternate	48Hours	0
404	84	Original	96Hours	0
405	84	Alternate	96Hours	0
406				
407	85	Original	48Hours	0
408	85	Alternate	48Hours	0
409	85	Original	96Hours	0
410	85	Alternate	96Hours	0
411				
412	86	Original	48Hours	0
413	86	Alternate	48Hours	0
414	86	Original	96Hours	0
415	86	Alternate	96Hours	0
416				
417	87	Original	48Hours	0
418	87	Alternate	48Hours	0
419	87	Original	96Hours	0
420	87	Alternate	96Hours	0
421				
422	88	Original	48Hours	0
423	88	Alternate	48Hours	0
424	88	Original	96Hours	0
425	88	Alternate	96Hours	0
426				
427	89	Original	48Hours	0
428	89	Alternate	48Hours	0
429	89	Original	96Hours	0
430	89	Alternate	96Hours	0
431				
432	90	Original	48Hours	0
433	90	Alternate	48Hours	0
434	90	Original	96Hours	0
435	90	Alternate	96Hours	0
436				
437	91	Original	48Hours	0
438	91	Alternate	48Hours	0
439	91	Original	96Hours	0
440	91	Alternate	96Hours	0
441				
442	92	Original	48Hours	0
443	92	Alternate	48Hours	0
444	92	Original	96Hours	0
445	92	Alternate	96Hours	0
446				
447	93	Original	48Hours	0
448	93	Alternate	48Hours	0
449	93	Original	96Hours	0
450	93	Alternate	96Hours	0
451				

HRIPT Study C07-0006
Challenge Phase
Sample 07-258-CRS
October 15-19, 2007

	A	B	C	D
1	Subject	Site	Time	Sample
502	105	Original	48Hours	0
503	105	Alternate	48Hours	0
504	105	Original	96Hours	0
505	105	Alternate	96Hours	0
506				
507	106	Original	48Hours	0
508	106	Alternate	48Hours	0
509	106	Original	96Hours	0
510	106	Alternate	96Hours	0
511				
512	107	Original	48Hours	0
513	107	Alternate	48Hours	0
514	107	Original	96Hours	0
515	107	Alternate	96Hours	0
516				
517	108	Original	48Hours	0
518	108	Alternate	48Hours	0
519	108	Original	96Hours	0
520	108	Alternate	96Hours	0

HRIPT SCORING SCALE

Erythema: (Reaction completely fills the patch area)

0 = No redness
0.5 = Doubtful reaction
1 = Minimal redness
2 = Moderate redness
3 = Intense redness

Secondary reactions:

E = Edema
P = Papules
V = Vesicles
B = Bullae
S = Spreading (reaction beyond the patch area)

Other Notations:

A = Reaction to adhesive tape
X = No patch applied
(.) = Subject Absent
L = Subject reported lost patch
N9G = No ninth grade. Subject wore nine induction patches but was absent for the final scoring.

Criteria for moving a patch: Erythema ≥ 2; Secondary Reactions V, B or S.

Data Interpretation
HRIPT Induction Phase

A cumulative score for the induction phase of the Human Repeat Insult Patch Test was adapted from the Berger/Bowman cumulative irritant scoring system. This single cumulative score is provided for informational purposes. It does not replace the fourteen-day cumulative irritant patch test.

A patch score is the combination of a numerical and letter grade. All letter grades are converted to a numeric value as follows: E=1, P=2, V, B and S=3. The cumulative score is used for the final analysis (e.g., 2E= 2 + 1 = 3). An upper limit of 3 was chosen arbitrarily as the endpoint for differentiating between relatively mild products. It is meaningless in the context of cosmetic studies for a test agent to induce extreme irritation. Therefore, in the present study, a score of 3 or higher is considered a 3 throughout the remainder of the test. The following classifications are used:

Scoring Range	Clinical Observation	Interpretation
0 to 681	No evidence of irritation under the test conditions	Mild Test Agent. No irritation anticipated with normal use.
682 to 1363	Minimal erythema, no edema or papules under the test conditions	Mild Test Agent. Slight chance of mild irritation in normal use.
1364 to 2044	Moderate erythema, papules and/or edema under the test conditions.	Mild to Moderate Test Agent. Possibly mild in normal use but may produce irritation on sensitive skin.
2045 to 2507	Moderate erythema, papules, edema, glazing or cracking of the skin under the test conditions.	Cumulative Irritant. A high likelihood of producing skin irritation with continuous use.
2508 to 2700	Strong erythema, papules, edema, glazing, cracking and exudate on the skin under the conditions of the test.	Primary Irritant. Very high likelihood of producing skin irritation with even minimal exposure.

Personal Care Products Council
Committed to Safety, Quality & Innovation
1101 17th Street, N.W., Suite 300
Washington, D.C. 20036-4702

Memorandum

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

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

DATE: October 21, 2013

SUBJECT: Summary of an HRIPT on a Product Containing Rosmarinus Officinalis (Rosemary) Leaf Extract

Anonymous. 2009. Summary of an HRIPT of a hair spray containing 0.0013% Rosmarinus Officinalis (Rosemary) Leaf Extract.

Rosmarinus officinalis (Rosemary) Leaf Extract

Summary of HRIPT

A hair spray containing 0.0013% *Rosmarinus officinalis (Rosemary)* Leaf Extract was tested using Modified Draize Human Repeated Insult Patch Test (HRIPT) procedure to determine the potential of this product to induce irritation and contact sensitization. The product was tested neat under occlusive conditions and volatilized for 30 minutes prior to application.

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

A total of 102 subjects satisfactorily completed the study. Under the conditions of a Modified Draize HRIPT procedure, the tested product containing 0.0013% *Rosmarinus officinalis (Rosemary)* Leaf Extract produced transient, barely perceptible to mild patch test responses on some subjects. The skin reactivity observed in these subjects was considered not related to skin irritation or allergic reaction.

This study was conducted by Reliance Clinical Testing Services, Inc. Irving, TX from April 22 to May 29, 2009 in accordance with the spirit of Good Clinical Practice regulations described in 21 CFR, Part 50 (Protection of Human Subjects-Informed Consent) and Part 56 (Institutional Review Board).

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Memorandum

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

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

DATE: October 25, 2013

SUBJECT: Reproductive and Developmental Toxicity Concern for Rosemary Used as a Drug

At the September 2013 meeting the CIR Expert Panel requested additional details as to why the 1st edition of the *PDR for Herbal Medicines* cautions that rosemary not be used during pregnancy.

Neither the 1st edition nor the 4th edition of the *PDR for Herbal Medicines*[1] provides any details as to why the use during pregnancy caution is included. The PDR does include a daily dosage for rosemary used as an oral drug of 4-6 g, much larger than the amounts used in food (GRAS for use in human [21CFR182.20] and pet [21 CFR 582.20] food), and cosmetics. Exposure from cosmetic use of rosemary-derived ingredients is primarily via the dermal route of exposure which would further reduce the potential for systemic exposure.

It should also be noted that it is not uncommon for the 4th edition of *PDR for Herbal Medicines* to caution that a herbal medicine not be used during pregnancy. Pages I-235 to I-242 lists all of the herbal medicines in the PDR that include the caution that they should not be used during pregnancy.

Concerning pregnancy and lactation, the 2nd edition of the *Botanical Safety Handbook*[2] states:

> "Information on the safety of rosemary during pregnancy is conflicting. While some older references indicate that rosemary (perhaps referring to rosemary essential oil) was used to induce abortions (Casey 1960; Chadah 1988; Greshoff 1913), animal studies of rosemary or compounds isolated from rosemary have not indicated such activity. One animal study showed no significant adverse effects of a rosemary aqueous extract administered to pregnant rats, although a small statistically insignificant increase in preimplantation loss was observed (Lemonica et al. 1996). No teratogenic effects of the compounds D-camphor or 1,8-cineol were

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[1]Gruenwald J, Brendler T, Jaenicke C (eds). 2007. *PDR for Herbal Medicines*, 4th edition. Thomson Healthcare Inc, Montvale NJ.

[2]Gardner Z, McGuffin M (eds). 2013. *American Herbal Products Association's Botanical Safety Handbook*, 2nd edition. CRC Press, Boca Raton FL.

observed in other studies (Jori and Briatico 1973; Leuschner 1997). In rats administered the compound 1,8-cineol during pregnancy, 1,8-cineol was shown to cross the placenta, suggesting that caution is warranted for use during pregnancy(Jori and Briatico 1973). Although dried rosemary or rosemary tea may be safe in pregnancy, the essential oil and other concentrated extracts should not be used."

An Editor's Note in the *American Herbal Products Association's Botanical Safety Handbook* also states:

"Concerns for this herb are based on relatively higher doses used for therapeutic purposes in contrast to lower amounts generally used in cooking, and have not been associated with its use as a spice."

Based on the lower exposure from cosmetic use and conflicting information concerning potential reproductive and developmental toxicity, cosmetic use of rosemary-derived ingredients does not warrant the same concern as the use of rosemary as a drug.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: September 5, 2013

SUBJECT: Comments on the Draft Report on *Rosmarinus officinalis*-Derived Ingredients Prepared for the September 2013 CIR Expert Panel Meeting

Key Issue

Please indicate why Rosmarinic Acid is being included in this report. Other acids that are listed as cosmetic ingredients, e.g., Carnosic Acid, can also be obtained from *Rosmarinis officinalis*. What was the rational for including Rosmarinic Acid but not Carnosic Acid?

Additional Comments

Memo - What is the example of the "precedent of CIR including the acid of a botanical in the family of ingredients"? As plant-derived extracts likely contain multiple "acids", what is the protocol to determine which acid to include in the report?

Data profile - The constituents/impurities box for the leaf extract needs to be checked.

p.2 - As of July 2013, the European Union is following the Cosmetic Regulation EC No. 1223/2009. The Cosmetic Directive 76/768/EEC should no longer be cited.

p.3, 10 - If the most recent edition (4th edition, 2007) of the *PDR for Herbal Medicines* is not going to be obtained, then the text should indicate that the 1st edition is being cited.

p.5 - In the descriptions of the parenteral studies, did they actually follow the kinetics of Rosmarinic Acid, or just the radioactivity?

p.5 - What was the dose (or concentration) of rosemary oil used in the penetration enhancement study?

p.6 - The study concerning effects on melanogenesis should not be in the Immunologic Effects section.

p.8 - In the Genotoxicity section, please include the routes of exposure for the *in vivo* assays.

p.8, 11 - Rather than referring to "spirulina" as algae, it should be called cyanobacteria.

p.9 - Please correct: "(rosemary)-derived as used in cosmetics"

p.10 - In the Summary, please indicate that suppliers state that Rosmarinus Officinalis (Rosemary) Leaf Extract is normalized to 17% or 25% diterpene phenols as carnosol and carnosic acid.

p.10 - Please correct "he clearance phase"

p.29, Table 8 - Although the genus species may not have been specifically stated for rosemary reported to the VCRP, unlike many common names for plants, there are no other genus species associated with the common plant name rosemary.