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

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The 2014 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: February 21, 2014
Subject: Safety Assessment of Rosmarinus Officinalis (Rosemary)-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Final Report on the Safety Assessment of Rosmarinus Officinalis (Rosemary)-Derived Ingredients as Used in Cosmetics. There are 10 ingredients included in this report.

At the September meeting, the Panel issued an Insufficient Data Announcement (IDA) requesting:

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.

Some data were received in response to the IDA, but not enough to answer all the questions. Therefore, at the December 2013 meeting, that Panel issued a tentative report with the following mixed conclusion:

1. Rosmarinus officinalis (rosemary) leaf extract is safe at up to 0.2% in leave-on products, and it is safe as used in rinse off products. The leave-on limitation was set based on the maximum use concentration tested in dermal sensitization studies.
2. The data were insufficient for determining that safety of rosmarinus officinalis (rosemary) flower extract for use in cosmetics. Data on the chemical characterization of the flower were requested but not provided.
3. The Panel determined that remaining eight ingredients (rosmarinus officinalis (rosemary) extract; rosmarinus officinalis (rosemary) flower/leaf stem extract; rosmarinus officinalis (rosemary) flower/leaf/stem water; rosmarinus officinalis (rosemary) leaf; rosmarinus officinalis (rosemary) leaf oil; rosmarinus officinalis (rosemary) leaf powder; rosmarinus officinalis (rosemary) leaf water; and rosmarinus officinalis (rosemary) water) are safe in used in cosmetics.

Since the last meeting, the Council submitted a published paper that included some information on the chemical characterization of *Rosmarinus officinalis* flowers. This information has been included in the Constituents/Impurities section and in Table 4 of the report, and is indicated by underlining or horizontal borders. If the Panel finds this information sufficient for the chemical characterization of the flower, and if there are no other

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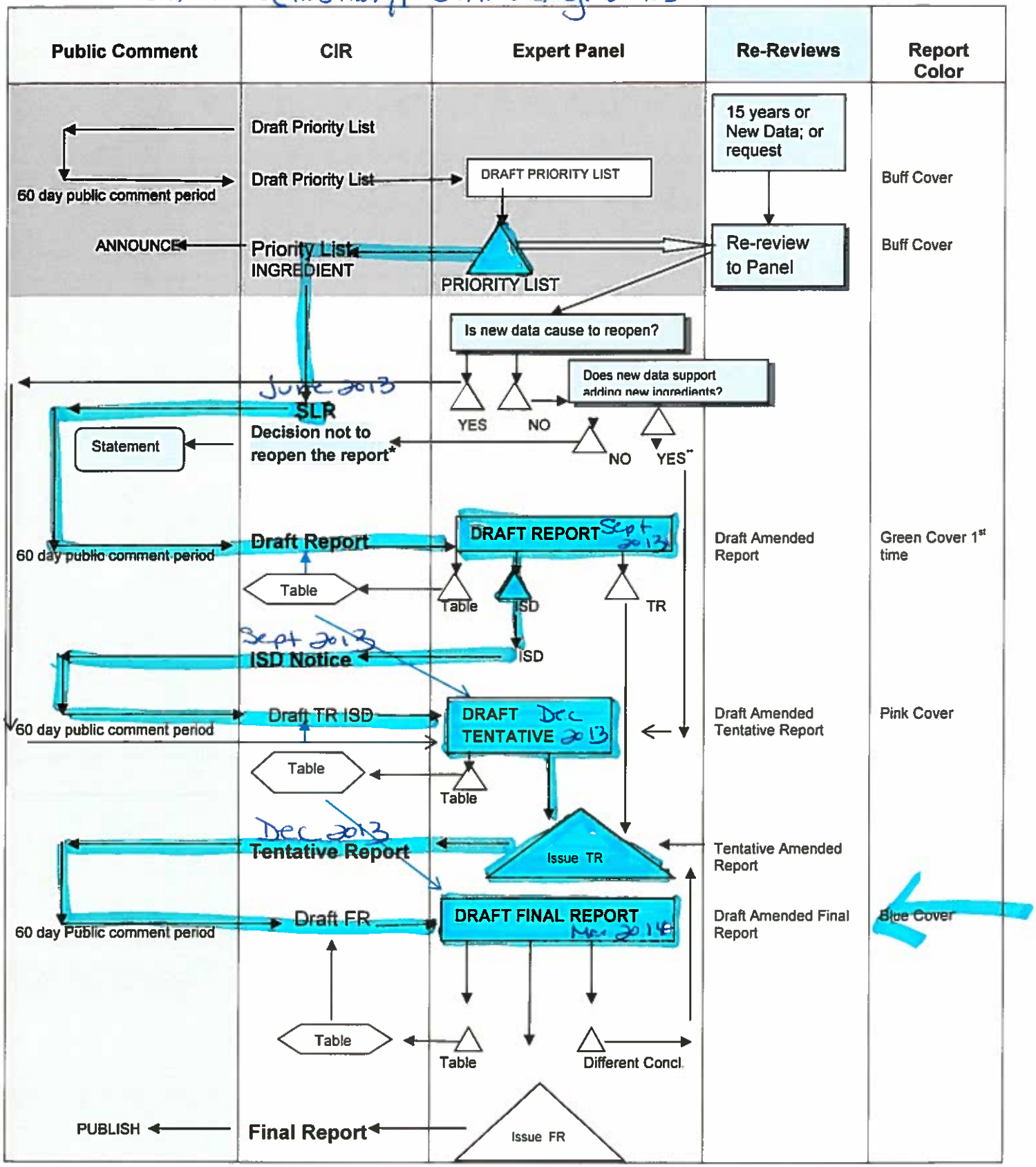
concerns on the safety of this ingredient, then the conclusion should be amended from insufficient data to safe as used.

Comments on the tentative report were also received from the Personal Care Products Council. These comments have been addressed. Additionally, updated concentration of use data were received; the update did not have an impact on the information already in the report. (The data submission is included with this report package.)

SAFETY ASSESSMENT FLOW CHART

Rosmarinus officinalis (Rosemary) - Derived Ingredients

Mar 2014



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.

The Panel issued a tentative safety assessment with the conclusion that the following eight *rosmarinus officinalis* (rosemary)-derived ingredients are safe as used in cosmetics.

rosmarinus officinalis (rosemary) extract
rosmarinus officinalis (rosemary) flower/leaf stem extract
rosmarinus officinalis (rosemary) flower/leaf/stem water*
rosmarinus officinalis (rosemary) leaf
rosmarinus officinalis (rosemary) leaf oil
rosmarinus officinalis (rosemary) leaf powder
rosmarinus officinalis (rosemary) leaf water
rosmarinus officinalis (rosemary) water

The Panel also concluded that rosmarinus officinalis (rosemary) leaf extract is safe at ≤0.2% in leave-on products and safe as used in rinse-off products, and that the available data are insufficient for determining that rosmarinus officinalis (rosemary) flower extract is safe for use in cosmetics because information on the chemical characterization of the flower was not provided.

Rosmarinus Officinalis (Rosemary)-Derived Ingredients Data Profile* – March 2014 – Monice Fiume

	Reported Use	Preparation/ Extraction	Constituents/ Impurities	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/ Tumor Promotion	Dermal Irr/Sens	Ocular Irritation
Rosmarinus officinalis L.			X							X				
Rosmarinus Officinalis (Rosemary) Extract	X	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

FULL PANEL – DEC 9 2013 – ROSMARINUS OFFICINALIS INGREDIENTS

DR. BELSITO: Yes. So this is Rosmarinus and there are a number -- 10 ingredients that we're looking at: The extract, the flower extract, the flower-leaf-stem extract, the flower-leaf-stem water, the leaf, the leaf extract, the leaf oil, the leaf powder, the leaf water, and the whole shebang water.

And we thought that the leaf extract was safe up to 0.2 percent in leave-ons based upon sensitization data and safe as used in rinse-offs; that the flower extract was insufficient for composition and concentration of use; and that the other ingredients, the extract and the water -- no, the flower extract was insufficient for composition and concentration of use. The leaf extract up to 0.2 percent based upon sensitization. And the other ingredients, basically the leaf oil, powder, water, water and leaf, so everything other than the flower and the leaf extract, were safe as used.

DR. SHANK: Hello?

DR. BELSITO: Yes.

DR. BERGFELD: Who is this?

DR. SHANK: This is Ron Shank.

DR. BERGFELD: Wonderful. Good morning.

DR. SHANK: Late, but I'm here.

SPEAKER: It's never too late, Ron.

DR. MARKS: Ron, I had your comments this morning, so with our team meeting I incorporated that in the discussion.

DR. SHANK: Thank you.

DR. MARKS: You're welcome. No, thank you for sending you comments in. That was very helpful.

DR. BERGFELD: We're now looking at Rosmarinus.

DR. SHANK: Okay.

DR. MARKS: Yeah, so we're in the full panel meeting now.

DR. SHANK: Yes.

DR. BERGFELD: So let's go back, Don, and give this again to us.

DR. BELSITO: Okay. So basically the leaf extract is safe up to 0.2 percent in leave-ons and safe as used in rinse-offs. The flower extract is insufficient for composition and concentration of use. And the others are safe as used. So basically the flower, insufficient; leaf extract, a limit; others, safe as used.

We had previously asked for what is this deodorization process, but in my reading it was deodorization was with food grade, so I wasn't sure why we were concerned about what that might be.

And then there was the whole issue of the botanical PDR not to use it in pregnancy, that I think we've addressed with additional data and also, in the discussion, pointing out that the exposure that caused issues with pregnancy was extremely high and was not applicable to cosmetic sue.

DR. BERGFELD: What did you do with the original request for 10 percent?

SPEAKER: That's the 0.2.

DR. BELSITO: That's the 0.2.

DR. BERGFELD: That's the 0.2, okay.

DR. MARKS: That's setting a limit. And the repro, Ron Shank, you didn't have any problems with that and your team?

DR. SHANK: No, I didn't.

DR. MARKS: Because just to make sure we address that.

DR. HILL: Okay. So I was the one that brought up the deodorization process and my concern was if it was some sort of a bleaching process, that there are chemicals that might be created by that that wouldn't otherwise be present. So that was what that was all about and I was really specifically asking, yes, that occurs with food grade. Is that also applicable to cosmetic grade?

DR. BERGFELD: I guess, Dan Liebler, if you have a comment n that and then maybe Curt.

DR. LIEBLER: Yeah, I remember Ron bringing it up in our discussion last time and I also thought about it a little bit during the review of this document. (inaudible) theoretically possible to something else (inaudible) that would be of concern, but it just strikes me as pretty unlikely. So I guess I didn't feel it needed to be in the discussion.

DR. HILL: Well, if we had chlorine-based or peroxide-based bleaching process, for example, then those things are not at all unlikely. So, I mean, it would be just nice if industry would come back and say, no, we're using carbon black or something that's totally innocuous, but I don't understand why I've got nothing on that.

DR. BELSITO: But it's possible that they don't bleach the cosmetic product.

DR. HILL: It's possible that they don't deodorize the cosmetic product.

DR. BELSITO: Deodorize it.

DR. HILL: I would think, if anything, even more so than food grade, you would want to deodorize cosmetic products. That's just -- maybe I'm thinking about that wrong.

DR. BELSITO: But they would deodorize it to get rid of some of the scent, I would imagine. I mean, that's what a deodorizer does. And in a cosmetic product you may want that, some of that fragrance.

DR. EISENMANN: The other thing there's a 90-day study on the deodorized product that was claimed.

DR. BELSITO: Right.

DR. HILL: Which -- what's the nature of the study? Tell me where it is in here again.

DR. EISENMANN: It's in one of the tables.

DR. BRESLAWEC: Table 10.

DR. HILL: Table 10.

DR. BRESLAWEC: At 400 milligrams per kilogram per day.

DR. HILL: By oral route?

DR. EISENMANN: Yes.

DR. HILL: For 90 days. Yeah, it should be okay then.

DR. BELSITO: And then the only other thing was that the study at high concentrations with the rosemary, there's a potential it said for Rosmarinus officinalis-derived ingredients to cause irritation. I think it's important to note that this was whole leaf that was applied to exzematous skin, so it's not clear what they meant by irritation. It simply could have been 43 of the 246 people got worse and some got better and some stayed the same. So I'm not even sure that it should remain in this document to put a whole leaf on exzematous skin.

DR. BERGFELD: Well, any comment? Jim?

DR. MARKS: Normally, unless there's a scientific issue with a document, we leave it in and then we just interpret it. So I guess the question is do we think this is scientifically valid and just delete it or do we leave it in and say it's exzematous skin and the meaning -- it's relatively meaningless? I guess --

DR. BELSITO: I feel -- I think we can leave it, but we -- just having that sentence "at high concentration there's a potential," I think (inaudible) potential at all, you know. When you put a leaf and petrolatum on the skin of eczematous patients, 43 of 246 got worse. What does that mean? So I wouldn't say there's a potential for irritation. If you leave it in I would say there's one report of application of a whole leaf to 246 people with eczematous skin and 43 of them got worse. The panel's not sure what that means.

DR. MARKS: That sounds perfectly fine.

DR. BERGFELD: And where would you put that, in the discussion?

DR. BELSITO: Yeah. I mean, if we're going to include it, we have to put it in the discussion.

DR. BERGFELD: Right, right, discussion.

DR. BELSITO: We're not limiting sensitive irritation here because we don't -- that's the only study and we're not even sure how to interpret it.

DR. BERGFELD: Okay. Any other comments? So then, Don, if you would just repeat your final conclusion.

DR. BELSITO: Okay. So the flower is insufficient for composition and concentration of use. The leaf extract is safe up to 0.2 percent in leave-ons and safe as used in rinse-offs. The other ingredients, the other 10 ingredients were safe as used. And the issue of reproductive toxicity and the PDR for botanicals has been addressed in the discussion.

DR. BERGFELD: That's a motion and it's been seconded. Should we move ahead with the vote? All those in favor, please indicate by raising your hand.

DR. LIEBLER: I'm in favor.

DR. BERGFELD: Then you three on the phone, all of you?

DR. LIEBLER: Yes, in favor.

DR. BERGFELD: Okay, thank you.

MS. FIUME: Can I ask for a clarification?

DR. BERGFELD: Sure.

MS. FIUME: The flower ingredient, is it just the flower extract or all three?

DR. BELSITO: Just the flower -- no, just the flower extract.

MS. FIUME: Okay, thank you.

Belsito Team – Dec 9 2013

DR. KLAASSEN: Okay. And we go right on to rosmarinus. If we can all find that. And -- okay, so the -- you people worked on this at the last meeting and we basically, the bottom line is we need to look at the dermal sensitization data, especially in regard to this 10 percent of the leaf extract if that's still needed. If a report with the conclusion of insufficient data should be issued and if further review of the panel finds that the existing data are sufficient, then a tentative report can be written.

And so Don is back with us. And we're just barely starting Rosmarinus.

DR. BELSITO: Okay.

DR. KLAASSEN: And the main concern here is sensitization and, Don, our expert on sensitization, so what's your input on that?

DR. BELSITO: Okay. So looking at this, I think the flower is the -- the flower ingredients are insufficient for composition and concentration of use. We have no information on that. I think the leaf extract is safe up to 2 percent in leave-ons and safe as used in rinse-offs because 2 percent is the highest we have for sensitization.

We had asked for sensitization up to -- I'm doing this off the top of my head since I just walked in, but I think 10 percent was the highest that was used --

DR. KLAASSEN: Yes.

DR. BELSITO: -- in the leave-on. And we don't have that information. So, I would say we have to limit it at 2, which is the highest sensitization data we have and so the leaf extracts are safe up to two in leave-on, safe as used in rinse-offs. The others are safe as used.

We had asked for information about the deodorization process. But that method of manufacturing seemed to be with food grade, so I'm not sure why we were concerned about what deodorization might involve -- I mean as I read it. And then, I think the pregnancy issues have been addressed and are well discussed in the document. So, I mean, I think there are still some insufficient, but the flower isn't used -- or at least we don't have information into, you know, concentration of use so.

DR. BRESLAWEC: We're not interested -- industry is not interested in pursuing the flower.

DR. BELSITO: Okay.

DR. BRESLAWEC: So that's not -- that's not an issue. I would like to point out that if you're going to say something about not using during pregnancy or use during pregnancy, you may want to say that the rosemary preparation should not be used as a drug during pregnancy because that is what the PDR for herbal medicines (inaudible).

DR. BELSITO: You know we could put that in the discussion. I didn't feel that it was -- based on the information that we got, that that was really an issue at all for cosmetic use.

DR. BRESLAWEC: Well, again --

DR. BELSITO: But if industry feels they'd like in the discussion something about the fact that the European equivalent to the PDR says not to use it during pregnancy, that's as a drug and much higher levels than what we're looking at.

DR. BRESLAWEC: We aren't particularly interested in putting it in. However, if the Panel felt that it needed to be in, then it should specify that it is a drug. That it shouldn't be used as a drug.

DR. BELSITO: Rachel?

MS. WEINTRAUB: Was the Panel concerned at all about the sperm reduction that was indicated in one of the studies?

DR. BELSITO: I read that. It -- again, I thought the levels were --

DR. SNYDER: They were extremely high concentrations.

MS. WEINTRAUB: Okay.

DR. BELSITO: Yeah.

DR. SNYDER: There's probably (inaudible) toxicities and the (inaudible) is highly sensitive to those types of -- those were extremely high concentrations and I looked at those pretty carefully and I didn't have any concern with cosmetic use.

MS. FIUME: Can I ask -- the discussion does address the developmental toxicity and that it is used -- the concentrations are higher than what would be seen in cosmetics. Is it okay as written or do you feel that more language would be needed with that?

DR. SNYDER: I'm looking to see if I edited any of that, but -- yeah, I didn't have any substantive changes to that.

DR. LIEBLER: Are you talking about the second to last paragraph on page 33 -- PDF 33?

DR. BELSITO: Yeah. Well, on PDF 33, we do have to add in the new data that we got on -- in wave two. That hasn't been added in there yet. The HRIPT up to 2 percent. But, you're down in the discussion. Is that correct?

DR. LIEBLER: Yeah. I was talking about the repro -- the PDR herbal medicine and that paragraph.

DR. BELSITO: Well, that all is going to have to be written based upon the information we got in wave two so.

MS. FIUME: The paragraph I was referring to was the one on the developmental toxicity being above concentrations found in cosmetics.

DR. LIEBLER: Right. And that's what I was responding to and I think that's fine.

DR. BELSITO: What page are you on?

MS. FIUME: PDF page 33.

DR. BELSITO: Thirty-three -- in the discussion.

DR. SNYDER: What section? What paragraph?

MS. FIUME: Discussion section, second paragraph from the end.

DR. BELSITO: Okay. That starts with according to the PDR for herbal medicines.

DR. LIEBLER: Right. So that's what I was responding to and I think that looks fine.

MS. FIUME: Thank you.

DR. BELSITO: Yeah. I had no comments on the discussion. Again, I just thought that the HRIPT at the 0.2 or the 2 percent level is not in the summary -- or at least I didn't see it -- for the leaf. If you go up -- this is also on page 33. Maximum concentration of 1.5 percent officinalis leaf oil was not an irritant or a sensitizer. But you don't have the data for the leaf.

MS. FIUME: I'll add that in.

DR. SNYDER: Yeah, so I did -- I apologize. I was hunting the wrong discussion. So I did have a comment on that paragraph which begins with according to the PDR. I thought that we -- that could be reduced down significantly to just noting that the PDR reference referred to use as a drug. And that we had data in rats only, at very high doses -- that it had some repro effects. And just really limit it to that. Not -- it needs to be in there that we're aware -- acknowledging that we're aware of the rat study and the results, but putting in the context that it was at extremely high doses. So do have a comment in here for that.

MS. FIUME: And it's in your --

DR. SNYDER: Yes.

MS. FIUME: Thank you.

DR. BELSITO: So how did you word that, Paul?

DR. SNYDER: I just specifically said that we had a dose that was at 500 milligrams per kilogram per day in rats. It was shown to be a -- to have some effects on the testes and not -- the panel was aware of this and it was not -- didn't consider it to be relevant to cosmetic exposures or something along that line.

DR. BELSITO: So instead of just saying the Panel discussed these facts stating that these effects were observed only at exposure concentrations well above those used in cosmetics -- you expanded that further?

DR. SNYDER: I just think -- I think whenever we have a known level, we need to -- we should just put it in because I think it's -- you know, 500 milligrams is a significant level. So I think we need to put it in there.

DR. BELSITO: So could you read that paragraph as you suggested it be added?

DR. SNYDER: Well, I didn't. I just put it as a comment.

DR. BELSITO: Oh, okay.

DR. SNYDER: I just said reduce down to maybe a couple sentences regarding the PDR reference. And then just specifically be more specific in the -- that it's a rat only study and it was at very high concentrations.

MS. FIUME: Does that address the PDR information as well? Because the PDR is general information. It was hard to find specific references for it, but it did refer to human use at very high concentrations during pregnancy.

DR. SNYDER: Right. But, as we discussed previously, as drug use -- not in -- what has to be put in the right context.

MS. FIUME: Okay.

DR. SNYDER: Yeah.

MS. WEINTRAUB: This may be a moot point, but I thought the language in the second clause of the first sentence -- and mixed results were obtained in reproductive and developmental -- and development toxicity studies in rats. Mixed results -- sort of a term.

DR. SNYDER: I don't like -- yeah.

MS. WEINTRAUB: Yeah.

DR. SNYDER: Nebulous. It doesn't really mean anything.

MS. WEINTRAUB: Yes.

DR. SNYDER: I think we need to make it clear that we understood what the results were and that we were not concerned.

DR. KLAASSEN: And that would be corrected by putting what was just mentioned. Be a little more specific there.

DR. BELSITO: And so what would you say? Instead of saying not used as a drug during pregnancy and some reproductive and developmental toxicity -- toxicities were observed in rats at doses --

DR. SNYDER: 500 milligrams -- you know, levels -- 500 milligrams per kilogram per day. At high levels and then indicate what the levels were and just not really go into much more detail than that.

DR. BELSITO: So, we would say during pregnancy and some reproductive and developmental toxicity -- or some reproductive and developmental -- developmental, I guess --

DR. SNYDER: Well, just say reproductive --

DR. BELSITO: -- effects --

DR. SNYDER: -- reproductive -- reproductive effects were seen in rats --

DR. BELSITO: -- were seen --

DR. SNYDER: -- at 500 milligrams per kilogram.

DR. BELSITO: -- in rats.

DR. SNYDER: Levels that are not relevant to cosmetic use or cosmetic --

DR. BELSITO: Milligrams per kilogram per day, right?

DR. SNYDER: Yes. Correct.

DR. BELSITO: Levels far in excess of what would be expected from cosmetic exposure?

DR. SNYDER: Correct. Yeah. Something along that line. And we could even say -- you could even put at the beginning of that a single study, because there was another study that was negative at 30 percent so.

DR. BELSITO: Well, that's how I took the mixed results, but --

DR. SNYDER: Okay.

MS. FIUME: Dr. Snyder, just so I'm clear, because I think I missed the beginning part. So, anything about the PDR for herbal medicines -- do you want that removed? Because that's -- that's human --

DR. SNYDER: No, no. That's fine.

MS. FIUME: Leave that in? Okay.

DR. SNYDER: Yeah, yeah. So there's a -- so, Don, when you stepped out, we had a discussion about the botanical things.

DR. BELSITO: Mm-hmm.

DR. SNYDER: That becomes relevant to this document. And Dan and I had both kind of come up with a similar idea or a thought that we should have the summary statement in the abstract. And I have some language here that you haven't heard yet, so I -- so I had inserted a sentence in all of the abstracts --

DR. BELSITO: Are we done with the rosmarinus? Do we have any further comment?

DR. SNYDER: Well, I think this goes in --

DR. BELSITO: Okay.

DR. SNYDER: -- it goes -- it's relevant to the abstract.

DR. BELSITO: Okay. So we're up in to the abstract.

DR. SNYDER: Yeah. So then after --

DR. BELSITO: Page of the PDF?

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

DR. BELSITO: Okay. I'm on the abstract.

DR. SNYDER: So I had inserted a general statement in all the abstracts as either the second or third sentence depending upon how the abstract was constructed that states because the final product -- because final product formulations may contain multiple botanicals, each containing similar components of concern, formulators are advised to be aware of these components and to avoid reaching levels that may be hazardous to consumers. With genus and species -- the specific genus and species -- derived ingredients, the panel was concerned that cosmetics containing x resulting in y, and specifically lay out what we were concerned about with that -- with those individual botanicals. Instead of leaving it just an open ended statement and having to go to the document to figure out what we were concerned with. So I thought that we should have each one of the abstracts be specific to the botanical- derived ingredient. Because sometimes we're aware that they're -- they contain sensitizers. Sometimes they contain other things that we're concerned with. And so just to put it on the -- just really put it right up front what we were concerned with.

DR. EISENMANN: I think part of the problem will be that the -- to include it in the abstract -- the variability of the composition of these ingredients. So you're -- in order -- it would be very difficult to select one -- and that one might not be in all of the ingredients in the -- I mean I think it's a good idea, but not necessary for the abstract, because it might be misleading to focus on one constituent concern in the abstract that might not be found in -- like an aqueous extract and it won't be found in an oil extract. Or it won't be in the essential oil and be -- you know, it'd be -- or it'd be in the root extract and not the leaf extract.

DR. SNYDER: Yeah. Well, that's kind of why I had so many iterations of it and that's also why I went to the wording final product formulations. It doesn't matter -- if the final product formulation uses ingredients derived from this plant, these are things you should be concerned about. The previous language was really -- caution is urged to avoid reaching levels for individual -- individual constituents. There's no detail there and so it -- so it was -- it really leaves the reader up to having to go dig it all out and figure out what -- and then to -- I thought that if we're really concerned about some of these constituents, we need to bring it to the forefront and specifically state what they are. I mean I don't think there's any limit to the length of the abstract.

DR. EISENMANN: Then thing is I think --

DR. BRESLAWEC: There is. There is a limit.

DR. EISENMANN: -- it depends on -- I mean if there's a constituent of concern, but for like these more general -- like the fragrance allergens where there might be multiple in an ingredient, I mean why would you highlight one versus another? But if there's really -- I'm trying to think of an example.

DR. SNYDER: Well, the fragrance allergens are an example where you could say that they do contain numerous fragrance allergens that sensitization is a concern. So with those I would be okay with being maybe a little less specific about. But I think that --

DR. BELSITO: So what you're talking would be like aflotoxins, thujone -- things like that? I mean, what are -- what, what?

DR. SNYDER: Well, I guess it would depend. I have some in here in other documents, but I just can't.

DR. BELSITO: I sort of, you know, agree with Carol. I think that makes --

DR. SNYDER: I think it mis --

DR. BELSITO: -- the -- it might work for some, but then for some, the abstract may exceed the length of what we need to get across. And then we'll get people in the habit of thinking everything they need to know is in the abstract, rather than referring them. I mean if we outline it very well in the discussion, you know, I think that -- you know, if you're a responsible manufacturer, you should be reading the whole darn document. Or at least reading the summary of all the data we looked at and the discussion and the conclusion. Not just going by what you see in an abstract. And the abstract just calls your attention to the fact that hey, folks, you need to go in and you need to read, you know, what the panel was concerned about and make sure that your levels are not exceeding.

DR. SNYDER: But --

DR. BELSITO: I do agree with I think, you know, what Dan was saying before. That, you know, if we have certain levels above which we don't want the total aggregate of a specific compound to exceed, because we have, you know, set those levels. Either IFRA has set them as fragrance levels or we have been concerned about neurotoxicity with a specific, you know, thujone or whatever at a certain level, you know, we should have that in the discussion -- that, you know, aggregate levels should not exceed x.

DR. SNYDER: Well, I just had a -- like this one -- the -- that statement says because formulations may contain more than one botanical ingredient, caution was urged to avoid reaching levels of toxicity for constituents. Well, then why do we even do a --

DR. BELSITO: Well, it should be constituents --

DR. SNYDER: -- why even do a review because, I mean -- I mean that's a non -- that doesn't mean anything really. I mean just avoid -- avoid the levels of toxicity and so I don't -- it doesn't really put it any context.

DR. BELSITO: I think you need to --

DR. BRESLAWEC: Would it help if you specified for constituents present in rosemary-derived ingredients?

DR. BELSITO: Or constituents of concern.

DR. BRESLAWEC: Or concern?

DR. GILL: Or concern found in this ingredient or that directs them back to the discussion.

DR. SNYDER: Right. But I think we have to be very specific about a genus and species because we're running into that issue that we're very specific of what we looked at and with botanicals we have to be more -- I think we need to be -- exert caution that we're talking about this specific genus and species and its constituents.

DR. GILL: But can we direct them to the body of the document and the discussion that would discuss that pall or do you want that in the abstract?

DR. SNYDER: I would be amenable to that. It's just that I felt that this language really puts it in the abstract because in some of these, that's the main thing that we're concerned about. I mean that's the concern we have. There's no other toxicity. It's these -- it's the cumulative effect of these components of concern. And so that was my only comment was that you could reach a level that could exhibit -- in cosmetics -- that could be of concern. And so I just felt that why are we -- why are we avoiding just putting it out there.

DR. BRESLAWEC: Well, I think the I mean it should.

DR. SNYDER: Yeah, I guess I don't know then.

MS. FIUME: Dr. Snyder --

DR. LIEBLER: The fact of the matter -- this is Dan. From a practical matter, it seems like the only time we could be that specific in the abstract, I suppose, is if there is an individual chemical substance or perhaps two that's, you know, unique to the botanical -- or that's in the botanical that we're reviewing, but also is coming from other botanical ingredients that might be stacked in.

I don't think that's the case with rosmarinus. So there's probably practically not a way to put all that into the abstract and it has to be in the discussion instead.

DR. BELSITO: Yeah, and in fact with this ingredient, you know, the thing that, you know, we were really concerned about is why, you know, the PDR for herbal medicines said not to take it during pregnancy. And we don't even know what the

component is that might be causing that specific effect. We just know that at 500 milligrams per kilogram there were some effects seen. So I don't even know that -- what would be limiting here? It -- you know, we're not seeing any of the fragrance sensitizers. We're not seeing anything that is given --

DR. SNYDER: No, we do have -- we do have -- we list them here on page -- we list them here. Specific examples of constituents could possibly induce sensitization -- caffeic acid, thujone, terpenes, (inaudible) acetate, limonene.

DR. BELSITO: Well, thujone is neurotoxicity, okay.

DR. SNYDER: So, I mean, but we do -- we do list --

DR. BELSITO: Yeah.

DR. SNYDER: And then I -- and then I did want to add one other thing to the -- to the issue is that it is GRAS ingredients, so that in combination with high doses -- we need to -- that needs to be inserted in that repro thing -- in that repro statement. And it is both an ocular and dermal irritant, so I think we should specify that in the discussion -- in the paragraph above that.

DR. BELSITO: So you're on page?

DR. SNYDER: Well, I have a PDF document, so I'm under the -- under the --

MS. FIUME: I think it was page 33.

SPEAKER: 33.

DR. BELSITO: Discussion.

DR. SNYDER: Under the draft discussion I have here in this document.

MS. FIUME: So, for the ocular irritant, I don't believe we have standard wording to avoid ocular irritation as far as I can recall. So is there some specific wording that you would like about the ocular irritation portion of the discussion?

DR. SNYDER: No, it was just that the document currently says it just causes irritation. And so I think that we probably should specify dermal or ocular if we can. Because in this case, it's both a dermal and an ocular irritant.

DR. BELSITO: Well, you know, I had problems trying to interpret that data because it was 234 patients who already had underlying eczema and so I'm not sure what that means or, you know, what was being tested. I mean you're taking, I assume, the whole leaf and putting it on the skin of individuals who have already an underlying eczema. Trying to find that. Books were easier.

DR. SNYDER: This one -- just under ocular irritation, it says rosemary oils reported to be a moderate ocular irritant. And I didn't -- I didn't look at the details of that reference. I just saw that -- under -- right after repeated dose toxicity --

DR. BELSITO: Right.

DR. SNYDER: -- there's ocular irritation.

MS. FIUME: It's on PDF page 28.

DR. BELSITO: Yeah. Yeah, I mean, the irritation was -- and it just says, you know, irritation potential of rosemary leaves tested undiluted with sufficient petrolatum for binding. The way I interpreted that study was they took patients who had eczema, they put some pet on the leaves and just placed the leaves on the skin and they saw some irritation. I mean that to me is -- I don't know what to -- how to interpret that, but considering they were putting a whole leaf on irritated skin and, I don't know, so the irritation looked worse because it was occluded with a leaf that they said it was irritating? I mean, I don't see this at the 2 percent concentration we're going forward with as being an irritant substance. I think what they were looking for was perhaps putting a whole leaf on eczema skin might improve the skin and they found that in 44 patients it looked a little worse afterwards. And in 190, it looked better or the same.

MS. FIUME: Dr. Belsito, can I clarify the concentration? It's 0.2 percent, not 2 percent.

DR. BELSITO: No. We got -- didn't we get data on a 2 percent, correct?

DR. SNYDER: Point -- we got -- .2. 1.5 of leaf oil or 1.5 leaf oil.

MS. FIUME: I don't believe there's a way to document on rosemary.

DR. BELSITO: Okay. Well, somehow I ended up with percent and --

MS. FIUME: I believe it's 0.2 percent and 1.5 for the essential oil.

DR. BELSITO: Okay. So 0.2. I stand corrected.

DR. SNYDER: There's a 0.2 percent leaf extract and a 1.5 percent leaf oil.

DR. BELSITO: So leaf extract safe up to 0.2 percent in leave-ons.

MS. FIUME: And then, Dr. Belsito, also as far as using the safe when nonirritating, under non-human for the rosemary leaf oil, there was a study where no details were provided. But undiluted leaf oil was moderately irritating. So would that argue at all for leaving in the safe when formulated to be nonirritating, or is does that not give enough information to include that caveat?

DR. BELSITO: But it was undiluted and what's the highest concentration of use of the leaf oil?

DR. SNYDER: We have a negative test at 1.5 for the leaf oil.

SPEAKER: 1.5.

DR. BELSITO: 1.5 is the highest concentration of use. Yeah, and we have a 4.4 percent leaf oil was not irritating to rat skin. And then, 10 percent in petrolatum was not irritant on a 48-hour closed patch test. So, I mean, I think we have data to suggest that at the concentrations being used irritation is not an issue.

MS. FIUME: So go ahead and remove that part from the discussion and conclusion?

DR. BELSITO: Yeah. I don't think irritation needs to be part of the, you know, discussion or conclusion -- particularly based upon, you know, the levels we're talking about. I mean -- I mean, what did we -- okay. No discussion.

Yeah, I mean -- you know, first of all, I don't know what to make of the data with the leaf. And then the only other irritation we had was undiluted leaf oil causing irritation. You know, I think that if you wanted to say anything, you could say when the leaf was applied to eczematous skin, it caused some irritation and undiluted leaf oil caused irritation. However, at the concentrations that are being used in cosmetic formulations, this would not be an issue at all. Or simply not discuss it at all.

SPEAKER: What's it mean in this first sentence under the human where it says sufficient petrolatum for binding? What the for binding mean?

DR. BELSITO: To make it stick to the skin.

SPEAKER: Okay.

DR. BELSITO: So, like when you are doing patch testing sometimes with like a piece of glove, for instance. You'll put a little petrolatum to get it stick and tape it on.

SPEAKER: Okay.

DR. BELSITO: So do we want to keep that sentence about irritation in the discussion and just point out that it was seen under situations that aren't to be observed at all in cosmetic use or remove it?

DR. SNYDER: I think that there's potential there to be confusing if we don't address. We can summarize that we didn't feel that it was an irritant and because of the reasons that you have alluded to.

DR. BELSITO: So we're going to just modify that sentence and point out the leaf applied to eczematous skin and undiluted oil. And that it's not pertinent to the use levels in cosmetics. Okay.

Okie doke. Anything else.

SPEAKER: That's it.

DR. BELSITO: Okay. So --

DR. LIEBLER: Don.

DR. BELSITO: Yes, Dan.

DR. LIEBLER: The only other point is I had no concerns about the deodorizing chemistry. I think (inaudible) -- he'll raise that in the full panel meeting and I'm not sure it should be anything we follow-up on. I don't think there's anything there.

DR. BELSITO: Yeah, I mean, that's what I thought, too, because that was actually in rosemary for consumption was and --

DR. LIEBLER: Yeah.

DR. BELSITO: Okay. So to go back, we're saying that the flower is insufficient for position and concentration of use and industry is not really interested in the flower anyway. The leaf extract is safe up to 0.2 percent in leave-ons and safe as used in rinse-offs. The others are safe as used. The deodorization goes completely out of the discussion and our needs. And the repro effects we've added into the discussion pointing out that there were some observed in doses in rats at 500 milligrams per kilogram per day and that far exceeds the level that would be seen from cosmetic use.

DR. SNYDER: So, could you review that? The safe is as used except for the --

DR. BELSITO: No, the flower is insufficient completely, so all the flower-derived ingredients here are insufficient. All the leaf extracts, the water, et cetera -- .2 percent in leave-ons, safe as used in rinse-offs. And the others that are --

DR. SNYDER: I think the leaf extract, we have safe -- the sensitization data safe at --

DR. BELSITO: 0.2.

SPEAKER: No, I think we -- well, we have a 1.5 percent.

DR. BELSITO: That's leaf oil.

DR. SNYDER: Oh, I'm sorry. Yeah.

DR. BELSITO: Okay. Anything else. Okay.

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DR. MARKS: Okay. That's just for informational purposes. So next I have was rosmarinus officinalis, rosemary.

DR. BERGFELD: Insufficient.

DR. MARKS: So, you're already did you hear Wilma, Tom? She's already taken the thunder out of this. Wilma said "insufficient" over there. We saw the first report of this in September. We gave an insufficient data announcement, and the memo from Monice. Is Monice here?

DR. HELDRETH: She's not.

DR. MARKS: So, Bart, are you going to go ahead and take care of this?

DR. HELDRETH: Yes.

DR. MARKS: At any rate, there were four needs requesting to follow the dermal sensitization. We did not get that, so we're going to have to move forward obviously with an insufficient conclusion. The chemical characterization of the flower, the deodorizing process, and the issue of pregnancy, which was in the PDR. Ron Shank also felt insufficient, "Need to have human skin sensitization for the leaf extracted, 10 percent." And the other three items, apparently he was not concerned about.

DR. BERGFELD: I think we got the fourth.

DR. MARKS: Did we get the fourth?

DR. BERGFELD: There was some mention of it in the text.

DR. ANSELL: Yeah.

DR. SLAGA: Yeah.

DR. BERGFELD: So we didn't get one through three.

DR. SLAGA: the first one (inaudible) that I have a concern. The rest of it can be done.

DR. MARKS: Okay. Good, Tom. And I think we're all on the same page then is that we need 10 percent dermal sensitization for leaf extract. And the reasoning is that is that undiluted leaf extract is a sensitizer. So at what level is this a non sensitizer?

DR. BERGFELD: What is the threshold?

DR. MARKS: Yeah, what's the threshold? Yeah?

DR. ANSELL: We can have sensitization data at lower concentrations.

DR. MARKS: Right, but not even close, 0.2 percent. This is being used up to 10 percent.

DR. ANSELL: So we would find it appropriate to set up a limit to exclude the 10 percent, "safe as used."

DR. SLAGA: I mean, we could set it at two percent.

DR. MARKS: Yeah, we've done that before.

DR. ANSELL: Yeah.

DR. MARKS: Yeah, okay. Interesting. So we could move

DR. BERGFELD: We have two options.

DR. MARKS: Yes. And for some reason I didn't think of that second option.

DR. ANSELL: Well, we have reached out to the company, and they are not going to do live data.

DR. BERGFELD: Okay, so that's good.

DR. ANSELL: So we would just as soon proceed.

DR. BERGFELD: Proceed. That we should include in the comments that the company has not responded. Not only not responded, but they haven't

DR. ANSELL: The data is not available.

DR. BERGFELD: The data is not available. Requested, but not available.

DR. ANSELL: The request and their response really doesn't go to the question of whether it's safe or not.

DR. BERGFELD: That has nothing to do with that. It has to do with the data lacking. We've made a request. There's been no response, and we're proceeding with what we have. That's what I'm trying to say. But I think you have to present it that way because otherwise you'll hang out for that 10 percent.

DR. MARKS: Well, that'll be in the discussion. Well, you know, it's interesting because we haven't done it before. We just say this is the limit.

DR. BERGFELD: This is all the data we have.

DR. MARKS: And this is the data we have. And then if anybody wants to come forward with the 10 percent, they can.

DR. BERGFELD: At this point, it went out as an insufficient data announcement, did it not?

DR. MARKS: It went out as an insufficient data announcement. We can now issue it as a tentative report with "safe," with concentration of 0.2 percent. There we go. Thank you, Jay. Tom, does that seem reasonable to you? Am I correct? That's what I have highlighted, the 0.2 percent of the leaf extract.

DR. SLAGA: I have down insufficient at 10 percent, but could be safe at 50.

DR. BERGFELD: Right.

DR. MARKS: Okay.

DR. HELDRETH: So safe as used except for the leaf extract, 0.2.

DR. MARKS: Yeah. Let me see who it is tomorrow. Belsito will be the one, I believe, who's presenting it, but I will either second or propose a counter motion that we issue a tentative, so it would be a tentative report with a conclusion "safe with a concentration of 0.2 percent" for the leaf extract.

DR. BERGFELD: And that was 0.2 or

DR. MARKS: 0.2. Yeah, it's in the let me see. It's in the last paragraph of the memo from

DR. BERGFELD: Yeah.

DR. MARKS: I'm making some notes on my computer. Tom, I'm making a couple of changes to my notes in the computer, and this is not as how do I want to say not as easy as just using a pen or pencil and paper. Bart?

DR. BERGFELD: My finger is sore, Tom. Could we look at the abstract when you're done then?

DR. MARKS: Sure. Abstract, that's what page?

DR. BERGFELD: That is, it looks like it's 24.

DR. MARKS: Twenty four.

DR. BERGFELD: Uh huh.

DR. MARKS: Okay, abstract.

DR. BERGFELD: It appears to me it's (inaudible). There are just a bunch of phrases in here.

DR. MARKS: I just want to go

DR. BERGFELD: So you'll have to put in the limitations that you're adding.

DR. MARKS: Yes. Yeah, that last sentence in the abstract is Tom, we're looking at the abstract. Wilma made the comment that it looks like it's a little maybe skimpy. I'll use that word.

DR. BERGFELD: Well, they have a word restriction. I guess that could be with the correction of what you just did with the restricted concentration.

DR. MARKS: Yeah, you can see.

DR. BERGFELD: "Drug formulations may contain more than one botanical. The caution is there to avoid reaching levels of toxicity for constituents. So you should good manufacturing practices to limit impurities." Why would that last sentence be there?

DR. MARKS: That's from the botanical boilerplate.

DR. BERGFELD: Yeah, but why would that be in the abstract?

DR. MARKS: That's because we have that. There's a portion that goes on the abstract, a portion that goes in the conclusion.

DR. BERGFELD: We said that in each one?

DR. MARKS: Yes.

DR. BERGFELD: I hadn't seen that.

DR. MARKS: Well, I think it's just we're coming down to perhaps the final edition of the botanical boilerplate. And we'll go over that. It's a little later on in the agenda.

DR. BERGFELD: When you say "toxicity of constituents," what do you incorporate in that terminology?

DR. HELDRETH: (Inaudible) cognitive effect from other botanicals.

DR. BERGFELD: It includes sensitization?

DR. MARKS: Uh huh.

DR. BERGFELD: I mean, that would be called a toxic effect?

DR. MARKS: Uh huh. Yeah, that's actually, as I recollect, in the boilerplate, it would be perhaps two or three significant constituents that you're concerned about the toxicity, and it'll actually name the constituents and the toxicity.

DR. ANSELL: They really are separate statements. The fact that a botanical is a complex mixture is different than the materials when they have an impurity, because they're not impurities. They're constituents.

DR. BERGFELD: Right.

DR. ANSELL: So whether we need to carry it into the abstract or not, I don't know. But it really is a very separate thought. You know, in one case we're talking about impurities. In the other case, we're reminding people that

DR. BERGFELD: Yeah. I don't think it belongs here.

DR. ANSELL: Yeah.

DR. BERGFELD: I think it belongs in the discussion.

DR. MARKS: Well, let's wait until we get the boilerplate. And this is the specific application, but let's hold that thought for the boilerplate.

DR. BERGFELD: Okay.

DR. MARKS: Because for the boilerplate it's going to be applicable obviously to all the botanicals. That's when we move forward.

DR. BERGFELD: I'm just writing "poor abstract."

DR. MARKS: Good.

DR. BERGFELD: I mean, it doesn't tell me enough. And it tells me

DR. MARKS: Do you want to talk to Monice so when she reads that she doesn't feel

DR. ANSELL: Feelings are hurt?

DR. MARKS: Yes, feelings are hurt. At any rate, so we're going to move forward issuing a tentative report "safe with a concentration of 0.2 leaf extract" would be the conclusion.

DR. BERGFELD: How about needs a different abstract?

DR. MARKS: Okay. Thank you, Jay, for providing that clarification and suggestion of moving forward. Rather than "insufficient," we'll put a limit. Okay.

SEPT 2013 – FULL PANEL

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

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

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ABSTRACT

The Expert Panel assessed the safety of 10 Rosmarinus officinalis (rosemary)-derived ingredients and concluded Rosmarinus Officinalis (Rosemary) Leaf Extract is safe at ≤0.2% in leave-on products and safe as used in rinse-off products and that the data are insufficient to support the safety of Rosmarinus Officinalis (Rosemary) Flower Extract as used in cosmetics. The other eight ingredients are safe as used in cosmetics. 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 final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Industry should use good manufacturing practices to limit impurities. (This conclusion may change upon review of constituent data added to the since the issuance of the final report.)

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 waters 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.

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] Rosemary has a spicy, harsh, bitter, aromatic taste. Bluish labiate flowers grow on the upper green part of the branches. Rosemary oil is produced mostly in Spain, France, and Tunisia.[4]

Rosmarinus officinalis L. is generally recognized as safe (GRAS) as a spice and as a 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

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 ethanol extract is sometimes deodorized or partially deodorized ethanol.[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.

An additional method of manufacturing the cosmetic ingredients 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").[9]

Both rosmarinus officinalis (rosemary) leaf extracts and rosmarinus officinalis (rosemary) leaf oil can be produced by supercritical fluid extraction with natural CO_2 and a small amount of ethanol as a solvent.[10-13] A supplier of the leaf extract reported that the essential oil is removed by multistep separation,[12] and a supplier of the leaf oil adds a small amount (<4%) of sunflower oil to increase solubility when blending.[13]

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.[14] The oil from *Rosmarinus officinalis* is also obtained by hydrodistillation of dried crushed aerial parts.[15] Essential oils prepared by a steam distillation process yields two distinct fractions, a water-insoluble fraction and a water-soluble fraction.[1] The water-insoluble fraction contains the term oil in the name and the water-soluble fraction contains water in the name. So, rosmarinus officinalis (rosemary) leaf water is the water-soluble fraction of the steam distillation of *Rosmarinus officinalis* (rosemary) leaves.

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 Regulations, specific fragrance allergen compounds are subject to declaration on the label if the concentration of a specified allergen exceeds 0.001% in leave-on and 0.01% in rinse-off products.[20] One supplier reported 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.[21]

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 safety assessment provided information on the amount of constituents present in the test article; when this information was available, it is included.

The actual amount of constituents present also varies according to the stage of development, variety of plant, season harvested, and origin of the leaves.[2,8,22,23] High-performance liquid chromatography analysis of dimethyl sulfoxide (DMSO) extracts of rosemary leaves indicated the highest accumulation rate of the phenolic diterpenes carnosic acid, carnosol, and 12-*O*-methylcarnosic acid, of rosmarinic acid, and of the flavones genkwanin and isocutellarein 7-O-glucoside was found in the young stages of plant development.[24] The diterpenes and rosmarinic acid, but not the flavones, were found in the flower, stem, and root extracts at lower concentrations than in the leaves during the early stages of plant growth, but the concentration of each, except for 12-*O*-methylcarnosic acid, tended to increase during flowering. Rosmarinic acid concentrations in the leaves also decreased once flowering started, while the level in the flowers was slightly increased during flowering. The flavones acted similarly to carnosic acid.

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.[25] 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.[26]

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.[14]

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 is urged to avoid reaching levels of toxicity for constituents of concern in the final formulation. 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[27] and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council)[28,29] 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 were not provided. For example, rosmarinus officinalis (rosemary) flower extract is reported to be used in 36 cosmetic formulations, but no use concentration data were reported. In other cases, no uses were reported in the VCRP, but concentration of use data were received from industry; 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 (e.g., up to 3% rosmarinus officinalis (rosemary) leaf extract in eye shadow formulations) or mucous membranes (e.g., up to 3% rosmarinus officinalis (rosemary) leaf extract in bath soaps and detergents).[28] 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.[30-33] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[30,33] 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.[30] 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.[34]

Non-Cosmetic

Rosmarinus officinalis L. is GRAS as a spice and as a 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.[35] 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.[36] 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. Also, rosemary oil is reported to have antimicrobial activities.[4]

Anti-inflammatory, antioxidant, and anti-microbial uses have been reported for rosemary.[22,37-39] Rosemary has traditional or folk medicine uses, some with negative 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,[15] 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.[40] 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.[8,23,41-43] 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.[43] The oral LD_{50} of rosmarinus officinalis (rosemary) leaves is >2 g/kg,[23] of rosmarinus officinalis (rosemary) leaf extract is >8.5 g/kg,[8] and of rosmarinus officinalis (rosemary) leaf oil is 5.5 g/kg bw.[42]

Repeated Dose Toxicity

Repeated-dose toxicity studies are summarized in Table 10.[8,42] 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 some studies were performed for up to 3 mos (dietary) with doses of up to 400 mg/kg bw/day. 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 with carbon tetrachloride, but not without, resulted in an increase in liver weights.[42]

Ocular Irritation

Rosemary oil is reported to be a moderate ocular irritant.[22] (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.[44,45]

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.[44] 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 of the extract reduced edema by 80%, 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.[44] 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 statistically significant reduced 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.[45] 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, and 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.[45] The mice were killed after 1 h. Inflammation was inhibited by 12, 28, and 54%, respectively.

Effect on Epidermal Hyperplasia

Two-hundred µl acetone, 1 nmol TPA, or 1 nmol TPA and 3.6 mg rosmarinus officinalis (rosemary) leaf extract in 200 µl acetone was applied twice a day for 4 days to the dorsal skin of mice.[45] Three or four CD-1 mice were used per group.

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 aqueous 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.[46] The release of the cytokines interleukin (IL)-1α and IL-6 was prevented by the extract.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Non-Human

Rosmarinus Officinalis (Rosemary) Leaf Extract

Oral administration of high doses of rosmarinus officinalis (rosemary) leaf extract adversely affected fertility in male rats.[47] 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 and 0.5 mg progesterone at 54 and 6 h, respectively, prior to 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.

Body weights of the male rats of the test groups were similar to those of the control group. Compared with the controls, the high dose group exhibited statistically-significantly reduced absolute weights and organ-to-body weight ratios of testes and male accessory sex organs, diameters of seminiferous tubules and Leydig cell nuclei, height of epithelia of the epididymes and seminal vesicles, germinal and interstitial cell counts, levels of sex hormones, and sperm density and motility. The numbers of degenerating cells were statistically-significantly increased in the high-dose group. Exposure of the males to the high dose reduced the number of pregnant females, implantations and viable fetuses, and increased the number of resorptions. Results from the low-dose groups suggested dose-response trends in these parameters, although statistically-significant differences compared with controls were observed only in the high-dose group.

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).[48] 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.[49] (Details were not provided.)

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 either a diet containing 2% of a methanol extract of *Rosmarinus officinalis* (rosemary) leaves or the basal diet.[50] 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 hours 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 35-50% of the uterine response; this was statistically significant.

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.[51] 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; 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.[8,15,42,52-56] 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.[8] Various extraction solvents were used. Rosmarinus officinalis (rosemary) leaf oil was not mutagenic *in vitro* in an Ames test.[53] *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;[15] no genotoxic effects were seen in a micronucleus test at 1500 mg/kg bw/day with leaves extracted using absolute ethanol.[42] A mixture containing 19% *Rosmarinus officinalis* (rosemary) leaves, 71.5% St. John's Wort, and 9.5% spirulina 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.[52] *In vitro*, rosmarinus officinalis (rosemary) leaf extract was shown to have anti-mutagenic potential.[56] *In vivo*, in micronucleus assays, rosmarinus officinalis (rosemary) leaf extract did not decrease the number of MNPCEs induced by a genotoxic agent.[42]

CARCINOGENICITY

Effects on Tumor Promotion

Studies examining the effects of *Rosmarinus officinalis* (rosemary)-derived ingredients in tumor promotion 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

Skin irritation and sensitization studies are described in Table 13. 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.[57] However, in a rabbit study, occlusive application to intact and abraded skin produced moderate irritation.[43]

In clinical testing, *Rosmarinus officinalis* (rosemary) leaves produced irritation (scores of +/-, +, or ++) in 44/234 patients with contact dermatitis or eczema.[58] 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.[9] Formulations containing up to 0.2% rosmarinus officinalis (rosemary) leaf extract were not irritants or sensitizers.[59-61] 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;[43] a formulation containing 1.5% rosmarinus officinalis (rosemary) leaf oil was not an irritant or a sensitizer in an HRIPT.[62]

Phototoxicity

Rosmarinus Officinalis (Rosemary) Leaf Extract

The phototoxicity of rosmarinus officinalis (rosemary) leaf extract extracted with supercritical CO_2, as a concrete (insoluble wax) extracted in hexane, or as an absolute extracted in hexane, was evaluated.[9] Photopatch tests were performed on two of

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 14.[63-71] In some of the studies, follow-up patch testing included photopatch tests; generally, reactions were stronger in the photopatch tests, compared to standard testing.[67,68] Some of the follow-up patch testing included carnosol; testing with carnosol resulted in positive reactions.[64,68]

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, essential oils, powders, or waters 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 in cosmetics, and the most common functions 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 some studies were performed for up to 3 mos (dietary) with doses of up to 400 mg/kg bw/day. 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 with carbon tetrachloride, but not without, resulted in an increase in 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.

A high dose (500 mg/kg/day) of *Rosmarinus officinalis* (rosemary) leave extract was a reproductive toxicant in a dietary study in male rats. In a study in gravid female Wistar rats, no statistically significant changes were observed after oral dosing with 26 mg/day of a 30% aq. rosmarinus officinalis (rosemary) flower/leaf/stem extract during preimplantation or during organogenesis. 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 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.

DISCUSSION

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. *Rosmarinus officinalis* is GRAS as a spice, and although that alleviates the concern of oral exposure with cosmetic use, dermal irritation and sensitization data are necessary to determine safety. Because the Panel did not receive dermal sensitization data of rosmarinus officinalis (rosemary) leaf extract at the highest reported use concentration (i.e., 10%.), the Panel set a use concentration in leave-on products at the highest concentration for which test data were available (i.e., 0.2%).

The rosemary plant itself is well-defined in the published literature, but the chemical characterization of the flower is not well-defined. Because information on the chemical characterization of the flower was not provided, the Panel found the data insufficient for determining that safety of rosmarinus officinalis (rosemary) flower extract for use in cosmetics. (*If the recently added constituent data sufficiently address the characterization of the flower, this paragraph will be deleted.)*

Additional information on the deodorizing process that is part of the preparation of some of the ingredients also was not received. After further discussion, the Panel stated that because the deodorizing process is part of the preparation of food-grade rosmarinus officinalis (rosemary) extract, and because data are included in this safety assessment on some ingredients that were deodorized and no adverse effects were found, the Panel was not concerned with obtaining additional information on this process or the by-products that might form.

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, linalyl acetate, limonene, and methyleugenol.

The 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.

One study evaluated the irritation potential of *Rosmarinus officinalis* (rosemary) leaves in patients with contact dermatitis or eczema. The Panel stated that because the test subjects were patients with eczematous skin, the report of irritation could not be interpreted for relevance to cosmetic use.

The Panel discussed the positive results observed in a reproductive and development toxicity study in male rats fed 500 mg/kg/day, as well as the caution in the *PDR for Herbal Medicines* stating that rosemary preparations should not be used as a drug during pregnancy. The effects in the rat study were observed at exposure concentrations that would be well above those used in cosmetic products, and the *PDR* refers to the use of rosemary as a drug at very high concentrations. Because these effects were observed only at very high concentrations, reproductive and developmental toxicity is not a concern with cosmetic use of *Rosmarinus officinalis* (rosemary)-derived ingredients, which are mostly used at very low concentrations.

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

The CIR Expert Panel concluded that the following eight *Rosmarinus officinalis* (rosemary)-derived ingredients are safe in the present practices of use and concentration in cosmetics described in this safety assessment:

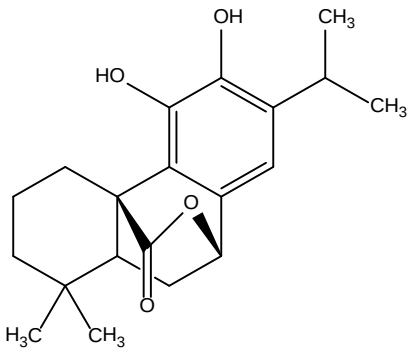
Rosmarinus Officinalis (Rosemary) Extract
Rosmarinus Officinalis (Rosemary) Flower/Leaf Stem Extract
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Water*
Rosmarinus Officinalis (Rosemary) Leaf
Rosmarinus Officinalis (Rosemary) Leaf Oil
Rosmarinus Officinalis (Rosemary) Leaf Powder
Rosmarinus Officinalis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

*Not reported to be in current use. If this ingredient was to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.

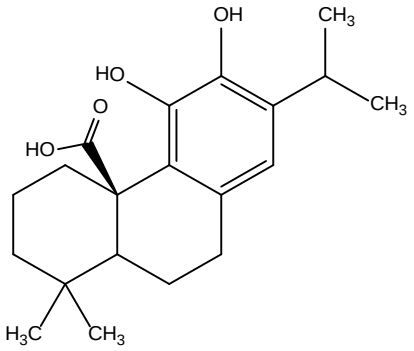
The Panel also concluded that Rosmarinus Officinalis (Rosemary) Leaf Extract is safe at ≤0.2% in leave-on products and safe as used in rinse-off products, and that the data are insufficient to support the safety of Rosmarinus Officinalis (Rosemary) Flower Extract as used in cosmetics. *(Note: This conclusion may change upon review of the constituent data that were added since the issuance of the tentative report.)*

FIGURES

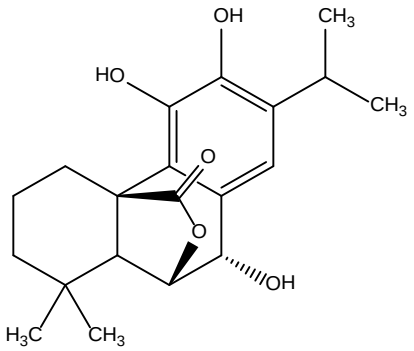
Figure 1. Principal diterpenes



1a. Carnosol

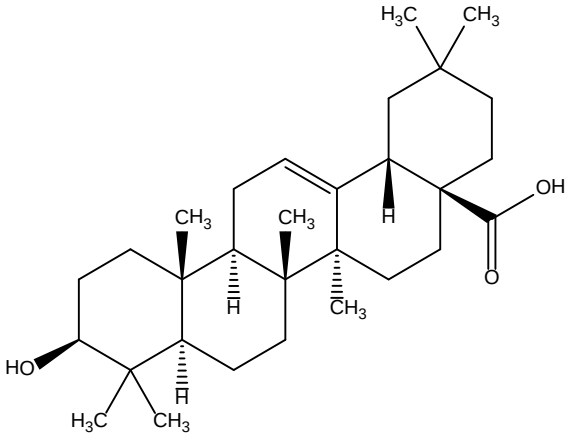


1b. Carnosic acid

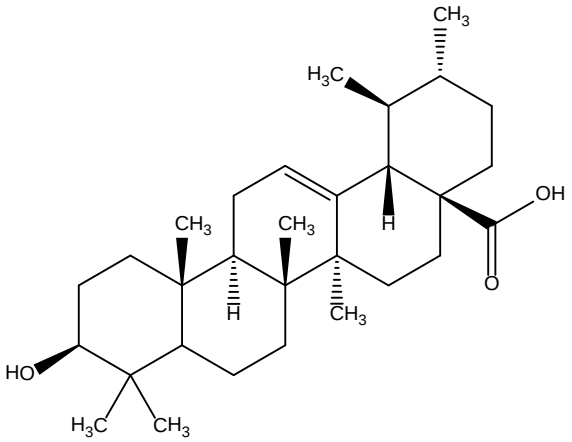


1c. Rosmanol

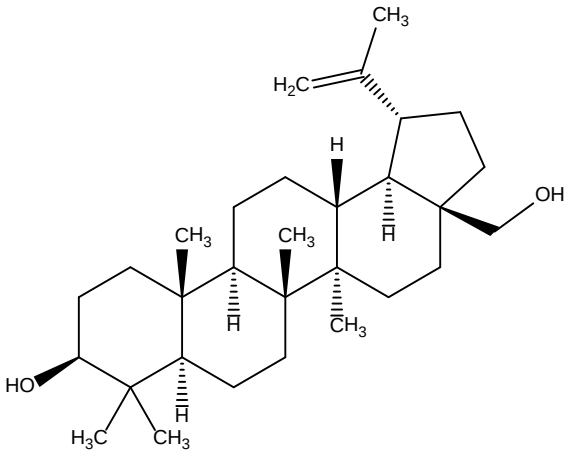
Figure 2. Principal triterpenes



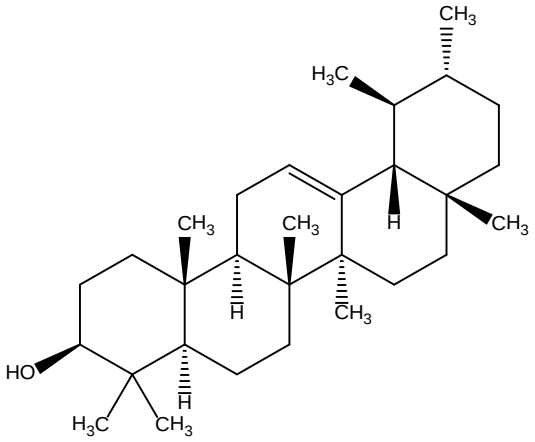
2a. Oleanolic acid



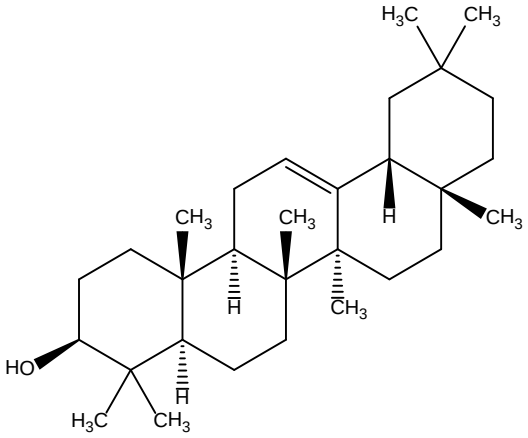
2b. Ursolic acid



2c. Betulin

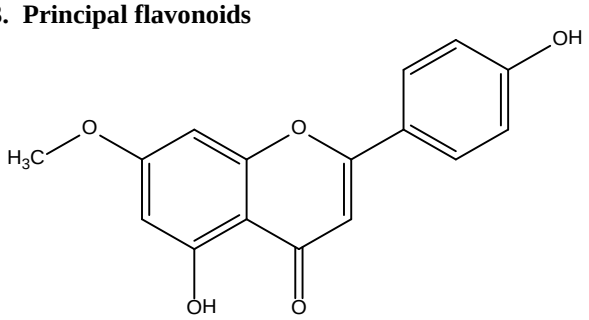


2d. α-Amyrin

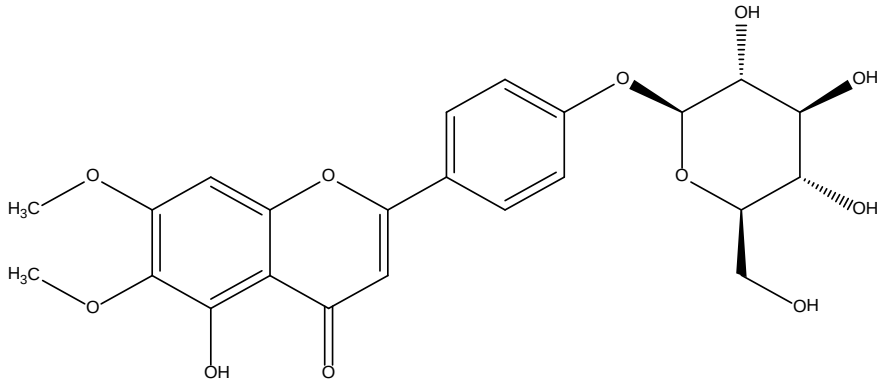


2e. β-Amyrin

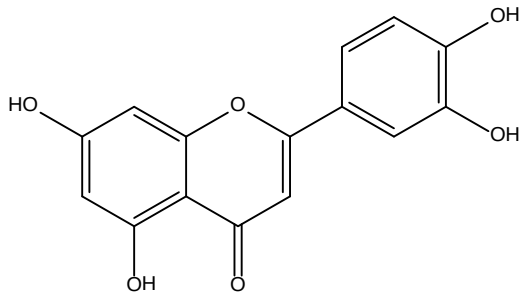
Figure 3. Principal flavonoids



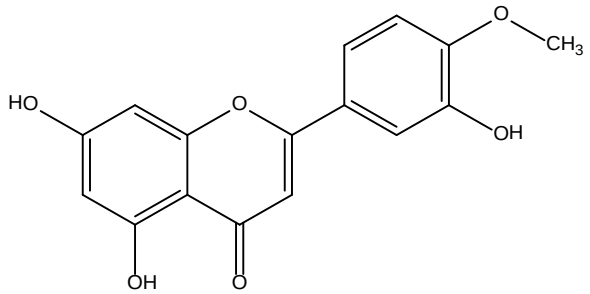
3a. Genkwanin



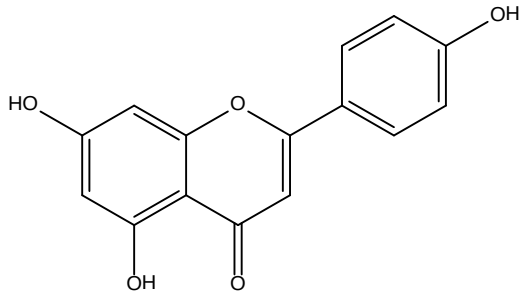
3b. Cirsimarin



3c. Luteolin

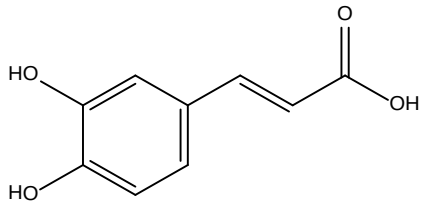


3d. Diosmetin

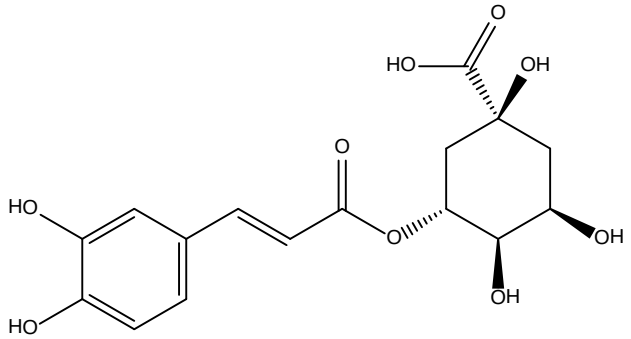


3e. Apigenin

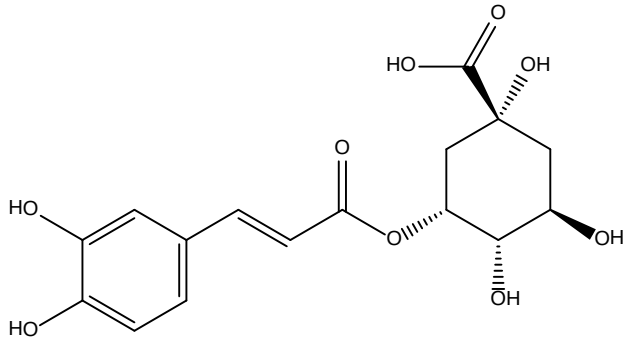
Figure 4. Phenolic acids



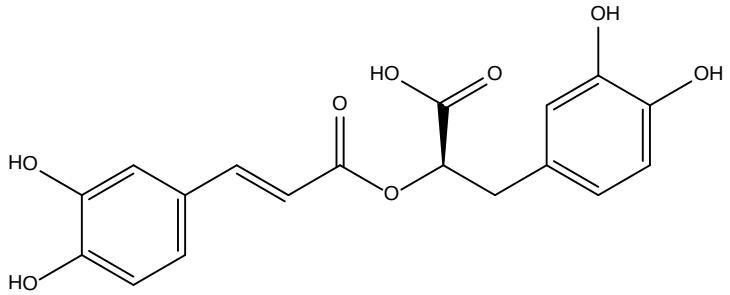
4a. Caffeic acid



4b. Chlorogenic acid

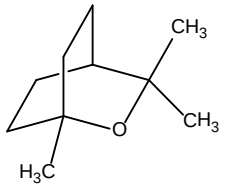


4c. Neochlorogenic acid

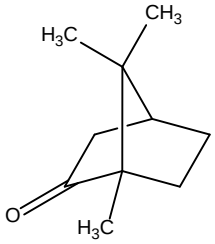


4d. Labiatic acid

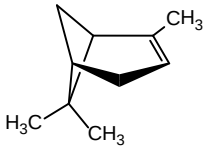
Figure 5. Principal Volatiles



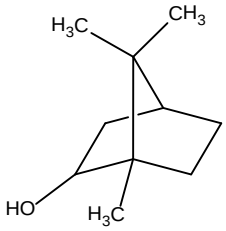
5a. 1,8-Cineole



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	37
	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)	10,11
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	14,36
	colorless, pale yellow, or pale green liquid with a camphorous odor	72
solubility	almost insoluble in water	36
	soluble in most vegetable oils; insoluble in alcohol and in propylene glycol	14
density (d^{25}_{25})	0.894-0.912	*36*
	0.907-0.920	72
index of refraction (n_D^{20})	1.464-1.476	36
	Rosmarinus Officinalis (Rosemary) Leaf Powder	
physical state and appearance	greyish-green to yellowish-green powder	37

Table 3. Chemical constituents by plant part (ppm) [73]

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) [73]

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) [73]

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) [73]

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) - 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	2,4,5
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 - 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	5,23,36,37,74
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	36,41,42,72,75
- From one sample (concentration in the oil): - monoterpenoid esters (24.76%): bornyl acetate (20.86%); linalyl 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%)	42
Flower	
- carnosic acid, carnosol, 12-*O*-methylcarnosic acid, at levels that are less than that found in the leaves - highest levels of rosmarinic acid are found in the flower - the flavones genkawanin and isoscutellarein 7-*O*-glucoside were not found in a DMSO extract	24
Seed	
- 560.5 µg/g α-tocotrienol; 300.3 µg/g β-tocotrienol; 109.4 µg/g γ-tocotrienol	76
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 - camphor (7.2%); berbonone (7.6%); linalool; verbenol; terpineol; 3-octanone; isobornyl acetate	4,77,78

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 [12,16]		
Essential Oil Content	<4	1.7
Phenolic diterpenes:		
rosmanol	n.s.	0.13
7-methyl-rosmanol	n.s.	0.32
carnosol	n.s	2.9
carnosic acid	> 16	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]

Constituent (ppm)	dried leaves	Extraction Method				
		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%[79] - caffeic acid is reported to penetrate skin and have UV photoprotective activity[80] - 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 animals of caffeic acid; no data were available on the carcinogenicity in humans, and IARC concluded that caffeic acid is possibly carcinogenic to humans[81] - 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[82]
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[80] -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[82]
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[80]
Diterpenes	
Carnosic Acid	- is a known antioxidant;[83] 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 route of elimination was the feces;[83] not mutagenic in an Ames test, with or without metabolic activation, at doses equivalent to 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;[45] 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]
Monoterpenes	these chemicals may be skin sensitizers[80]
d- Limonene	- d-limonene consumption has been estimated as 0.2 -2 mg/kg bw/day; in men, oral intake induced transient proteinuria[81] - 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;[84] - the few genotoxicity studies available indicated that *d*-limonene and its 1,2-epoxide metabolite are not genotoxic[84] - 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[84]
α-Pinene	negative in the Ames assay and a mouse micronucleus test[85]

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

Component	Toxicity information
1,8-Cineole	positive in a sister chromatid exchange assay; negative in a chromosomal aberration assay; negative in an Ames test[86]
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[87]
Linalool	safe at up to 4.3% (20% in consumer fragrance); listed as a fragrance allergen by the European Commission[80]
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[88]
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[89]
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[90]
Ursolic acid	topical application of carnosol isolated from rosemary inhibited TPA-induced ear inflammation and tumor promotion in mice[45]
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[80]

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

	# of Uses[27]	*Max. Conc. of Use (%)*[28]	*# of Uses*[27]	*Max. Conc. of Use (%)*[28]	*# of Uses*[27]	*Max. Conc. of Use (%)*[28]
	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]	0.00096-0.009[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[27]	*Max. Conc. of Use (%)*[28]	*# of Uses*[27]	*Max. Conc. of Use (%)*[28]	*# of Uses*[27]	*Max. Conc. of Use (%)*[28]
	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 may not equal the sum of total uses
NR – not reported
[a] Includes suntan preparations, and it 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	[43]
Rosmarinus Officinalis (Rosemary) Leaf Oil	-----	rabbits	not stated	not stated	not stated	>10 g/kg	[41]
			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 ex tract carnosol, carnosic acid, total diterpenes, respectively)	supercritical CO_2	Wistar rats	6 M/6F	corn oil	2 g/kg bw [8,23,41-43](gavage)	>2 g/kg	[23]
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	[42]
Rosmarinus Officinalis (Rosemary) Leaf Oil (see Table 5 for composition)	-----	rats	not stated	none stated	not stated	5 ml/kg bw	[43]

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	42
			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	42
			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	56
as above	-----	50 µg/ml (highest non-cytotoxic dose)	comet assay	human hepatoma cell line (HepG2)	not genotoxic	56
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	56
as above	-----	5 µg/ml (highest non-cytotoxic dose)	comet assay	human hepatoma cell line (HepG2)	not genotoxic	56
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	53

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	54
Rosmarinus Officinalis	hydro-alcoholic	6.43, 100, and 200 mg/kg bw	micronucleus assay	Wistar rats; 6/group	not genotoxic	54
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	42
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 ($p<0.01$)	42
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	15
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	15
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	15
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 CPA/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	15
mixture containing 19% Rosmarinus officinalis (rosemary) leaves, 71..5% St. John's Wort; 9.5% spirulina	-----	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	52
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	52

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	52
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	55
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	56
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	56
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	56
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	56
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	56
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	56
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	56
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	56
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	56
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	56

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	56
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`	56
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	56
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	56
			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	42
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	42

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. Effects on Tumor Promotion

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	45
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	45
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	45
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	91
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.	92

Table 12. Effects on Tumor Promotion

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	93

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. Dermal Irritations and Sensitization

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
4.4% rosmarinus officinalis (rosemary) leaf oil (and other essential oils)	tested at concentrations up to 40%	Lewis rats	ointment was applied to the shaved skin of Lewis rats twice daily, for 14 days	not irritating no gross or microscopic lesions were reported in the skin	57
rosmarinus officinalis (rosemary) leaf oil	undiluted	rabbits	applications were made to intact and abraded rabbit skin under occlusion; no other details were provided	moderately irritating	43
			HUMAN		
Rosmarinus officinalis (rosemary) leaves	undiluted in sufficient petrolatum for binding	234 patients with contact dermatitis or eczema	patch test	21 had +/- reactions; 18 had a + reaction; 5 had a ++ reaction; no subjects had a +++ reaction	58
Rosmarinus officinalis (rosemary) leaves extracted with supercritical CO_2	undiluted in petrolatum	20 subjects	epicutaneous test using Finn chambers	weak irritant 1 positive reaction	9
Rosmarinus officinalis (rosemary) leaves as an absolute (soluble in hexane)	undiluted in petrolatum	25 subjects	epicutaneous test using Finn chambers	weak irritant 2 positive reactions	9
	2% and 10%	23 subjects previously sensitized to peru balsam and/or perfumes or fragrance materials	epicutaneous test using Finn chambers	weak effect	

Table 13. Dermal Irritations and Sensitization

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Rosmarinus officinalis (rosemary) leaves as a concrete (insoluble waxes) extracted in hexane	undiluted in petrolatum	20 subjects	epicutaneous test using Finn chambers	no reactions	9
	2% and 10%	23 subjects previously sensitized to peru balsam and/or perfumes or fragrance materials	epicutaneous test using Finn chambers	weak effect	
cream containing 0.2% rosmarinus officinalis (rosemary) leaf extract	undiluted	20 subjects	a 24 h single insult occlusive patch test	not an irritant no reactions were observed, and the primary irritation index was 0.00	59
hair spray containing 0.0013% rosmarinus officinalis (rosemary) leaf extract	neat	102 subjects	modified Draize HRIPT induction: occlusive patches were applied for 24 h, and the sites were scored prior to the application of the next patch; patches were applied 3x/wk for 3 wks; the material was allowed to volatilize for 30 min prior to application challenge: 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	not an irritant or sensitizer transient, barely perceptible to mild responses were observed in some subjects, but was not considered related to skin irritation or an allergic reaction	61
sunscreen cream containing 0.2% rosmarinus officinalis (rosemary) leaf extract	neat	27 subjects	maximization test induction: an occlusive patch containing 0.1 ml of 0.25% aq. SLS was applied to the upper outer arm, volar forearm, or back of each subject for 24 h; the SLS patch was removed and an occlusive patch with 0.1 ml 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 challenge: 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	not a contact-sensitizer no reactions were observed	60
Rosmarinus officinalis (rosemary) leaf oil	10% in petrolatum	not specified	48-h closed patch test; details not provided	not an irritant	43
Rosmarinus officinalis (rosemary) leaf oil	10% in petrolatum	25 subjects	maximization test; details not provided	not a sensitizer	43

Table 13. Dermal Irritations and Sensitization

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
leave-on massage oil containing 1.5% rosmarinus officinalis (rosemary) leaf oil	neat	104 subjects	HRIPT induction: 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; 9 induction patches were applied. challenge: performed 12-14 days after induction at the original test site and a previously untested site for 48 h; sites were scored at 48 and 96 h patches of 0.5% SLS were used as a positive control, and deionized water as a negative control	did not induce allergic contact dermatitis no reactions were observed at induction or challenge	62

Abbreviations: human repeated insult patch test (HRIPT); sodium lauryl sulfate (SLS)

Table 14. 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	63
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	64
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	65
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)	66
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	67
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	68
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	69
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	70
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	71

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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

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

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

DATE: December 10, 2013

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

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Concentration of Use by FDA Product Category

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) 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

Ingredient	FDA Code†	Product Category	Maximum Concentration of Use
Rosmarinus Officinalis (Rosemary) Extract	03C	Eye shadow	0.01%
Rosmarinus Officinalis (Rosemary) Extract	03D	Eye lotion	0.01%
Rosmarinus Officinalis (Rosemary) Extract	03F	Mascara	0.05%
Rosmarinus Officinalis (Rosemary) Extract	05A	Hair conditioners	0.00004%
Rosmarinus Officinalis (Rosemary) Extract	05F	Shampoos (noncoloring)	0.00004-0.003%
Rosmarinus Officinalis (Rosemary) Extract	05G	Tonics, dressings and other hair grooming aids	0.001%
Rosmarinus Officinalis (Rosemary) Extract	07B	Face powders	0.05%
Rosmarinus Officinalis (Rosemary) Extract	07C	Foundations	0.051%
Rosmarinus Officinalis (Rosemary) Extract	07E	Lipstick	0.011%
Rosmarinus Officinalis (Rosemary) Extract	10A	Bath soaps and detergents	0.0005-0.16%
Rosmarinus Officinalis (Rosemary) Extract	10B	Deodorants not spray aerosol	 0.0098% 0.0098-0.012%

Rosmarinus Officinalis (Rosemary) Extract	11E	Shaving cream (aerosol, brushless and lather)	0.009%
Rosmarinus Officinalis (Rosemary) Extract	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.04%
Rosmarinus Officinalis (Rosemary) Extract	12C	Face and neck products not spray	0.05%
Rosmarinus Officinalis (Rosemary) Extract	12D	Body and hand products not spray	0.00096%
Rosmarinus Officinalis (Rosemary) Extract	13A	Suntan products not spray	0.01%
Rosmarinus Officinalis (Rosemary) Extract	13B	Indoor tanning preparations	0.00096%
Rosmarinus Officinalis (Rosemary) Flower/Leaf/Stem Extract	10B	Deodorants not spray	0.0024%
Rosmarinus Officinalis (Rosemary) Leaf	05G	Tonics, dressings and other hair grooming aids	0.002%
Rosmarinus Officinalis (Rosemary) Leaf Extract	01B	Baby lotions, oils and creams	0.012%
Rosmarinus Officinalis (Rosemary) Leaf Extract	02A	Bath oils tablets and salts	0.0002%
Rosmarinus Officinalis (Rosemary) Leaf Extract	02B	Bubble baths	0.0004%
Rosmarinus Officinalis (Rosemary) Leaf Extract	02D	Other bath preparations	0.04%
Rosmarinus Officinalis (Rosemary) Leaf Extract	03B	Eye liner	0.02-0.063%
Rosmarinus Officinalis (Rosemary) Leaf Extract	03C	Eye shadow	0.13-3%
Rosmarinus Officinalis (Rosemary) Leaf Extract	03D	Eye lotion	0.002-0.1%

Rosmarinus Officinalis (Rosemary) Leaf Extract	04A	Colognes and toilet waters	0.001%
Rosmarinus Officinalis (Rosemary) Leaf Extract	04E	Other fragrance preparations	0.5%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05A	Hair conditioners	0.0001-0.11%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05B	Hair sprays aerosol pump spray	 0.0016% 0.0001-0.005%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05E	Rinses (noncoloring)	0.0002%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05F	Shampoos	0.00005-0.11%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05G	Tonics dressings and other hair grooming aids spray	0.00002-0.5% 0.0004%
Rosmarinus Officinalis (Rosemary) Leaf Extract	05I	Other hair preparations (non-coloring)	0.00001%
Rosmarinus Officinalis (Rosemary) Leaf Extract	06G	Hair bleaches	0.04%
Rosmarinus Officinalis (Rosemary) Leaf Extract	07B	Face powders	0.0002%
Rosmarinus Officinalis (Rosemary) Leaf Extract	07C	Foundations	0.001-0.0015%
Rosmarinus Officinalis (Rosemary) Leaf Extract	07D	Leg and body paints	0.014%
Rosmarinus Officinalis (Rosemary) Leaf Extract	07E	Lipstick	0.00001-0.009%
Rosmarinus Officinalis (Rosemary) Leaf Extract	07F	Makeup bases	0.001%
Rosmarinus Officinalis (Rosemary) Leaf Extract	08B	Cuticle softeners	0.005%
Rosmarinus Officinalis (Rosemary) Leaf Extract	08G	Other manicuring preparations	0.053%
Rosmarinus Officinalis (Rosemary) Leaf Extract	10A	Bath soaps and detergents	0.001-3%

Rosmarinus Officinalis (Rosemary) Leaf Extract	10E	Other personal cleanliness products	0.002-0.02%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00001-0.38%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12B	Depilatories	0.0002-0.01%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12C	Face and neck products not spray	 0.00004-0.1%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12D	Body and hand products not spray spray	 0.0005-10% 0.002%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12F	Moisturizing products not spray	 0.0013-0.5%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12G	Night products not spray	 0.012%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12H	Paste masks and mud packs	0.001-0.06%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12I	Skin fresheners	0.4%
Rosmarinus Officinalis (Rosemary) Leaf Extract	12J	Other skin care preparations	0.005-0.013%
Rosmarinus Officinalis (Rosemary) Leaf Extract	13A	Suntan products not spray	 0.05%
Rosmarinus Officinalis (Rosemary) Leaf Oil	02A	Bath oils, tablets and salts	0.5-0.97%
Rosmarinus Officinalis (Rosemary) Leaf Oil	04C	Powders (dusting and talcum)	0.0003%
Rosmarinus Officinalis (Rosemary) Leaf Oil	05A	Hair conditioners	0.05-0.12%
Rosmarinus Officinalis (Rosemary) Leaf Oil	05B	Hair sprays aerosol	 0.007%

Rosmarinus Officinalis (Rosemary) Leaf Oil	05E	Rinses (noncoloring)	0.04%
Rosmarinus Officinalis (Rosemary) Leaf Oil	05F	Shampoos (noncoloring)	0.00001-0.32%
Rosmarinus Officinalis (Rosemary) Leaf Oil	05G	Tonics, dressings and other hair grooming aids	0.006-1.5%
Rosmarinus Officinalis (Rosemary) Leaf Oil	07C	Foundations	0.02%
Rosmarinus Officinalis (Rosemary) Leaf Oil	07E	Lipstick	0.008%
Rosmarinus Officinalis (Rosemary) Leaf Oil	07F	Makeup bases	0.0036%
Rosmarinus Officinalis (Rosemary) Leaf Oil	10A	Bath soaps and detergents	0.0002-0.61%
Rosmarinus Officinalis (Rosemary) Leaf Oil	11A	Aftershave lotions	0.0012%
Rosmarinus Officinalis (Rosemary) Leaf Oil	11E	Shaving cream (aerosol, brushless and lather)	0.0039%
Rosmarinus Officinalis (Rosemary) Leaf Oil	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.015-0.04%
Rosmarinus Officinalis (Rosemary) Leaf Oil	12C	Face and neck products not spray spray	 0.032-0.55% 0.011%
Rosmarinus Officinalis (Rosemary) Leaf Oil	12D	Body and hand products not spray spray	 0.002-1.5% 1.5%
Rosmarinus Officinalis (Rosemary) Leaf Oil	12F	Moisturizing products not spray	0.005%
Rosmarinus Officinalis (Rosemary) Leaf Oil	12H	Pastes masks and mud packs	0.01%
Rosmarinus Officinalis (Rosemary) Leaf Powder	05A	Hair conditioners	0.05%

Rosmarinus Officinalis (Rosemary) Leaf Water	03D	Eye lotion	0.00016%
Rosmarinus Officinalis (Rosemary) Leaf Water	03F	Mascara	0.000069%
Rosmarinus Officinalis (Rosemary) Leaf Water	05A	Hair conditioners	0.00022%
Rosmarinus Officinalis (Rosemary) Leaf Water	05F	Shampoos (noncoloring)	0.00019-0.25%
Rosmarinus Officinalis (Rosemary) Leaf Water	05G	Tonics, dressings and other hair grooming aids	1%
Rosmarinus Officinalis (Rosemary) Leaf Water	07C	Foundations	0.00009%
Rosmarinus Officinalis (Rosemary) Leaf Water	07E	Lipstick	0.005%
Rosmarinus Officinalis (Rosemary) Leaf Water	11E	Shaving cream (aerosol, brushless and lather)	0.00015-0.07%
Rosmarinus Officinalis (Rosemary) Leaf Water	12C	Face and neck products not spray	0.36%
Rosmarinus Officinalis (Rosemary) Leaf Water	12D	Body and hand products not spray	0.00015-0.002%

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

†Product category codes used by FDA

Information collected in 2013
Table prepared: June 5, 2013
Updated June 13, 2013: added Rosmarinus Officinalis (Rosemary) Leaf Oil
Updated November 25, 2013: Rosmarinus Officinalis (Rosemary) Extract: indicated that the suntan product for which 0.1% use concentration was reported is not a spray.

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Memorandum

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

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

DATE: February 7, 2014

SUBJECT: *Rosemarinus officinalis*: Composition of flowers and other plant parts

The attached paper, that is not yet cited in the CIR report, includes some information on the composition of the flowers of *Rosmarinus officinals*.

Del Baño MJ, Lorente J, Castillo J, et al. 2003. Phenolic diterpenes, flavones and rosmarinic acid distribution during the development of leaves, flowers, stems, and roots of *Rosmarinus officinalis*. Antioxidant activity. Journal of Agricultural and Food Chemistry, 51: 4247-4253.

DMSO extracts of leaves, flowers, stems and roots from rosemary plants at various ages were studied. In the results section (p.4249), the study authors state: "The chromatograms obtained for flower, stem, and root extracts are similar, although the relative proportions of each compound differ, and peaks 5 [genkwanin] and 6 [isoscutellarien 7-O-glucoside] are absent from the flower, stem and root extracts." The authors also state that no flavones were detected in the flowers, stems and roots. Figure 4 of the paper (p.4250) shows that the levels of carnosic acid, carnosol and 12-O-methylcarnosic acid in the flowers are less than found in leaves, while figure 5 shows that with the exception of young leaves, the highest levels (about 1.5% dry weight) of rosmarinic acid are found in the flower.

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Memorandum

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

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

DATE: December 5, 2013

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

Key Issue

As the *PDR for Herbal Medicines* concerns the drug use of rosemary, it is not necessary to include the recommendation that rosemary not be used as a drug during pregnancy in the CIR report. The concern about use during pregnancy is a recommendation that is not relevant for the food or cosmetic use of this herb. This would also be consistent with other CIR reports that do not include citations to the *PDR for Herbal Medicines* concerning drug use.

Additional Comments

Table of Contents - The table of contents is not helpful if the pages of the report are not numbered.

Preparation/Extraction, Rosmarinus Officinalis (Rosemary) Leaf Oil - The description of the product produced by CO_2 extraction needs to be moved to the extract subsection.

Preparation/Extract - If the waters are left in the report, please add a description of how waters are produced (see the Introduction of the *Dictionary* for a general description of how plant waters are produced).

Constituents/Impurities - The European Cosmetics Directive (incorrectly called Guideline) 76/768/EEC is no longer in force. Instead, please refer to the new European Cosmetics Regulations.

Toxicological Studies, Genotoxity - When referring to a specific study in the text, please include references to make it easier to find the additional details in the Tables.

Reproductive and Developmental Toxicity, Human - What toxic side effects may occur with components of the essential oil? At what doses do these side effects occur?

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Skin Irritation/Sensitization, Non-Human - What tissues/organs did they examine microscopically in reference 47? It currently states: "No gross or microscopic lesions were reported." Does this just refer to the skin, or were other organs examined?

Skin Irritation/Sensitization, Human, Rosmarinus Officinalis (Rosemary) Leaf Extract - The identity of the materials studied in reference 12 is not clear. It states: "as a concrete (insoluble waxes) extracted in hexane" and "a concrete (insoluble waxes) extracted in hexane". Is there a difference between these two substances? As rosemary wax was removed from the report, it is not clear that information on insoluble wax needs to be included in this report.

Summary - Please indicate that the oils included in the report are "essential" oils.

Summary, Table 11 - Rather than calling spirulina an algae, it would be more appropriate to call it a cyanobacteria.

Table 5 - Please correct: "0.t3"

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Memorandum

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

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

DATE: January 15, 2014

SUBJECT: Comments on the Tentative Report: Safety Assessment of *Rosmarinus officinalis*-Derived Ingredients as Used in Cosmetics

Key Issue

The report needs to make clear that the ingredient named "oil" is an essential oil (not a triglyceride oil), and that the ingredients named "water" included in this report are "the water soluble fraction from the steam distilled plant material" (from the definition of the chemical class essential oils and water). As presented in the Introduction and Summary, it is not correct to substitute the word "solution" to describe the ingredients that are named as "waters". Only ingredients prepared by steam distillation of plant material are called "water" in the *Dictionary*. Solution is a much more general term not defined in the *Dictionary*, and it should not be used instead of the word "water".

In addition to being used in food, the antioxidant extracts of rosemary are used in cosmetics (hence some suppliers provided data to support the CIR review). Therefore, the Discussion should not imply that these extracts are not used in cosmetics. The CIR Expert Panel should expect that processes used to deodorize extracts (generally gentle heating, striping under vacuum and/or filtration through activated carbon or gels) do not significantly change the compounds in the extract. In addition, safety data on the deodorized extract support the safety of this ingredient.

If the cancer study of limonene is mentioned in Table 7, it needs to be clearly stated that renal tumors in male rats exposed to limonene occur by a mechanism that is not relevant to humans. The CIR Expert Panel has reviewed other male rat renal carcinogens and they consider alpha 2U-globulin nephropathy not relevant to humans.

For example see the abstract (truncated at 400 words) of the following reference for information on limonene:

Hard GC, Whysner J. 1994. Risk assessment of d-limonene: an example of male rat-specific renal tumorigens. Crit Rev Toxicol. 24(3):231-54.

"The naturally occurring food constituent d-limonene has been found to cause tumors at high doses only in the kidney of the male rat in association with the development of hyaline droplet nephropathy. In contrast, neither kidney tumors nor the associated nephropathy have been found in female rats or mice at much higher doses. Adult male rats produce large quantities of a specific low-molecular-weight protein in the liver, which is known as alpha 2U-globulin (alpha 2U-g). With administration of sufficient doses of d-limonene to male rats, this protein has been found to accumulate excessively in the P2 segment cells of renal proximal tubules, resulting in hyaline droplet formation as a manifestation of protein overload. Hyaline droplet accumulation is the first stage in a unique sequence of nephropathic lesions (also known as alpha 2U-g nephropathy), including granular casts in the outer medulla and linear mineralization in the papilla. The mechanism underlying protein accumulation appears to be the reversible binding of chemical to alpha 2U-g with subsequent prolongation of its half-life in the tubule cell. In the case of d-limonene, the minor metabolite d-limonene-1,2-oxide has been shown to be the primary chemical species that binds reversibly to alpha 2U-g, impeding the normal process of lysosomal proteinase degradation of alpha 2U-g. The ensuing nephropathy is associated with a sustained increase in compensatory renal tubule cell proliferation, which provides the putative mechanistic link with renal tumor formation possibly through tumor promotion of spontaneously initiated cells or enhanced spontaneous mutagenesis. This proposed mechanism has been supported by additional information, including negative genotoxicity tests for d-limonene and its oxide metabolites, experimentally verified tumor promotion, and enhanced cell proliferation primarily in P2 segment tubule cells in male F344 rats, but no such effects in the alpha 2U-g-deficient NBR rat. The mechanism of d-limonene tumor development does not appear to be possible in humans since neither the quantity nor the type of protein that binds d-limonene or d-limonene-1,2-oxide is present. The deduction that the renal tumors induced in male rats are not relevant to human carcinogenicity in the hazard evaluation step of risk assessment completes the evaluation of human risk for d-limonene. Consequently, it can be concluded that d-limonene does not pose any carcinogenic or nephrotoxic risk to humans."

Additional Comments

p.1 - In the General Characterization section, please call the "oil" "essential oil"

p.2 - In the description of the European allergen labeling regulations, it is not clear what is meant by "this substance".

p.4, 8 - How was liver weight affected in oral studies of Rosmarinus Officinalis (Rosemary) Leaf Oil?

p.4 - Please correct: "mice per groups"

p.8, p.10 - In the Summary and Discussion, please state that the study at 500 mg/kg/day was in male rats.

p.9, p.22, Table 4 - Please correct "linolyl actate" to "linalyl acetate" (the acetic acid ester of linalool)

p.10 - As it refers to the plant, *Rosmarinus officinalis* should be italicized (last line of first paragraph).

p.18-21, Table 3 - The columns for Resin Exudate, Sap, Essential Oil and Tissue Culture should be deleted from this table as there is little information about these fractions in the table. As tissue culture is not used to prepare any of the ingredients included in this report, the tissue culture column is not needed. Table 4 provides better information concerning the composition of the essential oil.

p.22, Table 4 - As none of the ingredients are derived from rosemary seed, the information on the tocotrienol levels in rosemary seeds should be deleted from Table 4.

p.24, Table 7 - Because the previous sentence mentions chlorogenic acid in addition to caffeic acid, it is not clear if the IARC conclusion is for caffeic acid or chlorogenic acid. "animal" needs to be corrected to "animals"; please correct "rout" and "equivalent of the concentration"

p.25, Table 7 - What dose of limonene is associated with transient proteinuria in men? What dose of limonene is associated with delayed prenatal growth? Please correct "slight increase is SCEs". The fact that linalool is considered a fragrance ingredient in Europe should not be cited to a CIR report (reference 78). Please correct "increase in in cancer". On what information is the IARC conclusion on Methyleugenol based? What doses or concentrations of alpha-Terpineol were used in the i.p. study, the irritation studies and the sensitization studies?

p.26, Table 8 footnotes - Please correct: "my not equal" "it t is not known"

p.27, Table 9 - Why are the references 8, 22, 39-41 included with the 2 g/kg bw dose cited to reference 22?

p.31, Table 11 - In the 8th row, cyclophosphamide should be abbreviated (CPA) to be consistent with the rest of the table.

p.40, Reference 79 - Please correct "Su mmary"