Safety Assessment of Camellia Sinensis-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.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, Ph.D; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢ cirinfo@cir-safety.org

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MEMORANDOM

To: CIR Expert Panel and Liaisons

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

Date: May 16, 2014

Subject: *Camellia sinensis* – Derived Ingredients As Used In Cosmetics

This is the Draft Final Report of Camellia sinensis-derived ingredients. In March 2014, the Panel concluded that camellia sinensis leaf extract is safe up to 0.86% in leave-on products and up to 1% in rinse-off products; and that camellia sinensis catechins is safe as used. There is not enough data to come to a conclusion of safety for the ingredients that are not derived from the leaves and stems. To make a determination of safety for these ingredients, the Panel indicated that the following data are needed:

- method of manufacture
- characterization of these ingredients
- human sensitization data, in particular for camellia sinensis leaf powder at 50%
- concentration of use in cosmetics

The CIR Science Support Committee has submitted comments, included with this packet, in which they suggest that portions of the conclusion be reconsidered:

- Catechins should not be safe as used if there are no uses reported. There is also concern about the positive guinea pig sensitization studies.
- The leaf extract only has data for “black tea” and not for other possible forms for which this ingredient may be used.
- The conclusion for the leaf extract could be extended to the other leaf-derived ingredients.

No new data were submitted to address the identified needs. Information from two repeated dose inhalation papers have been added to this safety assessment.

There has been no confirmation that camellia sinensis leaf water is used only as a fragrance. Therefore, the ingredient remains in this report.

The National Toxicology Program has issued a report on green tea extract for public comment but is not available for attribution. The abstract of this report, included in this package, contains robust summaries of the studies performed. The Panel should review the summaries and decide if any of this information is important enough to this safety assessment to wait for the data or if it would change the conclusions set by the Panel in March. If so, then the Panel may elect to table this report until this data is available to site. If the information does not significantly add to this report, the Panel may advance the progress of the safety assessment. The entire 230 page report is available at:
http://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2014/may/draft_tr585_508.pdf#search=Camellia%20sinensis

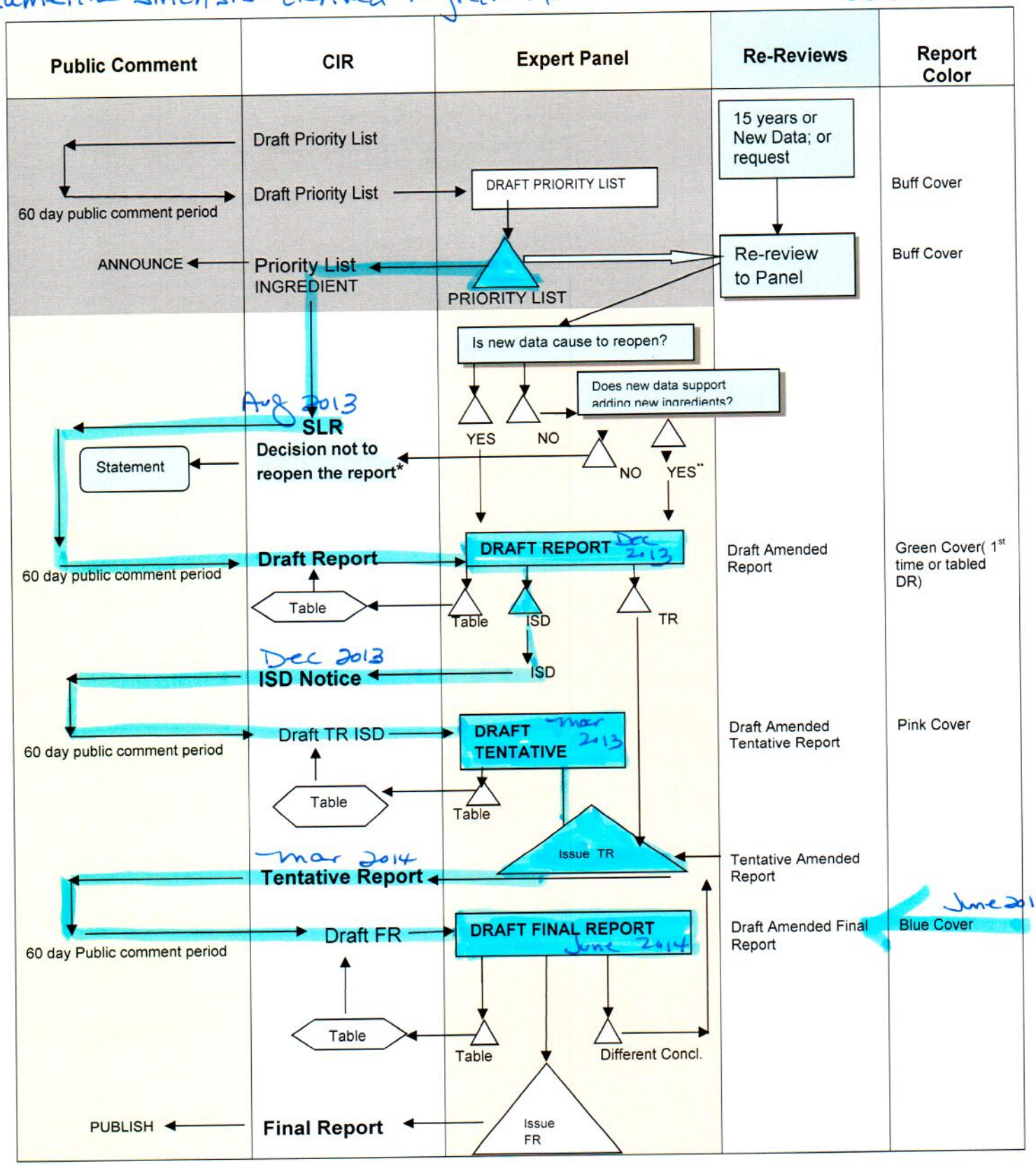
1620 L Street, NW Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

The Panel is to review the presented data and review the Abstract, Discussion, and Conclusion to ensure that they reflect the Panel's thinking. If the Panel is satisfied, and the report is not tabled for the NTP data, then the Panel is to issue a Final Report.

SAFETY ASSESSMENT FLOW CHART

Camellia Sinensis-derived ingredients

June 2014



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

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

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History
***Camellia Sinensis*-Derived Ingredients**

August, 2013 – SLR posted for comment.

December, 2013 – An insufficient data announcement was issued. The data needs were:

- Method of manufacture, including removal of impurities and constituents of concern (such as linalool)
- Composition data for camellia sinensis root extract, seedcoat powder, flower extract, and flower/leaf/stem juice
- Concentration of use data for camellia sinensis root extract, seedcoat powder, flower extract, flower/leaf/stem juice, and the catechins
- Human repeated insult patch test (HRIPT) on camellia sinensis leaf (100%), camellia sinensis stem/leaf extract (3%), and camellia sinensis catechins (at use concentrations)
- Confirmation that camellia sinensis leaf water is only used as a fragrance ingredient
- Information on the difference between leaf oil and leaf essential oil

Camellia sinensis seed oil was removed from the report because it was included in the oils report.

March, 2014 - Panel examined the draft report with the additional data and updated concentration of use information. A Tentative Report was issued with a mixed conclusion. The Panel concluded that camellia sinensis leaf extract is safe up to 0.86% in leave-on products and up to 1% in rinse-off products. Camellia sinensis catechins is safe as used. There is not enough data to come to a conclusion of safety for the ingredients that are not derived from the leaves and stems. To make a determination of safety of these ingredients, the Panel needs data on:

- method of manufacture
- characterization of these ingredients
- human sensitization data, in particular for camellia sinensis leaf powder at 50%
- concentration of use in cosmetics

The Panel also requests confirmation that camellia sinensis leaf water is used only as a fragrance.

No new data have been submitted to meet these data needs.

June, 2014 – The Panel is to issue a Final Report.

Camellia Sinensis-Derived Ingredients Data Profile for December, 2013. Writer - Lillian Becker																		
	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Camellia Sinensis Leaf Extract	X		X								X			X	X		X	X
Camellia Sinensis Catechins	X								X	X	X	X	X		X	X	X	X
Camellia Sinensis Flower Extract																		
Camellia Sinensis Flower/Leaf/Stem Juice																		
Camellia Sinensis Leaf			X															
Camellia Sinensis Leaf Oil			X															
Camellia Sinensis Leaf Powder			X															
Camellia Sinensis Leaf Water			X									X		X				
Camellia Sinensis Root Extract																		
Camellia Sinensis Seedcoat Powder																		
Camellia Sinensis Seed Extract																		
Camellia Sinensis Seed Oil *REMOVED*																		
Camellia Sinensis Seed Powder																		
Hydrolyzed Camellia Sinensis Leaf																		
Hydrolyzed Camellia Sinensis Seed Extract																		

Camellia sinensis-Derived Ingredients
Search Strategy

SciFinder – "camellia sinensis dermal" culled for toxicity and relevant terms. 17 results

Internet Search – "Camellia sinensis". Tea Association information; Committee on Diet, Nutrition, and Cancer; European Medicines Agency; FDA Drug application and GRAS submission; and IARC.

SciFinder – "camellia sinensis" and "UV". 19 hits ordered
And "inhalation". Papers on using *C. sinensis* to treat pulmonary MRSA.

Transcripts – *Camellia sinensis*-Derived Ingredients

Dr. Marks' Team

DR. MARKS: So, next, we're to camellia, which is -- we saw the draft tentative report and issued an insufficient data announcement at the December 2013 meeting, and there were a number of data needs -- method of manufacture, composition, concentration of use, HRIPT, differences between the leaf oil and essential oil. So, let's -- Tom and Rons, what's you feeling about these tea products? Should we go down each one of those needs as were bolded by Lillian? And, is Lillian here? Oh, yes. Good. Thank you.

So, method of manufacture, including removal of impurities and constituents of concern, such as linolol. (inaudible). There was some concern about whether the cosmetic is the same as the food.

DR. SLAGA: I thought we said it was last time.

DR. MARKS: Lillian, we didn't receive anything on that, did we?

MS. BECKER: We didn't by the time of this report. I'm trying to remember what came in Wave 2.

DR. HILL: It was Wave 2 and Wave 3. There is material --

MS. BECKER: Mm-hmm. Yes.

DR. MARKS: So, Ron, Ron, and Tom. I can't remember whether this was a concern by the Belsito team or by us.

DR. SLAGA: Well, to me, I think some of the needs last time were based on that this was the first time and therefore we'll see if we can get it, and I think there's enough information in Wave 1 and 2 and in the document that it's safe.

DR. MARKS: You're good.

DR. HILL: If you remember how this came, this actually was mixed with the other tea plant, wasn't it? Ginseng?

MS. BECKER: No.

DR. HILL: This wasn't the one that was split out from -- okay.

MS. BECKER: No. It wasn't with Ginseng now.

DR. HILL: Not Ginseng. Weren't there two types of tea and lumped into one report and then we -- okay. I got this crossed in my mind.

MS. GILL: Yes.

DR. HILL: Okay.

DR. MARKS: Composition. So, I don't get the sense that there's a concern at this point with the method of manufacture. Let's go to composition data for the root extract, seedcoat powder, flower extract, flower/leaf/stem juice.

DR. SHANK: We have in Table 5 the phenols in green and black tea, but what is meant by black tea? Is that leaf, leaf extract, water extract, flower, root? It doesn't say.

MS. BECKER: We don't know, just that it's black tea. The black, green oolong tea all has to do with when the leaf was picked and how it was processed, and it's from the same plant, and then what extract it is we don't know.

DR. SHANK: Okay. Well, I had only a data need, HRIPT on the leaf powder at 50 percent, and I don't know what to do with leaf water. Is that a fragrance or not? Those are the two I had.

DR. BERGFELD: I had a question on the leaf powder at 50 percent. Do you think it's used at a low enough concentration, not to be a worry? The leaf powder at 50 percent. Is it used in a low enough concentration not to be a worry?

MR. ANSELL: Our notes suggest that the 50 percent leaf powder as mentioned is as sold as a professional product, but it's actually applied in diluted form before use.

DR. MARKS: Yes, I had the same need as Ron Shank. I wanted an HRIPT for the leaf powder at 50 percent, since that's what we're told is the use concentration.

MS. BECKER: Well, though --

DR. MARKS: Even though you say it may get diluted, we don't know what it's diluted down to. Is that correct, Lillian? Fifty percent under the use?

DR. BERGFELD: It says face and neck products, not spray, up to 50 percent. Most of it's under.0-something.

DR. MARKS: Yes, but, obviously we have to pay attention to the --

DR. BERGFELD: Yes, either that or restrict it.

DR. MARKS: So, I had that -- let me see -- concentrate -- limit -- I had limits stem/leaf extract to 0.86 percent, again, based on the sensitization data. But, then, we come with the -- if, from the memo, you sent -- Lillian, I think that's Wave 3.

MS. GILL: Wave 2.

DR. MARKS: IFRA standard shows the tea left extract varies with category from 0.1 to 2.5 percent, and if IFRA's ruling on it that the tea left abstract is a fragrance, then should we even be reviewing it? That's from this memo dated March 14, 2014. So, it would make it a little simpler, because they really vary. Category 1 is .01 as I mentioned, and then if you look at Category 10 they divide their restrictions based on these 11 categories. So, I would say that the tea leaf absolute or the synonym extract, the leaf extract, should be eliminated from this report since it's covered by IFRA as a fragrance. And, then, I don't know about the leaf water. Did we get any feedback on the leaf water? Is that a fragrance?

MS. BECKER: We have not gotten anything that it's just used as a fragrance or used as a fragrance in other uses. But, we are scheduled to get their full report by end of March. So, if we find that it is used solely as a fragrance, to get the report. If we find out it is used as a fragrance, we will take it out.

DR. MARKS: And, what would you suggest to do with the tea leaf extract? Should we take that out, too, Lillian?

MS. BECKER: If it's used for other things besides a fragrance, we might want to keep it in, because it would be different concentrations. So, I'm checking the table real quick to see what else it's used for.

DR. MARKS: Okay. So, team, how do you want to deal with the -- if we limit -- if we say keep the leaf extract in? In Lillian's memo, it talks about HRIPTs. They were clean up to 0.86 percent, but then when we look at the IFRA recommendations, they make limits depending on what region of the body you're going to apply it. Category 1 is lip product. Going from there to Category 11 is in candies. That's not an issue for us, but 10 is hard-surface cleaners. That isn't an issue, but 8, 9 is rinse-off hair conditioners.

MS. BECKER: Mm-hmm. Yes. And, Dr. Marks, the leaf extract has the most number of potential uses or functions in cosmetics. It has a large list.

DR. MARKS: Yes.

MR. ANSELL: I think the IFRA limits are informative, but they'd be difficult to adopt wholesale, because they're exposure-based and not all the exposure categories are relevant. I'm not actually aware of whether the material is a dual-use product or not. I think we can find that out. But, until we conclude that it has no cosmetic applications, I would recommend that we keep the leaf extract present and, if necessary, with the limitation relative to the demonstrated HRIPTs.

DR. MARKS: Which is the 0.86.

MR. ANSELL: Yes.

DR. MARKS: It's safe.

MR. ANSELL: Because, from my notes, the 2.5 would be the 2.5 percent and the IFRA would be for like household cleaning products, and it would be hard to --

DR. MARKS: Right.

MR. ANSELL: -- adopt that. But, we do have data on the 0.86. We do have a number of ingredients which are dual use, both fragrance and cosmetic, and it's important I think to be informed by the IFRA assessments but not necessarily have to adopt them as such.

DR. MARKS: It actually -- Jay, the way you're looking at it, I think it's quite correct. The only one where there's a concentration that they approve higher than that in a personal care product would be a rinse-off. So, the .86 should be fine.

MS. BECKER: The list of functions are on PDF page 36.

DR. MARKS: So, let's summarize where we are at this point.

DR. HILL: I have one more question before you do that.

DR. MARKS: Sure.

DR. HILL: (Coughs) Excuse me. We don't have any use concentrations for camellia sinensis leaf.

DR. SHANK: It's no longer used, right?

DR. HILL: The leaf is no longer -- it says 38 leave-on applications. Am I missing something?

DR. SHANK: Was it in Wave 2?

DR. HILL: No.

DR. SHANK: Someplace we have that.

DR. HILL: But, the leaf itself is no longer used?

DR. SHANK: Based on teabags placed on the eyelids of (inaudible) --

MS. BECKER: Yes. And, the teabags -- they said that's no longer on the market, and it's now used.

DR. HILL: Was that the only leave-on? That says different leave-on uses. Is that the only one?

MS. BECKER: That was the one that was the high percentage at --

DR. HILL: Well, we didn't have any used concentrations on the other 37 uses? That's what I'm driving at.

MS. BECKER: All right. Okay.

DR. BERGFELD: Are you all comfortable with the seed and the --

MS. BECKER: Okay.

DR. BERGFELD: -- seedcoat powder, and the root, and the oil? I mean, there are lots of different parts of the plant that's being used there's no data on.

MS. BECKER: Okay. And, just to quickly answer Dr. Hill's question, the leaf. You're asking about the leaf, right?

DR. HILL: Leaf.

MS. BECKER: It's used up to 0.05, and it's diluted for bath in those uses.

DR. HILL: That wouldn't be leave-on, and it lists leave-on uses.

MS. BECKER: Right. And, we have no report from the Council of concentrations of use for those uses.

DR. HILL: Yes. So, if we're approving the safety with no idea of the concentration, that seems like a bad plan. And, I'm particularly interested, I guess, because there is no repeated dose toxicity of any kind on any of these, and, I guess, thinking as well as tea, but that comes back to the question that Dr. Bergfeld just asked. We don't grind up the seeds when we make tea. I don't think we use the root, in the U.S. at least for foodstuff.

MS. BECKER: However, we do have concentration of use for the seed extract.

DR. HILL: Yes. And, you're saying that to point out that they're all really low? Is that --

MS. BECKER: Just to fill in the information of the question.

DR. HILL: Okay. So, they are all really low? I'm looking for the table again.

MS. BECKER: The table's on page 39 of the PDF.

DR. HILL: I'm almost there.

MS. BECKER: And, yes, the highest concentration is 0.1 percent.

DR. HILL: Okay.

DR. MARKS: Okay. So, let me see if I have the Panel's -- have captured where the Panel is at this point. So, I would move that we have a tentative report, issue a tentative report tomorrow, with these ingredients safe. The exception that we would limit the stem leaf extract, or stem leaf -- yes, extract, to 0.86 percent. We have an insufficient of the leaf powder at 50 percent. We need an HRIPT. And, the leaf water may be a fragrance and deleted, based on what we find out from RIFM. And, all the other ingredients then would be safe, as I said. Does that sound -- Ron, Ron, and Tom, does that --

DR. SHANK: Sounds good. Well, there are no uses for root.

DR. MARKS: Yes, but, we --

DR. SHANK: It's not in Table, whatever it is, 7?

DR. BERGFELD: No. No root and no oil and no seed.

DR. MARKS: But, in the past, when we had ingredients or no uses we will still would say (inaudible).

DR. BERGFELD: But, rice was the key for us in the past. Every part of that rice kernel was different. So, how can you just say that the seed is okay? You haven't got anything on it --

DR. SHANK: Right.

DR. BERGFELD: -- or the root. You're dealing mainly with the leaf. So, wouldn't you say they were insufficient for those?

DR. SHANK: I would. Yes.

DR. BERGFELD: You said it in your initial tentative report that you needed concentrations of use of the root and the seed power and the flower. I forgot the flower. And, you get those.

DR. SLAGA: No, we didn't get any of them.

DR. BERGFELD: But, you don't have any chemistry on them either.

MR. ANSELL: We do have chemistry.

DR. BERGFELD: You have chemistry, I believe.

MR. ANSELL: Yeah, I'm trying to find the constituents of concern by plant part.

DR. HILL: I'm on 37. I think PDF, 38, isn't it? Maybe not.

MR. ANSELL: No, I think it's earlier than that. It's --

DR. BERGFELD: Twenty-three.

DR. SHANK: Twenty-three. Yeah. Thank you.

DR. BERGFELD: PDF page 23.

MR. ANSELL: Materials of concern in the leaf plant shoot predominant in the seeds, seed coatings.

DR. HILL: On my PDF 23 -- oh, no. Okay. That's 24.

DR. MARKS: So, let's go back to Lillian's memo and trying to arrive at a conclusion here. Are we going to go back to -- are we going to put insufficient for the root extract, the seedcoat powder, the flower extract? So, now we're down to we limit the stem/leaf extract to 0.86 percent insufficient for the leaf powder. We need an HRIPT. The leaf water may be a fragrance. What do we do with the rest of those? We aren't going to rule that they're safe.

DR. SHANK: When you say rest of those, what is --

DR. MARKS: Like the root extract, the seedcoat powder, the flower extract.

DR. SHANK: Insufficient.

DR. MARKS: Insufficient.

DR. HILL: I had flagged, too. It's just taken me a while to read back through -- I left my notes in disarray, but a lot of the -- what we're relying on there is the fact that these are being consumed

heavily as foodstuff, but those aren't. So, we're lacking data that we can rest on a little bit. I think it is insufficient.

DR. MARKS: And, we want the concentration of use. Is that it? So, there are one, two, three, four, five ingredients mentioned there. Does that cover the rest? Are there a couple of ingredients which we didn't mention?

DR. HILL: What did we say about the flower extract?

DR. MARKS: That's insufficient.

DR. HILL: Okay. So, I got a total of six. Flower extract, flower/leaf stem juice, root, seedcoat powder, seed extract, seed powder.

MS. BECKER: And, how about the hydrolyzed seed extract?

DR. HILL: Mmm. Yes. I would think that one would be in there, too.

DR. MARKS: So, I'm on page 5 in the PDF with the table with all the ingredients. Is there anything on there that -- let's see, other than seed/leaf extract? Let me see. So, we're limiting the concentration on the leaf extract. And, where is the seed extract? Down here. And, then, everything else is essentially --

DR. HILL: Insufficient.

DR. MARKS: -- insufficient. Is that right? The leaf powder we want at 50 percent, and everything else we want use concentration. Is that correct?

DR. HILL: I think so.

DR. MARKS: Do we have the (inaudible)?

DR. BERGFELD: Do you feel that you have the constituents though? Do you feel you have constituents in those? Because, you might want to ask for that. You have a summary statement. Is that the whole plant that they gave you that? On page 5 -- no, it was on another page -- 25.

DR. MARKS: So, do I have it summarized pretty well? We have leaf extract and seed extract. We set a limit, and then all the rest is insufficient. Either the powder or an HRIPT at 50 percent, and the rest for use.

MS. BECKER: Say that again, please. Leaf extract and --

DR. MARKS: So, limit stem and leaf extract to 0.8 percent. We have that information and that the HRIPT was good for that. Insufficient for the leaf powder -- 50 percent. We need an HRIPT. The leaf water may be a fragrance. That may be deleted, so that's also -- and then insufficient concentration of use -- concentration of use for the other ingredients.

MS. BECKER: Do you want further characterization of those ingredients, and do you want any testing, like an HRIPT, if there's a use concentration?

DR. MARKS: Right. I think it depends on what we get. We'll get as much as we can.

DR. HILL: What about the leaf oil?

DR. MARKS: That was deleted, wasn't it or not?

DR. HILL: Leaf oil? I don't think so.

DR. MARKS: Let me see. Which one --

MS. BECKER: Seed oil was deleted.

DR. MARKS: Okay. Does that sound reasonable, Tom, Rons? Tomorrow I'll present a tentative move that a tentative report be issued limiting the stem/leaf extract to 0.8 percent, insufficient for the leaf powder, and all the other ingredients. The leaf powder, we need an HRIPT. The other ingredients, we need the concentration of use, and then, depending on what we get from that, we may need some more, but, whatever you can find (inaudible). Does that sound reasonable?

DR. SHANK: Uh-huh.

DR. MARKS: Okay. Any other comments? Just diminished my thirst for tea. (Laughter) Okay. I have a feeling we're going to come up with safe one way or another, but --

DR. SHANK: Eventually.

DR. MARKS: Yeah, eventually. It's going to be painful getting there. Okay.

Dr. Belsito's Team

DR. BELSITO: …Okay. So, we are moving on to camellia sinensis- derived ingredients. In the interest of time, we are just going to keep going, and I'll take a bio break, and if anyone needs to duck out, because otherwise I think we will be here until tomorrow morning possibly.

SPEAKER: We have four more.

DR. BELSITO: Yes, we have four more, but that doesn't mean anything. It only mean that there may be alcohol left at the bar for us this time. Okay. Camellia sinensis.

DR. LINTNER: I'll be here tomorrow.

DR. BELSITO: Thank you, Dr. Lintner, very much.

DR. LINTNER: Thank you very much. See you tomorrow.

DR. BELSITO: Yeah. Okay.

(Recess)

DR. BELSITO: At the December meeting we evaluated ingredients and found that leaf extract is save as used, catechins are safe at 0.1 (inaudible) used in cosmetics. And the -- and insufficient data announcement was issued for the other ingredients. Is that correct?

SPEAKER: Mm-hmm.

DR. BELSITO: Additional data requested included method of manufacture, the composition data for the root extracts, (inaudible) cauliflower or extract flower -- stem leaf through concentration of leaves for all ingredients. HRIPT and leaf at a 100 percent stem leaf extract at 3 percent, and catechins at use confirmation, and clarification that tea leaf water is used only as a fragrance.

We've got some new data, and I don't know what's happening but have to wring this, suddenly like PDR is not opening -- PDF rather. Some new data is added to report, information that the leaf is no longer in teabags for the eyes at 97 percent, so that request for 100 percent goes away.

We have HRIPT on the leaf extract at 0.86 percent new use data indicated that the leaf is used at a maximum of 0.5 in a bubble bath, and 50 percent on the face and neck product. And no additional data were received on method of manufacture composition, concentration of use, difference between oil and essential oil, or leaf water only as a fragrance, but we did get data from -- where from -- this is the one where we got the data on --

DR. SNYDER: QRA, yeah.

DR. BELSITO: -- QRA on leaf water.

MS. EISENMANN: It's on -- it's tea leaf absolute.

DR. BELSITO: Tea leaf absolute.

MS. EISENMANN: So it's (inaudible) --

DR. BELSITO: Yeah, it's here someplace, and I'd better get it someplace.

SPEAKER: Oh, it's down here. Yeah, here it is.

DR. BELSITO: Tea leaf absolute. But its synonym is camellia sinensis leaf extract, if you read under the synonyms. So, I'm assuming the leaf extract is used as a fragrance, and that's what they're talking about.

MS. EISENMANN: This one. This leaf -- the leaf extract with alcohol, yes.

DR. BELSITO: No. But here it says synonyms, camellia sinensis leaf extract, it doesn't say leaf extract to alcohol.

MS. EISENMANN: Other than the name is -- I'm saying because it's tea leaf absolute, I presume that's how they name --

DR. BRESLAWEC: Don't they use -- I saw naming principles that there's an ISO Standard for botanical names, and that may -- I think that's what they are using, so it probably has some

kind of other meaning, and I don't know what it is.

MS. EISENMANN: Oh. So it was one of the things that there's -- as an absolute ethanol extract of tea leaves, tea leaves absolute.

DR. BELSITO: Hmm?

DR. LIEBLER: Where are we?

DR. BELSITO: On camellia sinensis-derived ingredients.

DR. LIEBLER: Yeah. But is there a document paper referring to it, and way to --

SPEAKER: No.

DR. BELSITO: No. It's wave --

SPEAKER: Three documents.

DR. BELSITO: Wave 3 document from (inaudible)

SPEAKER: I see. We are sorry. Okay.

DR. LIEBLER: So the question is, what do they mean by tea leaf absolute, it has heavily (inaudible) ingredients.

DR. BELSITO: Yes.

DR. LIEBLER: Okay. (Inaudible)

DR. BELSITO: Well, the synonym is tea leaf extract, so I'm assuming that what people call the absolute is also tea leaf extract and the extract is the fragrance. And if in the cosmetic dictionary, is there any other listed use of leaf extract other than as a fragrance?

MS. EISENMANN: Yes.

MS. BECKER: Yes. It's the one that has the most other uses.

DR. BELSITO: So then we need to review it?

MS. BECKER: Yes.

DR. LIEBLER: All the skin conditioning is in here.

MS. EISENMANN: Miscellaneous?

DR. LIEBLER: Or the miscellaneous.

MS. EISENMANN: Miscellaneous, the difference --

MS. BECKER: Leaf extracts and antifungal agent, and antimicrobial agent, and --astringent. White stabilizer, oral care agent it has --

DR. LIEBLER: Or covered.

MS. EISENMANN: It's a natural ingredient.

DR. LIEBLER: We are so covered.

MS. BECKER: Plus skin-conditioning agent is used.

MS. EISENMANN: No. The oil -- the leaf oil is defined -- in the dictionary, it's in the chemical class, essential oils and water. So it's safe to assume that the leaf oil is the essential oil.

SPEAKER: Okay.

MS. EISENMANN: Okay?

DR. BELSITO: But absolute doesn't mean essential oil?

MS. EISENMANN: Correct. I'm just saying had that question -- it did respond because we felt the dictionary answered that question.

DR. BELSITO: Oh, Christ. Of all the times for my PDF to act up. Okay. I can't search my comments, but I can at least open the document, so I'll scroll down. I'll open it up to other people. So, basically, I'm thinking, and this is only from memory, because I'm scrolling down, and not seeing any comments at this point, that we really didn't get a lot of new information other than, there wasn't a 97 percent, and we got and HRIPT on leaf extract at 0.86 percent.

But the leaf is used to the maximum of 0.5 but up -- in a bubble bath, but up to 50 percent in the face product, and we have this QRA on the leaf extract that tells us the different concentrations of use that would be safe for different consumer products for the leaf extract, and so --

MS. BECKER: Also and we told you that a summary of RB teas, from several different

kinds of teas.

DR. BELSITO: Right. Yeah. I've got my comments on Wave 2, and they say Wave 2 -- those comments weren't necessarily on Wave 2. I can't open this document, so help me out folks. Talk about it yourselves.

DR. LIEBLER: I'm not sure how much of our (inaudible) data were satisfied by the Wave 2.

DR. BELSITO: So, we are basically that the -- found that the leaf extract is safe as used, and the catechins are safe at 0.1 percent, and all of the other ingredients are insufficient. Is that correct?

DR. LIEBLER: Right.

DR. BELSITO: Okay. Yeah. I've just scrolled to my first comment, which is on the conclusion. Okay. Same conclusion as before -- Oh, same conclusion as before, or the is the blurb that we got about the seed, the general composition of the seed, was that sufficient to allow or to pass the seed extracted, 0.1 percent, but we had no concentrations for the powder?

So we've got a little blurb about the concentration of the seed in this document, and I guess I'll have to continue to scroll down. I don't know why it won't open my comment section. It just circles around when I try to get it to open my comments.

(RECESS)

DR. LIEBLER: But for all these ingredients where we have no concentration -- or frequency of use or concentration data, do we still keep them? Or are we going to go insufficient for all of them?

MS. BECKER: In general, we tend to keep them.

DR. BELSITO: You know, I mean, we just go insufficient so -- but I guess the only question is before we just set 0.2 percent and the -- or leaf extract safe as used, and catechins safe at 0.1 percent is used in cosmetics. And again, I'm just going to have to scroll down. I tried doing it and it's still not bringing up my comments for reasons that I don't know. I just raised the issue in a general conclusion. There must be a blurb we got about some components of the flower that -- technology is wonderful when it works. Yeah?

MS. BECKER: Nothing in Wave 2 or 3.

DR. BELSITO: Yeah but -- or seeds rather, not flowers. So on page 23, PDF 23, it says, "Constituents reported to be predominantly in *C. sinensis* seeds, include caffeine, glucothia, saponins, stearic acid, theospomine and theobromine. Constituents reported to be in *C. sinensis* seed coat include caffeine and theobromine. Is that enough for us to rule on the seed and seed coat, or do we need more specific constituent information?

DR. LIEBLER: That's not enough.

DR. BELSITO: Okay. I'm just saying we did get some.

DR. SNYDER: Others, in particular -- just to know that a little -- some of the others were in other components, right.

DR. LIEBLER: Right.

DR. BELSITO: Okay. Fine. So then, it doesn't change our conclusion, so we don't have the data. So then we just have the same conclusion as before, that the leaf extract is safe as used. The catechins are safe up to 0.1 percent as used in cosmetics, and the others are insufficient for all the reasons that we asked for before.

DR. SNYDER: The catechins are based on a negative. Tested 0.1 percent. We don't have concentration.

DR. BELSITO: Right. We don't have -- which is why we said that.

DR. SNYDER: Okay.

DR. BELSITO: Okay. Anything else with these *Camellia sinensis*-derived ingredients? Okay. Seeing no comments, and moving on along, and let's hope that the thought with my search was only with camellia, and then not that tea brought me down.

DR. MARKS: Tea. So a draft tentative report on these tea-derived ingredients was issued in December of last year. An insufficient data announcement. There are a number of needs and our team felt that we could move forward with a tentative report that limits the leaf extract to 0.86 percent. Insufficient for the leaf powder at 50 percent. We need an HRIPT to support the safety of that ingredient. The leaf water may be a fragrance, and that may be deleted. We still don't know the answer to that yet. And then insufficient for concentration of use and composition of the other 11 ingredients -- the roots, seed, flower, stem, catechin. So we're still a lot of needs. A lot of insufficients. The only one we felt we could move forward safe was limiting the leaf extract.

I'm sure you have --

DR. BELSITO: No, I mean, we just felt -- I mean, we learned that the tea bags at 100 percent weren't used, so we thought that moved it down to the safe as used, the catechins at 0.1 percent, and all of the other data needs that we had asked for before still exist.

Did I hear you say method of manufacturer and composition data?

DR. MARKS: Yes.

DR. BELSITO: Okay. You know, excuse me, so you wanted to limit the leaf --

DR. MARKS: To 0.86. 0.86 percent. We've got -- that was really the data we received that showed that the leaf of the HRIPT --

DR. BELSITO: The leaf extract or the leaf?

DR. MARKS: Leaf extract.

DR. BERGFELD: Leaf stem extract.

DR. MARKS: That's actually in Lillian's memo right after the needs. It's in that second paragraph, HRIPTs, cosmetic products containing leaf extract at 0.86 percent. When you look at the studies, it's nonsensitizing.

MS. BECKER: The studies are on page 32, PDF 32.

DR. MARKS: So I think on the other things, the modifications you made are fine.

DR. BELSITO: Well, we do have a QRA from RIFM on the leaf extract.

DR. MARKS: Yes. We discussed that, and having all the categories, we decided the ones where there were high concentration, the categories wouldn't be used as a cosmetic product. So that's how we came back to the concentration we had had before with that HRIPT of 0.86 percent.

DR. BELSITO: And what is the use concentration on this?

Find table.

UNIDENTIFIED SPEAKER: Three percent.

DR. BELSITO: Three percent?

MS. BECKER: The table is on page 39 of the PDF.

DR. MARKS: I have up to 2 percent is what I see. That's why I think we need to put -- we don't have data --

DR. BELSITO: Up to 2 percent on leave-ons. So are you going to limit it in rinse-offs to 0.86, as well?

DR. MARKS: No, I don't think we have to.

DR. BELSITO: So then your limit is restricted to leave-ons?

DR. MARKS: Yes.

DR. HILL: The use there right now says 1 percent, so 0.86 percent for leave-on, 1 percent for rinse-off doesn't seem at all unreasonable with the data we have; right? I think. One percent on rinse-off is what state-of-the-art is according to our report.

DR. BELSITO: Right. Yeah.

DR. HILL: But 2 percent for leave-on is what we're questioning, isn't it?

DR. BELSITO: Yeah, but you said you were going to restrict it to 0.86, which would be --

DR. HILL: But not for rinse-off. Not for rinse- off.

DR. BELSITO: Not for rinse-off. So that's what I wanted to clarify there.

DR. MARKS: Thank you, Don.

DR. BELSITO: For some reason I didn't have any problems with it. So they did a dermal non-human with 100 percent of the leaf extract was dermally applied to New Zealand rabbits. Note, that was irritation. Dermal human.

So it's all over the board. Yeah, so the HRIPT, yeah, I see what you're referring to.

So I'm fine with that, you know, if you want 0.86.

DR. BERGFELD: It's going to go out for comment.

DR. BELSITO: Yeah. And you could probably stretch it to one, but if you want to be compulsive and go by the number they used and stay with 0.86 percent.

Okay. So your motion was the leaf extract safe up to 0.86 percent and leave-on safe as used in rinse-offs. The catechins safe at 0.1 percent. The other constituents, insufficient for all of the data that we had requested before.

I'll second that if my teammates are okay with it.

DR. BERGFELD: Everyone shaking their heads are agreeable to that?

UNIDENTIFIED SPEAKER: Yes.

DR. BERGFELD: All right. Any other comments? Seeing none, I'll call the question. All those in favor? Excuse me. Unanimous.

(Motion passed)

Safety Assessment of Camellia Sinensis-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.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, Ph.D; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢ cirinfo@cir-safety.org

ABSTRACT

Cosmetic ingredients derived from *Camellia sinensis* (tea) plant parts function as antioxidants, and skin-conditioning agents – humectant and miscellaneous. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed relevant animal and human data related to these ingredients. The use of the leaf ingredients in beverages result in larger oral exposures than those from cosmetic uses. Therefore, oral toxicity potential was not the focus of this safety assessment. Because formulations may contain more than one botanical ingredient, caution was urged to avoid reaching levels of toxicity for constituents. Industry should use good manufacturing practices to limit impurities. The Panel concluded that camellia sinensis leaf extract is safe up to 0.86% in leave-on products and up to 1% in rinse-off products. Camellia sinensis catechins is safe as used. The available data are insufficient to determine that the remaining non-leaf/stem-derived ingredients are safe under the intended conditions of use in cosmetics.

INTRODUCTION

This is a safety assessment of cosmetic ingredients derived from *Camellia sinensis* (tea) plant parts. The functions of these ingredients include: antifungal agent; antimicrobial agent; antioxidant; cosmetic astringent; fragrance ingredient; light stabilizer; oral care agent; skin protectant; skin-conditioning agent – emollient; skin-conditioning agent – humectant; and skin-conditioning agent – miscellaneous (Table 1).[1] The 14 ingredients in this report are:

- camellia sinensis leaf extract
- camellia sinensis catechins
- camellia sinensis flower extract
- camellia sinensis flower/leaf/stem juice
- camellia sinensis leaf
- camellia sinensis leaf oil
- camellia sinensis leaf powder
- camellia sinensis leaf water
- camellia sinensis root extract
- camellia sinensis seedcoat powder
- camellia sinensis seed extract
- camellia sinensis seed powder
- hydrolyzed camellia sinensis leaf
- hydrolyzed camellia sinensis seed extract

It is not known if camellia sinensis leaf water is solely used as a fragrance ingredient. If the fragrance-only function is confirmed, it will be removed from this report. The safety of fragrance ingredients is reviewed by the Research Institute for Fragrance Materials (RIFM).

Camellia sinensis seed oil was included in a 2011 CIR safety assessment of plant based oils with the conclusion that it was safe in the present practices of use and concentration.[2]

The *C. sinensis*-derived ingredients in this safety assessment are from edible plant sources. Exposures to the leaf-derived ingredients in beverages results in much larger systemic oral exposures than would result from cosmetic uses. Therefore, the oral toxicity potential of the leaf-derived cosmetic ingredients will not be addressed in this report. While data on the potential for reproductive toxicity, genotoxicity, and carcinogenicity are presented, the primary focus of this report is on the potential for irritation and sensitization.

CHEMISTRY

Definition and Description

The definitions and functions of *Camellia sinensis*-derived ingredients are provided in Table 1.

CAMELLIA SINENSIS

There are four varieties of the *C. sinensis* plant: *sinensis*, *assamica*, *pubilimba*, and *dehungensis*. The first two are most commonly used to prepare tea for human consumption. The type of tea (i.e., white, green, oolong, black) depends on time of year harvested, age of leaves when harvested, location/soil/climate, and processing after harvest. The processing of tea for a beverage is referred to as fermentation, because it was originally believed that the leaves were fermented, but the process actually involves an enzymatic oxidation.[3,4] It is not known which of these teas or which specific processes are used to produce cosmetic ingredients.

The *C. sinensis* is native to East, South and Southeast Asia.[4-6] However, it is also cultivated in other tropical and subtropical regions. The leaves of this evergreen shrub can be lanceolate to obovate, up to 30 cm long (usually 4 - 15 cm) and 2 - 5 cm broad, pubescent, sometimes becoming glabrous, serrate, acute, or acuminate. The plant has a strong taproot. The 3 – 5 cm, yellow/white flowers are globular and have a delicate fragrance.

These plants are not the source of, nor are they related to, tea tree oil, which is derived from *Malaleuca alternifolia*.

CONSTITUENTS

The constituent groups of fresh green leaf *C. sinensis* are provided in Table 2. The constituent group having the highest concentrations is the flavanols (25.0% dry weight), which is followed by proteins (15.0%) and polysaccharides (13.0%).[4]

Other constituent groups found in *C. sinensis* plant parts include:

Amino acids – The most abundant amino acid is one not typically found in proteins, theanine (5-*N*-ethylglutamine).[4,7]

Carotenoids – These are present in low levels in the leaves. They include neoxanthin, violaxanthin, lutein, chlorophylls a and b, and β-carotene.[4,8,9] Seventy-nine pigments, 41 chlorophylls and 38 other carotenoids have been detected.[10]

Enzymes – Fresh *C. sinensis* leaves contain high levels of the enzyme polyphenol oxidase.

Methylxanthines - Theobromine can range from 0.16% - 0.2% of a dry-weight leaf.[4,11,12] Dried leaves contain not less than 2% caffeine (dried weight). Increased use of nitrogen fertilizer can increase caffeine content by up to 40%. Theophylline is present at < 0.04% dry leaf weight.

Flavonoids – These include flavonols, flavanols, and glycosides. Flavanols include catechins, which are present in small amounts, and may occur as flavonols and glycosides.[4,13,14] Flavonols reported to be in leaf extract are kaempferol, quercetin, and myricetin.[4,15]

Catechins - These polyphenolic molecules are a subgroup belonging to the flavanol family.[4,16-18] They typically make up 20% - 30% of the weight of tea leaves. Catechins are especially concentrated in the leaves of green tea wherein they account for 30% - 40% of the dry weight of the leaves. The most abundant type of catechin in green tea is epigallocatechin gallate (EGCG; 12%). The other catechins are catechin (C), epicatechin (EC), gallocatechin (GC), epigallocatechin (EGC), catechin gallate (CG), gallocatechin gallate (GCG), and epicatechin gallate (ECG; Figure 1).

Minerals elements - Potassium is the most abundant mineral element, present at 40% of the total mineral element content of dry matter of fresh leaves. The leaves are rich in fluoride and they also accumulate aluminum and manganese.[4,19,20] Other elements present in mineral form include calcium, magnesium, sodium, phosphorus, and sulfur. Minor elements include boron, barium, chromium, copper, iron, molybdenum, nickel, rubidium, strontium, and zinc.[19] Trace elements include silver, arsenic, beryllium, bismuth, cadmium, cerium, cobalt, cesium, mercury, indium, lithium, lead, rare earth elements, antimony, selenium, tin, tellurium, thallium, uranium, vanadium, ytterbium, and zirconium.

Volatiles – There are a large number of volatile constituents in fresh leaves. *Trans*-2-hexenal and *cis*-3-hexenol are present in the greatest amounts.[4,14,21,22]

Climatic conditions during cultivation may affect the content of theanine, standard α-amino acids (i.e., isoleucine, leucine, valine, alanine, threonine, and glutamine), quinic acid, EC, EGC, EGCG and caffeine levels in *C. sinensis* leaf extract (as green tea).[23,24] Soil conditions and cultivation methods may markedly affect mineral levels.[19]

Constituents reported to be predominately in *C. sinensis* seeds include caffeine, glucothea saponin, stearic acid, theasponin, and theobromine.[25]

CONSTITUENTS OF CONCERN

Linalool and several compounds containing linalool (i.e., *R*-linalool, linalool-oxide-(*cis*-furanoid), linalool-oxide-(*cis*-pyranoid), linalool-oxide-(*trans*-pyranoid), linalool-β-D-glucopyranoside, and linalool-oxides) have been reported in the leaves (6 -1984 ppm), leaf essential oil (31800 – 198 400 ppm), and shoot (600 – 10300 ppm) of *C. sinensis* (Table 3).[25]

Quercetin and several compounds containing quercetin (i.e., quercetin-glucosides) have been reported in the leaf (760 - 10000 ppm), plant, and shoot of *C. sinensis* (Table 3).

Constituents reported to be predominately in *C. sinensis* seeds include caffeine, glucothea saponin, stearic acid, theasponin, and theobromine.[25]

Constituents reported to be in *C. sinensis* seed coat include caffeine and theobromine.[25]

SAMPLE ANALYSIS

Constituents in medical grade *C. sinensis* extract include methylxanthines, flavanols (10% - 25%), flavonols, flavones, phenolic acids, amino acids (including theanine, 3%), terpene saponins, polysaccharides, proanthocyanidins, vitamins, and minerals (Table 4).[16,26-30]

Analyses of three lots of *C. sinensis* catechins (each prepared as a food additive) indicated 28% - 90% total catechin monomers and 37% - 100% polyphenols.[31]

CHARACTERIZATION

As herbal supplements, extracts are characterized by the drug/extract ratio (DER), which is the ratio of the quantity of herbal substance used in the manufacture of an herbal preparation (given as a range) to the quantity of the herbal preparation obtained in the finished product.[32] The specifications for *C. sinensis folium* as an herbal supplement in the European Union (EU) for the dry extract, purified (DER 45-56:1, extraction solvent: water) corresponds to 55% - 72% (-)-epigallocatechin-3-*O*-gallate.[26,32] The decaffeinated dry extract (DER 6:1 to 10:1, solvents such as alcohol, methanol, acetone, or water or mixtures of these solvents) contains not less than 60% of polyphenols, calculated as (-)-epigallocatechin-3-*O*-gallate, not less than 40% of (-)-epigallocatechin-3-O-gallate, and not more than 0.1% of caffeine, calculated on the anhydrous basis.

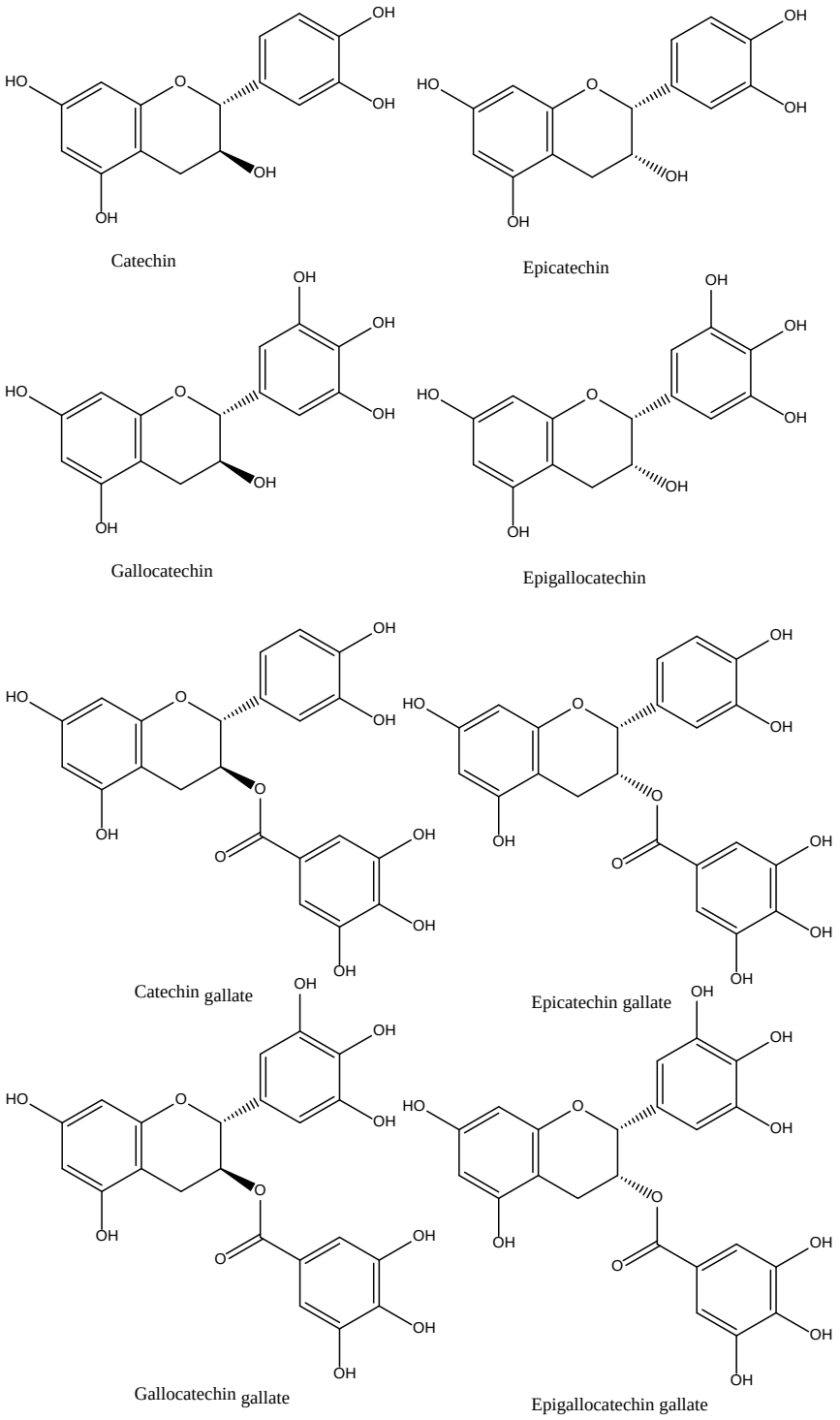

Figure 1. Catechins from *Camellia sinensis*

Physical and Chemical Properties

C. sinensis catechins have an astringent taste and are soluble in water.[4,16]

Three lots of oolong tea with *C. sinensis* catechins were stable for 18 months in unopened packaging at -20°C.[31] Total catechin monomers were decreased from 100% to 97% and 98% after 6 months of storage at 25°C in polyethylene terephthalate (PET) bottles and steel cans, respectively. At 37° for 2 months, catechin content was decreased to 96% in both types of containers.

A sunscreen with *C. sinensis* (2%, 3%, 4%, or 5%) in the form of green tea extract was stable for up to 6 months.[33]

Method of Manufacture

No information on the method of manufacture for *C. sinensis*-derived cosmetic ingredients was discovered or submitted. The methods below are general to the processing of *C. sinensis* for food or food ingredients and it is unknown if they apply to cosmetic ingredients. The makeup of the *C. sinensis* extract will differ with the manufacturing process.

C. sinensis leaf in the form of green tea consists of whole or cut young, unfermented, rapidly heat-dried leaves.[17,26] The fresh leaves are processed by a method designed to prevent the enzymatic oxidation of catechins. The enzymes are inactivated by heat (pan-fried or steamed).

There are different harvesting and manufacturing processes for white, green, black and oolong teas for drinking.[17,19,26,34] White tea is made from very young leaves and leaf buds. Green tea is made from new, fully-formed leaves. These two types of tea are minimally processed, steamed, and dried. Black tea and oolong tea are made from older, fully-formed leaves. Oolong tea is withered, and rolled during "fermentation", then fired and dried. Black tea is withered, crushed, and rolled during "fermentation" then fired and dried. Phenolics content typically differs substantially between green and black teas (Table 5).

Catechins are isolated through an initial hot water extraction with ethyl acetate, and then separation by chromatography, followed by spray-drying.[35] The spray-dried catechins may be recrystallized. Two other processes for the extraction of catechins from *C. sinensis* leaves are conducted with or without enzymatic treatment with tannase. The initial extract is further extracted with water and ethanol, and then filtered through multiple media. The product of the process without tannase is sterilized above 100°C., whereas the product obtained with the tannase treatment is sterilized below 100°C.

The presence of minerals and elements in an extract depends on the extent of entrapment in the organic matrix, the degree of solubility/choice of solvent, the duration of extraction, temperature, pH, and agitation.[19] Most elements, especially the metals, are complexed with the flavonols, catechols, tannins, and polyphenols.

The most widely used method for preparing Essential Oils from plants is associated with steam distillation.[1] The condensate from steam distillation produces two distinct fractions that contain the volatile ingredients from the plant. The water insoluble fraction contains the "oil". The water soluble fraction contains ingredients from the plant that are water soluble. The water insoluble fraction from steam distilled plant materials is identified as "oil" in the International Nomenclature of Cosmetic Ingredients (INCI) name. The water soluble fraction from the steam distilled plant material is identified as "water" in the INCI name.

Impurities

No published data on impurities of these cosmetic ingredients were discovered and no unpublished data were submitted. The information below applies to impurities found in *C. sinensis* as a food or as food ingredients.

In analyses of twelve *C. sinensis* catechins lots extracted as food ingredients, arsenic (< 0.2 ppm), cadmium (< 0.1 ppm), lead (, 0.4 ppm), and tin (not more than 150 ppm) were below levels of detection.[31] Three lots of *C. sinensis* catechins were analyzed for other components: caffeine (≤7%), organic acids (≤10%), protein and amino acids (≤10%), saccharide (≤12%), fiber (≤1%), fat (≤1%), and ash (≤5%). No microbial contamination was detected.

Ten commercial *C. sinensis* teas for drinking were analyzed for metals.[36] The ranges for metal content were: zinc 1.05 – 3.21 mg/kg; iron, 5.47 - 8.41 mg/kg; manganese, 1.27 – 2.73 mg/kg; copper, 0.01 – 0.93 mg/kg; nickel, 0.01 – 0.64 mg/kg; lead, 0.26 – 1.25 mg/kg; and cadmium, 0.01 – 0.05 mg/kg. The authors asserted that differences in content of the samples were attributable to differences in geographic region of cultivation.

Aflatoxigenic molds and aflatoxins have been reported to be present on *C. sinensis* teas for drinking.[37] In a sampling of 27 commercial black teas (7 branded, 20 nonbranded), aflatoxigenic molds were detected in one branded and 6 unbranded (25.9%) tea samples. Only one of the samples (nonbranded) had detectable aflatoxins (19.2 µg/kg). In black teas that had been spiked with aflatoxins, most of the aflatoxins residue was still present in the leaves after boiling in water, but only 30.6% was present in the final beverage.

It was reported that levels of 712 – 1530, 166 – 280, 1.7 – 7.5, and 1.51 – 2.63 µg/g of aluminum, iron, chromium, and lead, respectively, were found in commercial tea samples (n = 2) using electrothermal atomic absorption spectrometry (ETAAS) and inductively coupled plasma atomic emission spectrometry (ICP-AES; Table 6).[38] For two types of green tea, the ranges were 605 – 620, 1486 – 1550, 4.5 – 4.7, and 2.20-2.34 µg/g, respectively. For infusions of these teas, the levels for aluminum, iron, copper, and zinc were 149 – 367, 7.6 – 11.0, 0.7 – 3.2, and 36 - 50 µg/g, respectively. For green tea infusions, these values were 124-127, 22 – 23, 0.2 – 0.5, and 31-32 µg/g, respectively.

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 7).[39] A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for these ingredients.[40,41]

Data were available from both the VCRP and the Council for the following ingredients:

- Camellia sinensis leaf extract was reported to be used in 1083 leave-on, 747 rinse-off, and 35 bath cosmetic

products.[39] There are reported uses in every exposure type (Table 7). Usage of cosmetic ingredients called "green tea" and "green tea extract" were also reported in the VCRP. Since these are technical names for camellia sinensis leaf extract, the VCRP numbers for these three listings were combined. Camellia sinensis leaf extract was reported to be use up to 2% in leave-on products (the highest concentrations in body and hand products) and up to 1% in rinse-off products (the highest concentration in bath soaps and detergents).[40] It is also reported to be used in products diluted in the bath at up to 0.1% (the highest concentration in bubble baths).

- Camellia sinensis leaf was reported to be used in 38 leave-on, 15 rinse-off, and 1 bath product.[39] Camellia sinensis leaf was reported to be used up to 0.05% in bubble baths.[40] A previously reported product of tea bags for the eyes at 97% is no longer sold.[40,42]
- Camellia sinensis leaf powder was reported to be used in 11 leave-on, 10 rinse-off products, and 1 bath product.[39] Camellia sinensis leaf powder was reported to be used up to 7% in leave-on and up to 0.01% in rinse-off products (highest concentration in bath soaps and detergents).[40] It is also used in a professional face and neck product that is diluted before use at 50%.
- Camellia sinensis leaf water was reported to be used in 26 leave-on and 10 rinse-off products.[43] Camellia sinensis leaf water was reported to be used up to 30% in mascara.[40]

Data were available only on the frequency of use (VCRP) for the following ingredient; no concentration of use data were reported by industry:

- Camellia sinensis leaf oil was reported to be used in 24 leave-on products and 9 rinse-off products.[39]

Data were available only on concentration of use for the following ingredient; uses were not reported in the VCRP:

- Camellia sinensis seed extract was reported to be used in leave-on products up to 0.1% (highest concentration in moisturizing creams and lotions) and in rinse-off products up to 0.0013% (highest concentration in bath soaps and detergents).[40]

There were no frequency of use or concentration of use data reported for:

- Camellia sinensis catechins
- Camellia sinensis flower extract
- Camellia sinensis flower/leaf/stem juice
- Camellia sinensis root extract
- Camellia sinensis seedcoat powder
- Camellia sinensis seed powder
- Hydrolyzed camellia sinensis leaf
- Hydrolyzed camellia sinensis seed extract

Non-Cosmetic

Tea, under the previous name Thea sinensis, is generally regarded as safe (GRAS) by the FDA. (21 CFR 582.20)

In Europe, C. sinensis preparations are used to treat asthenia and as an adjuvant treatment in weight loss/control.[26] Preparations are also used in cutaneous treatment of external genital and perianal warts (*condylomata acuminata*) in immune-compromised patients.[26,44]

In the United States, green tea products are used as dietary supplements, primarily for purported weight loss and antioxidant properties.[17,18,45-54] Other health benefits attributed to green tea include prevention and/or control of atherosclerosis, hypertension, coronary heart disease, diabetes, metabolic syndrome, obesity, and cancer as well as antibacterial, antiviral, antifungal, and neuroprotective effects.

Annual tea consumption varies from country to country, ranging from negligible to approximately 3 kg per person.[55] Worldwide average consumption is approximately 0.5 kg per person.

In 2012, over 79 billion servings of tea were consumed in the United States (over 3.60 billion gallons).[56] Of this, Americans consumed approximately 84% black tea, 15% green tea, and the rest oolong and white tea.

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Dermal/Percutaneous

CAMELLIA SINENSIS CATECHINS

When camellia sinensis leaf extract (0.32, 0.68, 1.03, 1.35 mg/cm^2 in methanol; as green tea) was applied to full thickness pig ear skin using a Franz cell, there was a dose-dependent penetration of the catechins EGCG, EGC, and EC.[57] Saturated solutions of camellia sinensis were formulated using water, polyethylene glycol 400, citrate/phosphate buffer (pH 5.5), and a 50:50 mixture of polyethylene glycol 400 and the buffer. The solutions were applied to drug-in-adhesive

transdermal patches under occlusion in methanol and applied to the pig skin. The receptor cell was sampled periodically for 48 h.

Penetration by the catechins was fastest in the buffer solution and slowest in polyethylene glycol 400 solution. In the buffer solution, EGCG permeated the skin at 1.37 ± 0.40 and 1.88 ± 0.45 μg/cm^2 at 24 and 48 h, EGC permeated at 0.189 ± 4.10 x $^{10-2}$ and 0.342 ± 7.48 x 10^{-2} μg/cm^2, EC permeated at 32.4 ± 11.3 and 71.2 ± 35.2 μg/cm^2, respectively. In the mixed solution, EGCG permeated the skin at 1.27 ± 0.38 and 1.62 ± 0.18 μg/cm^2 at 24 and 48 h, EGC permeated at 0.128 ± 1.71 x 10^{-3} and 0.392 ± 0.004 μg/cm^2, EC permeated at 22.2 ± 17.3 and 40.2 ± 43.8 μg/cm^2, respectively. In polyethylene glycol 400solution, EGCG permeated the skin at 1.37 ± 0.40 and 1.88 ± 0.45 μg/cm^2 at 24 and 48 h, EGC permeated at 0.189 ± 4.10 x $^{10-2}$ and 0.342 ± 7.48 x 10^{-2} μg/cm^2, EC permeated at 32.4 ± 11.3 and 71.2 ± 35.2 μg/cm^2, respectively. In water, EGCG permeated the skin at 0.27 ± 0.15 and 0.66 ± 0.30 μg/cm^2 at 24 and 48 h, EGC permeated at 0.06 ± 0.02 and 0.10 ± 0.03 μg/cm^2, EC permeated at 1.32 ± 0.22 and 2.34 ± 0.34 μg/cm^2, respectively.

Caffeine in the buffer solution permeated at 0.32 ± 0.05 and 0.49 ± 0.01 μg/cm^2 at 24 and 48 h; 173 ± 24.6 and 368 ± 52.9 μg/cm^2 in the mixed solution; 46.8 ± 3.43 and 88.9 ± 0.08 μg/cm^2 in the PEG-400 solution; and 28.4 ± 2.46 and 50.2 ± 1.54 μg/cm^2 in water, respectively.[57]

When EGCG was dermally applied in a transdermal gel (50 mg/kg; 28.6 μg/cm^2) to female SKH-1 mice (n = 4, 5, or 6), EGCG was detected in the skin, plasma, liver, small intestines, and colon for at least 24 h.[58] The test material was administered once. Over the next 24 h, blood was collected under anesthesia and dorsal skin was removed, fractioned into epidermis and dermis, and analyzed. Liver, small intestine, and colon tissues were removed and analyzed.

In the total plasma, the C_{max} was 44.5 ± 8.4 ng/mL, the $t_{1/2}$ was 94.4 ± 13.2 h, and the $AUC_{0\rightarrow24}$ was 881.5 ± 123.4 ng/mL/h. The C_{max} for the epidermis and dermis were 1365.7 ± 613.8 ng/mL and 411.2 ± 21.5 ng/mL, respectively; the $AUC_{0\rightarrow24}$ was 5978.3 ± 2779.9 and 1729.5 ± 259.4 ng/g/h, respectively. The $t_{1/2}$ was 9.3 ± 4.3 and 10.9 ± 1.6 h, respectively.

The C_{max} of EGCG in the liver was 164.8 ± 83.0 ng/g with a $t_{1/2}$ of 74.6 ± 20.1 h and an $AUC_{0\rightarrow24}$ 2494.8 ± 673.6 ng/g/h. The C_{max} in the small intestine was 203.1 ± 64.0 ng/g with a $t_{1/2}$ of 26.8 ± 5.6 h and an $AUC_{0\rightarrow24}$ 2802.8 ± 588.5 ng/g/h. The C_{max} in the colon was 77.0 ± 22.4 ng/g with a $t_{1/2}$ of 21.3 ± 3.2 h and an $AUC_{0\rightarrow24}$ 715.0 ± 107.3 ng/g h. The C_{max}, $t_{1/2}$, $AUC_{0\rightarrow24}$ for EGCG in the urine were 177 ng/mL, 3427.9 ng/mL h, and 70.0 h, respectively.[58]

Antimicrobial Activity

CAMELLIA SINENSIS LEAF EXTRACT

The decaffeinated methanolic extract of the leaves of *C. sinensis* exhibited in-vitro antimicrobial properties against 111 bacteria comprising 2 genera of Gram-positive and 7 genera of Gram-negative bacteria.[59] The extract was active in the range of 10 - 50 μg/ml. A few strains were sensitive at lower concentrations (5 μg/ml). In decreasing order of sensitivity, the bacterial groups were: *Staphylococcus aureus*, *Vibrio cholerae*, *Escherichia coli*, *Shigella* spp., *Salmonella* spp., *Bacillus* spp., *Klebsiella* spp. and *Pseudomonas aeruginosa*.

When the above extract (30, 60 μg/mouse) was intraperitoneally administered to a Swiss strain of white mice (n = 20; control = 60), the mice were protected from a challenge of a medium lethal dose injection of *S. typhimurium*.[59] In the control group (no *C. sinensis*), 48 mice died. In the low-dose group, 4 mice died and no mice died in the high-dose group.

Dermal Effects

CAMELLIA SINENSIS LEAF EXTRACT

There was decreased healing time and no adverse effects in burned rabbits (n = 5) administered an aqueous camellia sinensis leaf extract (100%; 0.05 mL) compared to controls.[60] The rabbits were burned with a heated glass rod applied to shaved skin, then the extract, antibiotic, or nothing was administered. The rabbits were observed for 5 weeks. The size of the wounds decreased faster with the extract and the antibiotic compared to controls. Closure time for the treatment groups was 8 – 10 days for antibiotics and 7 – 9 days for the extract. At five weeks, the wounds were almost healed in the treated groups (0.25 ± 0.02 cm^2) while the average size of the wound in the control group was 0.92 ± 0.15 cm^2. Hair growth also began sooner in both of the treated groups. Microscopic examination showed skin with a more normal appearance in the camellia sinensis leaf extract group compared to the antibiotic and controls groups.

Anti-Inflammatory Effects

CAMELLIA SINENSIS EXTRACT

When saponins (0, 50, 100, 200 mg/kg) extracted from *C. sinensis* leaf were orally administered to rats prior to a subcutaneous injection of carrageenan (1%; 0.5 mL) in a rat hind-paw edema assay, edema in response to carrageenan was mitigated in a dose-dependent manner.[61]

Cytotoxicity and Cellular Effects

CAMELLIA SINENSIS EXTRACT

Camellia sinensis extract (10, 50, 100 μg/mL) was not cytotoxic to rat pheochromocytoma (PC12) cells when exposed in vitro for 24 h.[34] However, at higher concentrations (250, 500, 100 μg/mL), the extract was cytotoxic with < 40% viability at the two highest concentrations. When the cells were incubated with the extract and hydrogen peroxide (250 μM),

hydrogen peroxide poisoning was mitigated by the extract at 5, 100, and 250 μM.

Camellia sinensis water extract (as Korean green tea) had a 50% inhibitory dose (ID_{50}) of 2.05% (0.28 mg/mL dry matter) in the inhibition of protein synthesis in Sprague-Dawley rat hepatic cells.[62] The 25% effective dose (ED_{25}) for lactate dehydrogenase (LDH) release was 1.84% (0.25 mg/mL). Camellia sinensis extract (in the form of black tea) had an ID_{50} of 2.50% (0.46 mg/mL) for protein synthesis and an ED_{25} for LDH release of 5.11% (0.94 mg/mL).

CAMELLIA SINENSIS LEAF EXTRACT

In a 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl-tetrazolium bromide (MTT) test (n = 6), camellia sinensis leaf extract (0, 0.00013%, 0.0006%, 0.0032%, 0.016%, 0.08%, 0.4%, 2%, and 10%) was cytotoxic at 2% and 10% to human keratinocytes.[63] Morphological modifications of the cells were observed at 0.4%. The test substance was a cold extract of green tea using water/propylene glycol (10% dry plant material) prepared in the same manner as that used to prepare tea for drinking.

When human keratinocytes were incubated in camellia sinensis leaf extract (0.05% and 0.1%) there was a 43% protection against oxidation when the cells were exposed to UV radiation (312 nm; 160 mJ/cm^2; time not provided).[63]

EGCG induced apoptosis at 400 and 800 μM in neonatal human dermal fibroblasts.[64] At 200 μM EGCG, a decrease in the proportion of cells in the S and G_2/M phases of the cell cycle and an increase in the proportion of cells in the G_0/G_1 phase was observed. Regulation of the expression of pNF-κB was concentration dependent but EGCG did not affect NF-κB expression. cDNA microarray analysis revealed that EGCG (200 μM) down-regulated cell cycle-related genes. A/B cyclins and cyclin-dependent kinase 1 was reversibly effected by EGCG (200 μM).

TOXICOLOGICAL STUDIES

The *C. sinensis*-derived ingredients in this safety assessment are from consumable sources and exposure to these ingredients in beverages would result in much greater oral doses than those from oral exposures from the use of cosmetic products. Consequently, their oral toxicity potential is not addressed in this report. Though data are presented on the potential for reproductive toxicity, genotoxicity, and carcinogenicity, the focus in this report is primarily on the potential for irritation and sensitization.

Acute Toxicity

Oral – Non-Human

CAMELLIA SINENSIS LEAF EXTRACT

When camellia sinensis leaf extract (2 g/kg; 1.94 mL/kg) was orally administered to Sprague-Dawley (SPF) rats (n = 5/sex), it was concluded that the minimum lethal dose is > 2 g/kg.[65] The test substance was administered after 16 h on a hydric diet. After administration, the rats were observed for 6 h for clinical signs and then followed for 14 days. There were no effects on weight gains and there were no mortalities. Necropsy was unremarkable. The test substance was a cold extract of green tea using water/propylene glycol (10% dry plant material) and prepared in the same manner as that used to prepare tea for drinking.

The above experiment was repeated with an extract of black tea (2 g) provided to the laboratory as a brown powder with the same conclusion.[66] Decreased motility and ptosis of the eyelids was observed in all rats 1 h after administration. Necropsies were unremarkable.

The oral LD_{50} of a Chinese tea extract (0.85% solids) was >2000 mg/kg for mice.[67]

The oral LD_{50} of a green tea extract (1.6% solids) was >2000 mL/kg for rats.[67]

The oral LD_{50} of a oolong tea extract (1.0% solids) was >2000 mg/kg for mice.[67]

Dermal – Non-Human

CAMELLIA SINENSIS CATECHINS

The dermal LD_{50} of EGCG (2000 mg/kg extract; 1860 mg EGCG/kg; 4 mL/kg) was > 1860 mg/kg for HanBrl:WIST (SPF) rats (n = 5/sex).[35] The acute dermal toxicity test was conducted in accordance with the Organization for Economic Co-operation and Development (OECD) guideline number 402 under semi occlusion. The day before the study, the backs of the rats were clipped with an electric clipper exposing approximately 10% of the total body surface. The dressing covering the test site was removed at 24 h and flushed with lukewarm tap water and dried. The rats were observed twice daily for 15 days. Macroscopic examination of all animals was performed at day 15.

There were no signs of systemic toxicity in any of the rats. A slight to moderate erythema was observed in all treated rats after removal of the dressing, which persisted for up to 5 days. Body weights were within standard range for this strain and age of rat. No abnormal macroscopic findings were observed at necropsy.[35]

Repeated Dose Toxicity

Inhalation - Human

CAMELLIA SINENSIS CATECHINS

There were no adverse effects, such as respiratory tract obstruction, allergic bronchial spasm, or skin eruption, including laboratory changes observed when subjects suffering from cerebrovascular diseases (n = 36) inhaled catechins (3.7 mg/mL in saline; 2 mL; 43% of catechins composed of EGCG) or the vehicle (n = 33) three times/day for 7 days.[68] The test substance was delivered by a handheld nebulizer. The sputum of the subjects all tested positive for methicillin-resistant Staphylococcus aureus (MRSA). Total catechin content was 73.0% (31% (-)-EGCG, 21% (-)-EGC, 8.6% (-)-EC, 8.6% (-)-ECG, 2.9% (-)-GCG, and 0.8% (-)-CG.

No adverse effects were observed when tea catechins extract (10 or 20 mg/mL in saline; 2 mL; ≥ 30% tea polyphenol and ≥10% EGCG; assumed to be C. sinensis) were inhaled using a nebulizer by subjects (n = 26) being treated for MRSA three times per day for 79 days.[69]

No adverse effects were observed when tea catechins extract (10 or 20 mg/mL in saline; 2 mL; ≥ 38% tea polyphenol and ≥14% EGCG; assumed to be C. sinensis) were inhaled using a nebulizer by subjects (n = 26) being treated for MRSA three times per day for 79 days.[70]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

CAMELLIA SINENSIS LEAF EXTRACT

There were no adverse effects when pregnant Wistar rats (n = 6) were orally administered camellia sinensis extract (0, 84, 167, 501, and 1336 mg/mL/d; in the form of black tea).[71] The caffeine content was 4.14% (865 mg for the highest dose). The test material was administered either on gestation days 1 – 7, 8 – 14, or 15 – 21. Internal examinations of the dams were conducted by laparoscopy under anesthesia on gestation day10 (early dose groups) or 15 (mid dose groups). Pups were examined daily until the appearance of hair and the opening of the eyelids. The test doses were calculated to be equivalent to 1.5, 3, 9, and 24 cups of tea. There were no mortalities. There were no differences in number of pregnancies, number of uterine implants, number of viable implants, implantation index, pre-implantation loss, post-implantation loss, gestation index, number of pups born, litter index, live birth index, and viability index compared to controls. There were no differences in length of the implants/fetus, gestation duration, cranial length, cranial diameter, and tail length of pups. There were no differences in time taken to open eyes, eruption of incisors and appearance of fur. There were no gross morphological birth abnormalities observed.

CAMELLIA SINENSIS CATECHINS

Unpublished studies were submitted to the FDA for the approval of a topical ointment as a drug that contains up to 15% camellia sinensis catechins to treat warts.[72] These studies are summarized in Table 8. In oral studies, there were increased resorptions at 1000 mg/kg/d in rats. In subcutaneous studies, the test substance was not well tolerated; subcutaneous lesions with necrosis developed. There were spontaneous abortions, increased resorptions, and increased fetal malformations at doses as low as 12 mg/kg/d. Intravaginal administrations up to 0.15 ml/d yielded fewer adverse effects.

When camellia sinensis catechins (1400, 4200, 14000 ppm in feed; EGCG 90%, ECG ≤3.01%, GCG ≤0.12%, other catechins ≤0.54%) were administered to pregnant Wistar (SPF) rats (n = 25) on gestation days 6 - 20, there were no adverse effects observed.[73] All rats survived treatment and there were no clinical signs. There was a transient reduction in feed consumption in the high-dose group and an increase in water consumption in the mid- and high-dose groups. There were no treatment-related macroscopic findings in the dams. There was no effect to embryo/fetal survival, fetal weights, or sex ratios.

In a two generation study of camellia sinensis catechins (1200, 3600, 12000 ppm in feed) using Sprague-Dawley rats (n = 30/sex), there were no adverse effects in either generation. The rats were treated for 10 weeks and then paired for mating. The diet continued through gestation until after weaning. The dams were killed and necropsied after weaning. The pups were culled to 25/sex and the above treatment repeated with mating taking place after 8 weeks.

The offspring of the high-dose group had decreased growth rates, and there was an increase in pup loss. A growth effect among pups was also observed at 3600 ppm, but only in the second generation. Both sexes of the F_1 generation in the high-dose group showed decreased absolute kidney and liver weights. The F_1 males had decreased spleen and prostate weights, but the females' spleens were normal. Histological examination revealed no abnormalities. The lowest dose was considered the overall NOAEL. The authors derived a NOAEL of 200 mg/kg body weight per day EGCG preparation. Because dams consumed twice the amount of feed during the crucial lactation period, during which effects occurred, twice the lowest dose (i.e., 2 x 100 mg/kg/d) was estimated to be the NOAEL.[73]

GENOTOXICITY

CAMELLIA SINENSIS CATECHINS

Catechins were not genotoxic in multiple in vitro and in vivo assays including Ames tests (up to 5000 µg/plate), mouse micronucleus assays (up to 2000 mg/kg), and micronucleus assays. A polyphenol mixture was lethal at 2000 mg/kg/d to mice. Mixed results were reported in a mouse lymphoma assay at concentrations > 100 µg/mL (Table 9).[67,72,74-76]

CARCINOGENICITY

CAMELLIA SINENSIS LEAF EXTRACT

In 1997, the International Agency of Research in Cancer (IARC) listed green tea in group 3, meaning that it is not classifiable according to its carcinogenicity to humans.[55]

Camellia sinensis extract (125, 250, 500 mg/kg/d; as green tea; 85% - 95% catechins w/w, 55% EGCG) did not increase the incidence of neoplastic or non-neoplastic lesions in the organs and tissues of p53 transgenic heterozygous mice (n = 25).[72] The mice were treated by gavage daily for 26 weeks. p-Cresidine and water served as controls.

Anti-Carcinogenicty

The catechins in *C. sinensis*, especially EGCG, have been shown to have preventive and treatment effects in cancer cell lines related to cancers of the prostate, lung, skin, pancreas, breast, and ovaries.[18]

In a population-based case-control study of residents of southern Arizona (n = 404, males = 238, females = 166; mean age 66.6 ± 10), subjects who consumed black tea within the last year had fewer instances of squamous cell carcinoma (SCC) of the skin (odds ratio 0.60) than controls, residents of Tucson, (n = 391, males = 226, females = 165; average age 66.2 ± 11.1 y).[77] Arizona was chosen because it has one of the highest risks of skin SCC worldwide. Variables were controlled for tanning ability, antioxidant intake, education, gender, smoking, and average sun exposure.

When female SKH-l mice (n = 28, 29) were orally administered *C. sinensis* as lyophilized green tea (0.3%, 0.9%; 3, 9 mg of tea solids/mL) in place of drinking water and exposed to UVB (30 mJ/cm^2) twice per week for 35 weeks, there was a decrease in the number of tumors per mouse by 35% and 94%, respectively, compared to controls exposed to UVB without *C. sinensis* treatment.[78] The tumor volume per mouse was decreased by 49% and 97%, respectively. The composition of the green tea polyphenol fraction was: (-)-epigallocatechin gallate (49.5%), (-)-epigallocatechin (11.5%), (-)-epicatechin gallate (11.4%), caffeine (7.6%), (-)-epicatechin (6.1%), (+)-catechin (0.5%), and gallic acid (0.4%).

When female SKH-1 mice (n = 29) were orally administered *C. sinensis* (as green tea for their drinking water; 1.25 g steeped in100 mL hot water; ~4 mg tea solids/mL) UVB-induced complete carcinogenesis was inhibited. This was not the case with decaffeinated green tea. The *C. sinensis* extract was administered for 2 weeks before and concurrently with twice per week treatment with enhanced UVB (280-320 nm; 75% - 80% total energy; 30 mJ/cm^2 for 25 – 30 s) exposure. There were increases in apoptosis in the epidermis observed, but no effect in non-UVB treated normal epidermis. The authors concluded that administration of green tea and caffeine may inhibit UVB-induced carcinogenesis, at least in part, by enhancing UVB-induced apoptosis.

Oral administration of *C. sinensis* (1.25% as green or black tea leaf extract; 1.25 g of tea leaf steeped in100 mL water; 4.0 or 4.4 mg tea solids/ml) as the drinking water to the UVB-treated mice decreased the number of tumors per mouse by 51% and 41%, respectively. Tumor volume/mouse was decreased by 79% and 70%, respectively. The mice were treated with gradually increasing doses of the test substances for 2 weeks before the start of the twice/week treatment with UVB for 40 weeks. The mice were killed 4 weeks after the end of the UVB administration. Decaffeinated green or black *C. sinensis* leaf extracts (1.25%) containing 3.6 or 3.9 mg of tea solids/mL, respectively, were less effective than regular green or black tea extracts, and decaffeinated black tea was less effective than decaffeinated green tea at inhibiting the formation of skin tumors. Adding 0.36 mg of caffeine/mL to the decaffeinated extracts either fully or partially restored the inhibitory effects on UVB-induced tumorigenesis.[78]

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

CAMELLIA SINENSIS LEAF EXTRACT

When camellia sinensis leaf extract (100%; 0.5 mL) was dermally administered to the clipped skin of albino New Zealand rabbits (n = 3), there were no signs of irritation.[79] The test substance was a cold extract of green tea using water/propylene glycol (10% dry plant material) and prepared in the same manner as that used to prepare tea for drinking. It was provided to the laboratory as a brown liquid. The test substance was applied to a 2.5-cm^2 gauze pad, which was then kept in contact with the skin for 24 h using hypoallergenic adhesive tape. The test site was examined within 1 h of removal and at 24 and 72 h after removal.

The above experiment was repeated as stated with an extract of black tea (0.5 g), provided to the laboratory as a brown powder, with a conclusion that the test substance was a slight irritant.[80] A slight to definite erythema was observed on all treated rabbits. Cutaneous dryness and a slight decrease in skin suppleness were observed. The test sites were observed at 1, 25, and 72 h after removing the pad.

Chinese tea extract (10%, 100%; 0.85% solids) was negative for dermal irritation in rabbits.[67] No further details were provided.

Green tea extract (100%; 1.6% solids) was negative for dermal irritation in rabbits.[67] No further details were provided.

Oolong tea extract (10%, 100%; 1.0% solids) was negative for dermal irritation in rabbits.[67] No further details were provided.

CAMELLIA SINENSIS CATECHINS

There were no signs of irritation when EGCG (0.47 g in 3 ml distilled water) was administered to the clipped flanks of male New Zealand White rabbits (n = 3) for 4 h under semi-occluded patch.[35] The tests were conducted according to the EC Commission Directive 92/69/EEC, B.4, ''Acute Toxicity—Skin Irritation'' and OECD guideline number 404 (1992). The dorsal fur of three male rabbits was removed with electric clippers 24 h before the administration of the test material. Each rabbit was treated with 0.5 g of EGCG preparation (93.4% EGCG) dissolved in 0.3 ml distilled water and applied to the skin of one flank using a semi-occlusive patch. After removing the patch, the skin was cleaned with water. Skin reactions and irritation effects were assessed at approximately 1, 24, 48 and 72 h after patch removal. Adjacent areas of untreated skin from each animal served as controls. There were no signs of toxicity observed.

In a preliminary study for a guinea pig maximization test, an intradermal injection of 0.09% EGCG was found to be the greatest tolerable dose.[35] A grade 3 erythema was produced, but not necrosis. At 48 h of dermal exposure, there was no reaction in the preliminary test at concentrations up to 50%.

Dermal – Human

When *C. sinensis* preparations (DER ranging from 1/1000 - ≥1/10; 0.1% - >10%) were used in dermal applications of ointments(compositions not provided) to treat genital warts, the following were among the adverse effects: erythema, pruritus, irritation/burning, pain, ulcer, edema, induration, and vesicles.[26] A full list of reported effects is provided in Table 10.

A black tea extract (100%; 1.0% solids) was negative in a patch test (n = 100). No further details were provided.[67]

CAMELLIA SINENSIS CATECHINS

In a trial of an ointment containing camellia sinensis catechins (10% and 15%) for the treatment of anogenital warts, there was no irritation or other adverse effects, reported.[81] The ointment was administered three times per day for up to 16 weeks. No adverse effects were reported during treatment, or during the 12-week follow-up, and the ointment was reported to be well tolerated.

CAMELLIA SINENSIS LEAF WATER

In a patch test (n = 10) of a mascara containing camellia sinensis leaf water (30%), there were no signs of irritation at 30 min, and 24 and 48 h after the removing the patch.[82] The test substance was administered to the inner side of the upper arm for 24 h.

Mucosal – Non-Human

CAMELLIA SINENSIS CATECHINS

Intravaginal administration of an ointment containing camellia sinensis catechins (15%) to pregnant SD rats (n = 25) from gestation day 6 to the end of lactation caused ulceration and erosion of the vaginal mucosa with inflammation for the duration of treatment.[72] The control group (no catechins) did not exhibit damage to the vaginal mucosa. The effects resolved when treatment stopped.

Ocular

CAMELLIA SINENSIS LEAF EXTRACT

Camellia sinensis leaf extract (100%; 0.1 mL) administered to the lower conjuctival sac of the right eye of albino New Zealand rabbits (n = 3) was a slight ocular irritant.[83] There was slight irritation of the conjuctiva at 1 h; there were no iris lesions. Two rabbits had a very slight superficial epithelial attack of the cornea. All signs of irritation were resolved within 24 h. The test substance was a cold extract of green tea using water/propylene glycol (10% dry plant material) and prepared in the same manner as that used to prepare tea for drinking. It was provided to the laboratory as a brown liquid. The eyes were examined 1 h after instillation and 1, 2, and 3 days later.

The above experiment was repeated with an extract of black tea (0.1 g), provided to the laboratory as a brown powder, with the same conclusion.[84] There was a slight irritation of the conjuctiva observed at 1h; there were no lesions of the iris. All rabbits had a slight epithelial attack of the cornea. All signs of irritation were resolved within 48 h.

Green tea extract100% 1.6% solids) was not irritating to the eyes of rabbits. No further information was provided.

CAMELLIA SINENSIS CATECHINS

The administration of EGCG preparation (0.093 g EGCG; 0.1 g total) into the eye of a single female New Zealand White rabbit resulted in moderate to severe irritation including reddened conjunctivae and sclera, discharge and chemosis.[35] A slight to moderate corneal opacity affecting the whole area of the cornea was observed up to 72 h after administration of the test material. No damage to the iris, and no corrosion or staining of the eye by EGCG was observed throughout this study. The test was done in compliance with OECD guideline number 405. Both eyes of the rabbits were examined at the beginning of the study. The lids were briefly held together after administration; the eyes were not rinsed. The animal was

observed for ocular irritancy for 17 days. Because EGCG was suspected to be an ocular irritant, a single animal was treated first and observed to recovery. Based on the results from this preliminary study, no additional rabbits were tested.

Sensitization

Dermal – Non-Human

CAMELLIA SINENSIS LEAF EXTRACT

Oolong tea extract (; 1.0% solids) was not sensitizing to guinea pigs (n not provided).[67] First induction was at 50%; second induction was at 25%. Challenge was at 5% and 10%. No further details were provided.

International Fragrance Association (IFRA) reported that in a local lymph node assay (LLNA) reported an EC_3 of > 1250 µg/cm^2 for camellia sinensis leaf extract (as tea leaf absolute).[85] Irritation was observed at higher concentrations (not provided) so the actual EC_3 could not be calculated.

CAMELLIA SINENSIS CATECHINS

In a sensitization assay using female GOHI (SPF) guinea pigs (n = 6), camellia sinensis catechins (5%, 10%, 30% in ethanol; 100 µL/8 cm^2; 4%, 8%, 24% EGCG) was sensitizing at challenge (1%, 3%, 5%, and 10%) as well as at a second challenge (0.1%, 0.5%, 1%, 3%, 5% and 10%) two weeks later.[35] The skin sensitization assay was performed using a procedure adopted from OECD guideline number 406 (OECD, 1992b). During the induction phase of the assay, an EGCG preparation (80% EGCG) was applied to the shaved right flanks of the guinea pigs 5 days/week for 4 weeks. Control animals were treated with ethanol. Treatment sites were left open between applications. During induction, new treatment sites were chosen whenever the irritation became considerable. Immediately following the induction period, the guinea pigs were challenged with EGCG (25 µL/2 cm^2 on the left flank). During the induction period the guinea pigs were observed for signs of erythema and edema on each test site. Challenge reactions were assessed at 24 and 48 h after application.

Irritation responses increased throughout the induction period starting with the fifth application; the 30% group had the greatest frequency of reactions. Erythema became evident in the 10% and 5% groups after the 13th and 16th administrations, respectively. In the 10% group, a slight erythema was observed in 2/6 guinea pigs after the 13th application, with all guinea pigs showing similar signs by the 16th application. For the 5% group, erythema was observed only for 3 days in 1/6 guinea pigs. Both EGCG preparations elicited positive effects in the test groups during the challenges.

Control animals showed no response after the first challenge; one or two of the six control guinea pigs had slight or well defined erythema after the second challenge with 0.8% or higher EGCG. Although there was a positive dose–response effect for the challenge, it did not clearly correlate to the induction doses. There were a greater number of reactions in the 5% induction group (6 at 24h, 5 at 48 h) than in the 30% induction group (2 at 24 h, 1 at 48 h). No mortalities or symptoms of systemic toxicity were observed in any of the guinea pigs, and body weights of the test animals were in the same range as those of the controls during the study period.[35]

In a maximization test using female Himalayan strain albino guinea pigs (n = 10; control n = 5), camellia sinensis catechins (0.1% in distilled water; 0.1 ml; 90% EGCG) was a sensitizer.[35] All guinea pigs had grade 3 or 4 erythema following challenge by dermal administration of the test material (50%; 0.15 mL). Grade 1 erythema was observed following the first test challenge in 3/10 in the test group and 0/5 in the control group. In a second challenge 1 week later, 9/10 in the test group showed stronger (grade 2) erythema. No mortalities or signs of systemic toxicity were observed in any of the guinea pigs and body weights of the test group were in the same range as those of the controls during the study period.

Dermal – Human

CAMELLIA SINENSIS LEAF EXTRACT

A facial line filler treatment product containing camellia sinensis leaf extract (0.86%; 150 µL; black tea) was not irritating or sensitizing in an HRIPT (n = 101).[86,87] The test substance was administered nine times on a 2 x 2 cm absorbent pad under occlusion. No reactions were observed in any of the 106 to complete the induction phase. No reactions were observed in any of the 101 to complete the challenge phase.

An eye cream containing camellia sinensis leaf extract (0.86%; black tea) was not irritating or sensitizing in an HRIPT (n = 638). The test substance was administered under occlusion.[87,88]

A black tea extract (100%; 1.0% solids) was negative in a HRIPT (n = 100). No further details were provided.[67]

Camellia sinensis leaf extract (as tea leaf absolute) was reported to have a no observed effect level (NOEL) of 480 µg/cm^2.[85]

CAMELLIA SINENSIS LEAF WATER

In an HRIPT (n = 110) of a mascara containing camellia sinensis leaf water (30%), there were no signs of irritation or sensitization.[89]

Phototoxicity

CAMELLIA SINENSIS LEAF EXTRACT

There were no signs of erythema on treated sites on the forearms of subjects (n = 6) treated with camellia sinensis

leaf extracts (10%; in the form of green or black tea) then exposed to UVA, B, and C.[90] Freeze-dried green and black tea extracts were used to make gels with 1% carbomer solution and sodium hydroxide. These were administered to a 4 cm^2 area. The controls were an untreated area and an area treated with just the gel. The arms were then exposed to UVA/UVB/UVC (UVA 4550 $\mu W/cm^2$; UVB = 2800 $\mu W/cm^2$; UVC = 500 $\mu W/cm^2$) for 2.5 min. Erythema was observed in the control and carbomer treated sites but not the treatment sites.

Photo Effects

CAMELLIA SINENSIS LEAF EXTRACT

A sunscreen containing various concentrations of camellia sinensis leaf extract (0, 2%, 3%, 4%, 5%; in the form of green tea) protected against photoaging and photoimmunology-related biological measurements in female human subjects (n = 20); especially at 3%.[33] The melanoma index decreased in a dose-dependent manner until 4%; effectiveness decreased at 4% and 5%. The same pattern was observed for the thickness of the stratum cornium and total epidermis measurements. Cytokeratins CK5/6, CK16 were overexpressed on the site irradiated with or without the base cream; the decreased effect followed the same pattern as the other markers. Matrix metalloproteinases MMP-2 and MMP-9 were slightly to moderately expressed on unirradiated skin. Expression of MMP-2 and MMP-9 was decreased on the 2%, 3%, and 4% sites.

The sunscreen was applied 30 min before each irradiation (290–400nm) at 1.5 x each individual's minimal erythemal dose (MED) and 6, 24, and 48 h after the last irradiation. The subjects' backs were irradiated on four consecutive days (duration of treatment was not provided). The MED of the subjects ranged from 25 to 40 mJ/cm^2, with an average of 32.46mJ/cm^2. Punch biopsies were obtained from all the seven sites 72 h after the last UVR exposure and analyzed. Standardized photographs were taken with a digital camera before each procedure and at the follow-up examinations.[33]

CAMELLIA SINENSIS CATECHINS

Topical treatment with green tea polyphenols (3 mg/2.5 cm^2 in acetone) on human skin decreased the UVB induction of cyclobutane pyrimidine dimer formation and erythema in a dose-dependent manner.[91] The polyphenols consisted of EC at 6%, EGC at 5%, EGCG at 65%, and ECG at 24%. Green tea polyphenols were administered to the buttocks of Caucasian subjects (n = 6) 20 min before the skin was exposed to 0.5%, 1.0%, 2.0%, or 4.0% of the previously established minimal erythema dose. The test sites were examined and skin punch biopsies taken 24 h after UVB treatment. Cyclobutane pyrimidine dimers and erythema were decreased in the treated sites exposed to 1.0%, 2.0, and 4.0% of a minimal erythema dose of UVB in a dose-dependent manner.

Metalloproteinase activity in cultured fibroblasts and keratinocytes decreased when incubated in EGCG (0.01, 0.1 μM in propylene glycol:ethanol 3:7) for 24 h before exposure to UVA radiation.[92] This indicated possible protection of the cells by EGCG from oxidative stress from UVA exposure. An artificial skin was prepared using human keratinocytes and dermal fibroblasts on a lattice of bovine type I collagen. The skin was incubated in EGCG for 24 h and washed. The skin was exposed to UVA (340 – 400 nm; 20 J/cm^2; duration not provided) 6 h later. Supernatant was collected 24 h after irradiation and analyzed.

The dermal administration of either EGCG (1 mg/cm^2 in a hydrophilic ointment ; >98% pure) or green tea catechins (0.2% in a hydrophilic ointment ; > 86% catechins) to female SKH-1 hairless mice (n = not provided) prevented single and multiple UV (180 mJ/cm^2) exposure-induced depletion of catalase activity and prevented the depletion of antioxidant enzymes (e.g., glutathione peroxidase, catalase, and glutathione).[93] Treatment also inhibited UVB-induced oxidative stress when measured in terms of lipid peroxidation and protein oxidation. The test substances were administered to the backs of the mice either once or daily for 10 consecutive days prior to UVB (290 – 320 nm) and UVA exposure. The mice were killed 24 h after the last UV exposure and the skin was biopsied. The green tea catechins were composed of: EC, 10.4%; EGC, 8.3%; EGCG, 55.8%; GCG, 4.4%; and ECG, 6.9%.

Female SKH-1 hairless mice were administered green tea catechins (0.2% in drinking water) for 10 days before and during UV exposure as described above. Treatment with green tea catechins prevented single or multiple UVB irradiation-induced depletion of antioxidant enzymes, oxidative stress, and phosphorylation of proteins. However, the photoprotective efficacy was less than that of topical treatments of EGCG and green tea catechins. The authors stated that this may be due to less bioavailability in skin target cells.[93]

Green tea catechins at 70 and 140 mg/L were reported to protect human retinal pigment epithelial (RPE) cells, in vitro, from the cytotoxic effects of UVB radiation.[94] The protective effect observed at these concentrations was suggested to be the result of the attenuation of the UVB-induced suppression of survivin gene expression and resultant suppression of mitochondrion-mediated apoptosis. However, 700 and 1400 mg/L appeared to have a toxic rather than protective effect on the UVB-irradiated cells. RPE cells were treated with green tea catechins for 2 h before or after exposure to UVB (100 μw/cm2) for 2 h. Viability of UVB-irradiated RPE cells decreased by 49.2% compared with unirradiated controls. The protective effects of catechin pretreatment were more effective than post-treatment. Viability of RPE cells was assessed by 3,(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay. Survivin gene expression was examined by real-time PCR analysis. Ultrastructure of RPE cells was examined by transmission electron microscopy. The composition of the catechins was: GC, 44.38; EGC, 85.47; C 14.09; EGCG, 344.73; GCG, 42.49; ECG 103.37; CG 8.80 mg/g.

CLINICAL USE

Case Studies

A 51-year-old man was diagnosed with hypersensitivity pneumonitis (HP) after undergoing catechin inhalation therapy for 1 month.[95] The diagnosis was based on the clinical course, bronchoscopy, and a challenge test. The subject was being treated for tuberculosis and had been administered the catechin inhalation therapy when MRSA was observed in his sputum. He was administered catechin-rich green tea extract solution (2 mL) dissolved in distilled water (50 mg/ml) once or twice daily using a handheld nebulizer. There were no initial symptoms, but the subject later noticed that he coughed frequently during and after inhalation of the extract.

OTHER ASSESSMENTS

An IFRA standard for tea leaf absolute (aka camellia sinensis leaf extract; CAS no. 84650-60-2) had the following restrictions for use: lip products, 0.01%; deodorants/antiperspirants, 0.02%; hydroalcoholics for shaved skin, 0.07%; hydroalcoholics for unshaved skin, 0.2%; hand cream, 0.1%; mouthwash, 0.3%; intimate wipes, 0.04%; hair styling aids, 0.5%; and rinse-off hair conditioners, 2.4%.[85] Based on animal data, green tea absolute was determined to be a moderate sensitizer. These limits were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients; a dose of 480 J.μg/cm^2 was the weight of evidence (WoE) no expected sensitization level (NESIL) used to develop the IFRA standard based on a QRA for sensitization.

In a safety assessment of *C. sinensis* as green tea used in dietary supplement products, the U.S. Pharmacopeia Dietary Supplement Information Expert Committee concluded that when supplements containing concentrated green tea extracts are used and formulated appropriately, there are no significant safety issues with the caveat that a caution statement be included in the labeling section.[96] The caution statement warns of the potential of liver damage when concentrated green tea supplements are consumed on an empty stomach. This does not apply to *C. sinensis* as a beverage.

There are several reviews regarding the protective effects of green tea extracts and its catechins, especially EGCG, against chemical carcinogens.[47,97-100]

According to Yang *et al*.[98], there are more than 133 studies published from 1991 to 2008 on the effectiveness of *C. sinensis* on cancers (Table 11). Inhibitory effects of tea and/or tea constituents on lung, oral, stomach, intestine, dermal, prostrate, breast, liver, bladder, pancreas, and thyroid cancers were found.

SUMMARY

This is a safety assessment of *Camellia sinensis* (tea)-derived cosmetic ingredients. These ingredients function mostly as antioxidants and skin-conditioning agents – miscellaneous. Because tea leaves are ingested in food and drink, this safety assessment does not address systemic toxicity but is primarily focused on the potential for irritation and sensitization.

The constituents of *C. sinensis* include amino acids, carotenoids, catechins, enzymes, flavonoids (including flavanols and flavonols), and glycosides. The concentrations of these constituents in plant parts is influenced by growing conditions, geographical location, soil conditions, and processing.

Camellia sinensis leaf extract was reported to be used in 1083 leave-on, 747 rinse-off, and 35 bath cosmetic products; it was used up to 3% in leave-on products, 1% in rinse-off products, and up to 0.1% in bath products. Camellia sinensis leaf was reported to be used in 38 leave-on, 15 rinse-off, and 1 bath product; it was used up 0.05% in bubble baths. Camellia sinensis leaf powder was reported to be used in 11 leave-on and 10 rinse-off products; it was used up to 7% in leave-on products, up to 50% in a professional product that is diluted before use, and up to 0.01% in rinse-off products. Camellia sinensis leaf water was reported to be used in 26 leave-on and 10 rinse-off products; it was used up to 30% in mascara. Camellia sinensis leaf oil was reported to be used in 24 leave-on products and 9 rinse-off products. Camellia sinensis seed extract was reported to be used in leave-on products up to 0.1% and in rinse-off products up to 0.0013%. There are no reported uses or concentrations of use for the rest of the ingredients.

The FDA considers *C. sinensis* to be GRAS for use as a food additive.

Catechins from camellia sinensis leaf extract penetrated pig ear skin as did caffeine. EGCG penetrated mouse skin.

Camellia sinensis leaf extract exhibited antimicrobial properties towards multiple bacterial species and wound-healing properties.

Camellia sinensis extract was not cytotoxic to rat pheochromocytoma cells up to 100 μg/mL but induced apoptosis to neonatal human dermal fibroblasts at 400 and 800 μmol/L.

The oral LD_{50} for rats was > 2 g/kg for camellia sinensis leaf extract as both green and black tea. The dermal LD_{50} of EGCG was > 1860 mg/kg for rats. There was slight to moderate erythema observed.

There were no adverse effects when up to 20 mg/mL tea catechins (assumed to be *C. sinensis*) were inhaled for up to 79 days by human subjects.

Reproduction and developmental studies of an ointment that contained up to 15% camellia sinensis catechins were conducted using rats. In oral studies, there were increased resorptions at 1000 mg/k/d in rats. In subcutaneous studies, the test substance was not well tolerated; subcutaneous lesions with necrosis developed. There were spontaneous abortions, increased resorptions, and increased fetal malformation as low as 12 mg/kg/d. Intravaginal administration up to 0.15 mL/d had fewer adverse effects.

Camellia sinensis extract had no adverse effects when orally administered to pregnant rats up to 1336 mg/mL/d in drinking water. In a two-generation study, camellia sinensis catechins up to 12000 ppm in feed caused no clinical signs and no effects to embryo/fetal survival, fetal weights, or sex ratios. The offspring of the high-dose group had decreased growth rates, and there was an increase in pup loss. While there were some decreased organ weights, histological examination revealed no abnormalities. The NOAEL was 200 mg/kg/d EGCG.

Catechins were not mutagenic in multiple in vitro and in vivo assays including Ames test (up to 5000 µg/plate), mouse micronucleus assays (up to 2000 mg/kg), and micronucleus assays. A polyphenol mixture was lethal at 2000 mg/kg/d to mice. Mixed results were reported in a mouse lymphoma assay at concentrations > 100 µg/mL.

Camellia sinensis extract at 500 mg/kg/d was not carcinogenic to p53 mice after 26 weeks.

Camellia sinensis leaf extracts, that contained 10% dry green or black tea, were not dermally irritating to rabbits. Camellia sinensis leaf extract at 100% caused no adverse effect to the skin of burned rabbits. Camellia sinensis catechins were not irritating to rabbits with intact skin at 0.47 g.

There were no adverse effects in a human patch test of mascara containing camellia sinensis leaf water at 30%. There were no adverse effects in a trial of an ointment containing camellia sinensis catechins at 10% and 15%.

C. sinensis preparations with > 10% plant material caused erythema, pruritus, irritation/burning, pain, ulcer, edema, induration, and vesicles in human dermal tests.

The intravaginal administration of an ointment containing camellia sinensis catechins at 15% caused ulceration and erosion of the vaginal mucosa with inflammation for four weeks in rats.

Camellia sinensis leaf extracts from green or black tea were slight ocular irritants. The administration of a preparation containing 0.093% EGCG into the eye of a single rabbit resulted in moderate to severe irritation including reddened conjunctivae and sclera, discharge and chemosis.

Camellia sinensis catechins were sensitizing to guinea pigs at 5%. In another guinea pig test, camellia sinensis catechins was a sensitizer at 0.1%.

Camellia sinensis leaf extract was not irritating or sensitizing in two HIRPTs conducted on two cosmetic products that contain this ingredient at 0.86%. A black tea extract was negative in a HRIPT at 100% (1% solids). In an HRIPT of a mascara product containing camellia sinensis leaf water at 30%, there were no signs of irritation or sensitization

There was no sign of erythema at treatment sites on the forearms of subjects treated with 10% camellia sinensis leaf extract in the form of green or black tea then exposed to UVA and B. Topical treatment with green tea polyphenols at 3 mg/2.5 cm^2 to human skin decreased the UVB induction of cyclobutane pyrimidine dimer formation and erythema in a dose-dependent manner. Metalloproteinase activity in cultured fibroblasts and keratinocytes decreased when incubated in EGCG at 0.01 and 0.1 µM for 24 h before exposure to UVA radiation. Multiple in vitro and in vivo studies demonstrated UV-protective effects of camellia sinensis catechins.

DISCUSSION

Tea, under the previous name *Thea sinensis*, is a GRAS substance for food. The *C. sinensis*-derived leaf ingredients in this safety assessment are consumed in beverages and exposure to these ingredients in beverages would result in much greater oral doses than exposures from use of cosmetic products. Consequently, their oral toxicity potential is not addressed in this report. Though data are presented on the potential for reproductive toxicity, genotoxicity, and carcinogenicity, the focus of the Panel was primarily on the potential for irritation and sensitization for the leaf-derived ingredients.

Linalool and several compounds containing linalool have been reported in the leaves ranging from 6 to 1984 ppm and in the leaf essential oil ranging from 31800 to 198 400 ppm in *C. sinensis* plants. Linalool is a dermal sensitizer that has been found to be used safely up to 4.3%. However, it should also be noted that oxidation products of linalool are thought to be the source of sensitization, rather than linalool itself.

Also, quercetin and several compounds containing quercetin have been reported in the leaf, plant, and shoot ranging from 760 to 10000 ppm. A positive genotoxic effect in an Ames assay has been reported and genotoxicity in in vitro tests and in some in vivo studies of i.p. exposures, but results were consistently nongenotoxic in oral exposure studies using mice and rats.

The Panel has noted that linalool and quercetin are found in *C. sinensis* leaves and essential oil and acknowledges that, depending on growing conditions and methods of manufacture, these constituents may or may not be found in the cosmetic ingredients. The Panel further noted that the use of other botanical ingredients that may contain linalool and quercetin in combination with *C. sinensis*-derived ingredients in a single formulation, or in formulations that are used at the same time or in close time proximity, could result in exposures that exceed levels of toxicological concern. Thus, cosmetic products containing one or more botanical ingredient(s) should be formulated to ensure concentrations of linalool and does not exceed the limit set by the Panel, and that total exposures to such constituents remain below the levels of toxicological concern, whether these products typically are used simultaneously or sequentially.

The Panel recognized that every leaf extract would likely be somewhat different and that the characterization of the composition of the plant-derived ingredients addressed in this safety assessment is broad. Nonetheless, the available composition data represent what would be found commonly in ingredients prepared in the manner described. The Panel assumes that the manufacturing process is the same for oral consumption and cosmetics. The conclusion regarding safety,

therefore, is valid only for ingredients prepared in a manner that produces a chemical profile similar to that described in this report. Extracts not prepared in a manner that produces similar chemical profiles, could be considered safe only if they have similar safety test profiles.

The Panel expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients.

Aflatoxins have been detected in dried C. sinensis leaves for drinking. The Panel believes that aflatoxins will not be present at levels of toxicological concern in *C. sinensis*-derived ingredients. The Panel recognizes the United States Department of Agriculture (USDA) designation of ≤ 15 ppb as corresponding to "negative" aflatoxin content. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

There were several studies showing photoprotective, not phototoxic effects. Therefore, the Panel is not concerned that phototoxicity is a problem.

There is not enough data to come to a conclusion of safety for the ingredients that are not derived from the leaves and stems. To make a determination of safety of these ingredients, the Panel needs data on:

- method of manufacture
- characterization of these ingredients
- human sensitization data, in particular for camellia sinensis leaf powder at 50%
- concentration of use in cosmetics
- confirmation that camellia sinensis leaf water is used only as a fragrance

Should this data be provided, the Panel would reopen this safety assessment.

CONCLUSION

The CIR Expert Panel concluded that camellia sinensis leaf extract is safe in cosmetics up to 0.86% in leave-on products and up to 1% in rinse-off products. Camellia sinensis catechins is safe as used. The Panel also concluded that the available data or information are insufficient to make a determination that camellia sinensis flower extract, camellia sinensis flower/leaf/stem juice, camellia sinensis leaf, camellia sinensis leaf oil, camellia sinensis leaf powder, camellia sinensis leaf water, camellia sinensis root extract, camellia sinensis seedcoat powder, camellia sinensis seed extract, camellia sinensis seed powder, hydrolyzed camellia sinensis leaf, and hydrolyzed camellia sinensis seed extract are safe under the intended conditions of use in cosmetics.

TABLES

Table 1. Definitions and functions of *Camellia s.*-derived ingredients in this report.[1]

Ingredient CAS No.	Definition	Function
Camellia Sinensis Leaf Extract 84650-60-2	The extract of the leaves of *Camellia sinensis.*	Antifungal agent; antimicrobial agent; antioxidant; cosmetic astringent; fragrance ingredient; light stabilizer; oral care agent; skin protectant; skin-conditioning agent – emollient; skin-conditioning agent – humectant; skin-conditioning agent - miscellaneous
Camellia Sinensis Catechins	A mixture of catechins obtained from the leaves of *Camellia sinensis.*	Antioxidants
Camellia Sinensis Flower Extract	The extract of the flowers of *Camellia sinensis.*	Skin-conditioning agents – miscellaneous
Camellia Sinensis Flower/Leaf/Stem Juice 1196791-49-7	The juice expressed from the flowers, leaves and stems of *Camellia sinensis.*	Antioxidant
Camellia Sinensis Leaf	The leaf of *Camellia sinensis.*	Skin-conditioning agent – miscellaneous
Camellia Sinensis Leaf Oil 68916-73-4	The oil derived from the leaves of *Camellia sinensis.* This is an essential oil.	Antioxidant; skin-conditioning agent - miscellaneous
Camellia Sinensis Leaf Powder	A powder derived from the dried, ground leaves of *Camellia sinensis.*	Exfoliant
Camellia Sinensis Leaf Water	An aqueous solution of the steam distillate obtained from the leaves of *Camellia sinensis.*	Fragrance ingredient
Camellia Sinensis Root Extract	The extract of the roots of *Camellia sinensis.*	Skin-conditioning agent – miscellaneous
Camellia Sinensis Seedcoat Powder	The powder obtained from the dried, ground seedcoats of *Camellia sinensis.*	Skin conditioning agent – miscellaneous
Camellia Sinensis Seed Extract	The extract of the seeds of *Camellia sinensis.*	Skin-conditioning agent – humectant
Camellia Sinensis Seed Powder	The powder obtained from the dried, ground seeds of *Camellia sinensis.*	Antioxidant; skin-conditioning agent – miscellaneous
Hydrolyzed Camellia Sinensis Leaf	The hydrolysate of Camellia Sinensis Leaf (q.v.) derived by acid, enzyme or other method of hydrolysis.	Skin-conditioning agent – humectant
Hydrolyzed Camellia Sinensis Seed Extract	The hydrolysate of Camellia Sinensis Seed Extract derived by acid, enzyme or other method of hydrolysis.	Antioxidant; skin protectant; skin-conditioning agent - miscellaneous

Table 2. Constituent groups of fresh green *C. sinensis* leaf.[4]

Constituent	% of dry weight
Flavonols	25.0
Flavonols and flavonol glycosides	3.0
Polyphenolic acids and depsides	5.0
Other polyphenols	3.0
Caffeine	3.0
Theobromine	0.2
Amino acids	4.0
Organic acids	0.5
Monosaccharides	4.0
Polysaccharides	13.0
Cellulose	7.0
Protein	15.0
Lignin	6.0
Lipids	3.0
Chlorophyll and other pigments	0.5
Ash	5.0
Volatiles	0.1

Table 3. Constituents of concern in *C. sinensis*.

Constituent	Effects	Reference
Linalool	Dermal sensitizer. Used safely at up to 4.3% (20% in a consumer fragrance).	[101]
Quercetin	Positive genotoxic effect in an Ames assay	[102]
	Consistently genotoxic in in vitro tests and in some in vivo studies of i.p. exposures, but was consistently nongenotoxic in oral exposure studies using mice and rats.	[103]

Table 4. Constituent groups in medical grade *Camellia sinensis* leaf extract.[16,26-30]

Constituent group	Constituent	Concentration (%)
Methylxanthines	Caffeine	2.5-4.2
	Theophylline	0.02-0.04
	Theobromine	0.15-0.2
Flavanols (flavan-3-ols)		10-25
	Monomers (catechins)	
	(-)-epicatechin (EC)	
	(-)-epicatechin-3-*O*-gallate (ECG)	
	(-)-epigallocatechin (EGC)	
	(-)-epigallocatechin-3-*O*-gallate (EGCG)	
	Dimers (theaflavins)	
	Theaflavin	
	Theaflavin 3-gallate	
	Theaflavin 3-*O*-gallate	
	Theaflavin3,3-*O*-digallate	
Flavonols		
	Quercetin (and its glycosides)	
	Kaempferol (and its glycosides)	
	Myricetin (and its glycosides)	
Flavones		
	Apigenin	
	Luteolin	
Phenolic acids		
	Chlorogenic acid	
	Gallic acid	
	Theogallin	
Amino acids	Theanine (5-N-ethyl glutamine)	3
	18 other amino acids	
Therpene saponins (theafolia saponins)	Aglycones	
	Barringtogenol C	
	R1-barringenol	
	And others	
Polysaccharides		13
Proanthocyanidins (tannins)		
Vitamins		
	Ascorbic acid	
	α-Tocopherol	
Other compounds		
	Fluoride	
	Chlorophyll	
	Organic acids	
Constituent group	**Constituent**	**Concentration (ppm)**
Elements		
	Copper	270
	Iron	13040
	Nickel	1340
	Sodium	1.800
	Potassium	262
	Magnesium	30,800
	Calcium	13,750
	Zinc	630.0
	Chromium	10.0

Table 5. Phenolic composition of green and black tea from young leaves and leaf buds.[53]

Constituent	Green tea (%w/w)	Black tea (%w/w)
Catechins	30-42	3-10
Flavonols	5-10	6-8
Other flavonoids	2-4	-
Theagallin	2-3	-
Gallic acid	0.5	-
Quinic acid	2.0	-
Theanine	4-6	-
Methylxanthines	7-9	8-11
Theaflavins	-	3-6
Thearubigins	-	12-18

Table 6. Trace elements in commercial teas and their infusions.[38]

Tea	Na (µg/g)	K (mg/g)	Rb (µg/g)	Ca (mg/g)	Mg (mg/g)	Al (µg/g)	Fe (µg/g)	Mn (µg/g)	Cu (µg/g)	Zn (µg/g)	Cr (µg/g)	Pb (µg/g)
Dried tea leaves												
Unbranded 1	75±5	17±1.6	50±2.3	4.50±0.21	6.23±0.31	757±28	211±20	420±37	32.3±2.1	87±6	5.8±0.4	1.51±0.14
Unbranded 2	84±4	14.5±0.7	41.5±1.8	4.42±0.23	2.34±0.15	712±36	185±15	372±29	21.4±1.7	93±8	3.6±0.1	1.82±0.16
Unbranded 3	65±5	11.3±0.4	43±1.7	6.24±0.35	3.52±0.20	925±44	187±21	738±53	40.3±3.4	97±7	7.5±0.3	2.00±0.13
Red Label	81±6	16.2±0.8	46.7±2.4	5.31±0.38	2.81±0.08	1530±67	280±24	864±47	33.6±2.8	96±10	3.5±0.1	1.58±0.17
Tata Gold	48±4	17.0±1.5	42.8±1.9	2.44±0.08	3.95±0.32	891±51	190±13	1130±96	21.9±2.3	111±8	5.7±0.3	2.63±0.14
Society	39±2	17.4±1.4	43.4±2.1	6.25±0.47	5.76±0.30	713±41	166±9	258±18	29.5±0.8	85±6	1.7±0.1	166±0.20
Tetley Green 1	18±0.8	10.2±0.4	17.2±0.7	3.87±0.28	1.97±0.10	605±29	1550±74	1120±65	8.2±0.2	80±7	4.5±0.2	2.20±0.19
Tetley Green 2	21±1	11.3±0.5	19.3±0.8	3.20±0.31	2.31±0.09	620±38	1486±82	1030±82	7.3±0.3	78±5	4.7±0.2	2.34±0.23
Aqueous infusion (percentage of total leached into the infusion)												
Unbranded 1	68 (90)	11.6 (68)	37 (74)	0.20 (5)	1.31 (21)	196 (26)	8.5 (4.3)	168 (40)	0.7 (2.2)	36 (42)	-	-
Unbranded 2	90 (107)	10.1 (70)	30 (75)	0.18 (4)	0.56 (24)	149 (21)	9.6 (5.2)	122 (33)	1.0 (5)	40 (43)	-	-
Unbranded 3	51 (73)	7.6 (67)	32 (74)	0.37 (6)	1.09 (31)	278 (30)	7.6 (4.1)	273 (37)	3.2 (8)	43 (44)	-	-
Red Label	78 (96)	11.3 (70)	33 (71)	0.27 (5)	0.76 (27)	367 (24)	11.0 (4.7)	259 (30)	2.3 (7)	40 (42)	-	-
Tata Gold	41 (85)	12.4 (73)	32 (75)	0.17 (7)	1.03 (26)	196 (22)	9.3 (4.9)	452 (41)	1.8 (8)	30 (45)	-	-
Society	42 (108)	12.0 (69)	30 (70)	0.31 (5)	1.44 (25)	192 (27)	7.6 (4.6)	80 (31)	1.2 (4)	38 (45)	-	-
Tetley Green 1	14 (77)	6.6 (65)	4.1 (23)	0.12 (3)	0.57 (29)	127 (21)	22 (1.4)	380 (34)	0.2 (3)	32 (41)	-	-
Tetley Green 2	19 (95)	7.5 (66)	4.8 (25)	0.10 (3)	0.72 (31)	124 (20)	23 (1.5)	360 (35)	0.5 (7)	31 (40)	-	-

Table 7. Frequency of use according to duration and exposure of *C. sinensis*-derived ingredients.[39-42]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Camellia sinensis leaf extract[1]		**Camellia sinensis leaf**		**Camellia sinensis leaf oil**		**Camellia sinensis leaf powder**	
Total/range	**1865**	**0.00002-3**	54	**0.05**	33	**NR**	22	**0.005-50**
Duration of use								
Leave-on	**1083**	**0.00002-2**	**38**	**NR**	**24**	**NR**	**11**	**0.005-7**
Rinse-off	**747**	**0.00002-1**	**15**	**NR**	**9**	**NR**	**10**	**0.01**
Diluted for (bath) use	**35**	**0.0001-0.1**	**1**	**0.05**	**NR**	**NR**	**1**	**50**
Exposure type								
Eye area	131	0.00002-0.87	6	NR[g]	NR	NR	1	0.3
Incidental ingestion	36	0.001-0.14[a]	NR	NR	5	NR	NR	NR
Incidental Inhalation-sprays	676[d]	0.0005[b,c]; 0.0001-0.0055[d]	31[d]	NR	NR	NR	8[d]	0.005-50[h]
Incidental inhalation-powders	590[d]	0.0003-0.0037[d];	NR	NR	1[d]	NR	6[d]	0.005-50[b]
Dermal contact	1484	0.00002-3	51	0.05	20	NR	22	0.005-50
Deodorant (underarm)	13[d]	0.0055[b, e]; 0.0055-0.023[f]	NR	NR	NR	NR	NR	NR
Hair-noncoloring	279	0.000055-0.0063	3	NR	8	NR	NR	NR
Hair-coloring	60	0.003-0.006	NR	NR	NR	NR	NR	NR
Nail	1	0.00002-0.53	NR	NR	NR	NR	NR	NR
Mucous Membrane	369	0.0001-1	1	0.05	10	NR	9	0.01
Baby	12	NR	NR	NR	1	NR	NR	NR

	Camellia sinensis leaf water		**Camellia sinensis seed extract**			
Total/range	**36**	**30**	NR	**0.001-0.1**		
Duration of use						
Leave-on	**26**	**30**	**NR**	**0.001-0.1**		
Rinse-off	**10**	**NR**	**NR**	**0.001-0.0013**		
Diluted for (bath) use	**NR**	**NR**	**NR**	**NR**		
Exposure type						
Eye area	4	**30**	NR	NR		
Incidental ingestion	NR	NR	NR	NR		
Incidental Inhalation-sprays	21[d]	NR	NR[d]	0.1[d]		
Incidental inhalation-powders	20	NR	NR	NR		
Dermal contact	36	NR	NR	0.001-0.1		
Deodorant (underarm)	NR	NR	NR	NR		
Hair-noncoloring	NR	NR	NR	NR		
Hair-coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	NR	NR	NR	0.0013		
Baby	NR	NR	NR	NR		

[1] "Green tea" and "green tea extract" are not INCI names of cosmetic ingredients but were listed in the VCRP. Since these are technical names for camellia sinensis leaf extract, these total were combined with this ingredient.
NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.
[a] Ingestible oral hygiene product – 0.14%
[b] Aerosol product(s)
[c] Pump hair spray – 0.0005%
[d] May or may not be an aerosol product(s) or powders that could be inhaled
[e] Deodorant pump spray – 0.0055%
[f] Not aerosol product(s)
[g] Tea bags for the eyes (97%) is no longer sold
[h] 50% in a professional product that is diluted with water for use

Table 8. Reproductive and developmental studies submitted to the FDA for the approval of an ointment containing 15% polyphenols.[72]

Species (n); administration	Results
Oral	
Pregnant rats (6-7); 0, 125, 250, 500, 750, 1000 mg/kg ointment in water (assume by gavage) on gestation days 6-15	Complete resorptions in 2/6 dams in the highest dose group. No other treatment related effects.
Sprague-Dawley rats (27); 0, 250, 500, 1000 mg/kg ointment on gestations days 6-18 by gavage	Body weight gains were decreased in all treatment groups compared to controls (14%, 7%, 10%, respectively). No effects on fertility, embryo/fetal development.
Rabbits (not provided); 0, 62.5, 125, 250, 500, 1000 mg/kg ointment on gestations days 6-18 by gavage	No treatment related effects observed.
White rabbits (not provided); 0, 100, 300, 1000 mg/kg ointment on gestations days 6-18 by gavage	Mortality due to gavage trauma. Body weight gains were decreased in the low- and high-treatment groups (-31%, +10%, 84%, respectively). Feed consumption was decreased in the high-dose group. No effects on fertility, embryo/fetal development.
Subcutaneous	
Rabbits (6); 0, 37.5, 150 mg/kg/d on gestation days 6-19	High-dose group- irritation with severe subcutaneous lesions/necrosis at injection sites. Treatment was discontinued after 6 days. One rabbit aborted. There was body weight loss, decreased feed consumption, and embryonic resorptions. Two fetuses from separate litters had umbilical hernia (one with hyperflexed limb), one fetus had a short tail. Low-dose group-Local irritation, decreased body weight gain. Increased early and late resorptions, Decreased corpora lutea, implants, litter size. No effect to fetal weights.
Rabbits (at least 6); 0,4, 12, 36 mg/kg/d on gestation days 6-19	High-dose group-severe local irritation at injection sites, decreased weight gain and feed consumption, decreased fetal weight. Abortions on gestation day 26. Decreased fetal weights. There were 3 malformed fetuses from 2 litters. Number of corpora lutea, pre-implantation loss, number of implantations, and sex ratios were similar to controls. Mid-dose group- one abortion on last day of gestation. 6 fetuses (from 5 litters) were malformed. One aborted fetus had a domed head. Number of corpora lutea, pre-implantation loss, number of implantations, and sex ratios were similar to controls. Low-dose group- Seven fetuses (from 4 litters) were malformed. Control group had 3 malformed fetuses from 2 litters. Blood tests show no accumulation of EGCG in the plasma during treatment.
Intravaginal	
Sprague-Dawley rats (25); 0.15 ml administered 4 days before mating through gestation day 17	No adverse effect on reproductive ability or embryo/fetal development. There were no mortalities. There were no differences in feed consumption.
Rats (25); 0.05, 0.10, 0.15 mL/d administered gestation day 6 - weaning	4 rats in the high-dose group and 3 in the mid-dose groups died possibly due to parturition complications. Dam in high-dose group killed after both pups died. There were no clinical signs observed. High-dose group-Increased stillborn pups (23 from 6 dams). There was decreased litter size and live birth index. There were no other treatment-related effects on pre- and –postnatal development. Controls-5 stillborn pups from 3 dams
Rats (25); 0, 0.05. 0.10, 0.15 mL/rat/d administered gestation day 6 – weaning. F1 generation were paired (25) and were mated untreated	F_0 - High-dose group-4 dams killed due to possible parturition complications. 20 dams delivered successfully with 23 stillborn pups from 2 litters. Mid-dose group-3 dams killed due to possible parturition complications. 22 dams delivered successfully with 9 stillborn pups from 7 litters Low-dose group-22 dams delivered successfully Controls-5 stillborn pups from 3 litters. F_1 – No mortalities. One male in the mid-dose group was missing the tip of his tail and one female had dental abnormalities. No clinical signs, body weight gains, pinna unfolding, incisor eruption, eye opening, surface righting, gripping pupillary and auditory reflex, age of vaginal opening, and balano-preputial separation were normal. Water maze field tests were normal. All mating and fertility parameters were normal.

Table 9. Genotoxicity studies of *C. sinensis* extracts and constituents.

Assay	Ingredient/constituent (concentration)	Results	Reference
	In vitro		
Ames test (*S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* WP2*uvr*A);	Polyphenol mixture containing 51.4% EGCG and 4 other catechins (0-5000 µg/plate in sterile water); Metabolic activation at 4% and 10%	Not mutagenic with or without metabolic activation. Not cytotoxic.	[74]
Ames test (*S. typhimurium* strains TA97, TA98, TA100, TA102)	Camellia sinensis flower extract (0.008, 0.04, 0.1, 1.0, 5.0 mg/plate; water extract) with and without metabolic activation	Not mutagenic with or without metabolic activation.	[76]
Ames test (*S. typhimurium* strains TA97, TA98, TA100, TA102, TA1535)	EGCG (88.1%-95% pure) (50-5000µg/plate) with and without metabolic activation	Not mutagenic with or without metabolic activation.	[75]
Ames test (*S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* WP2*uvr*A)	Chinese tea extract (0.85% solids) (5000µg/plate)	Negative	[67]
Ames test (*S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* WP2*uvr*A)	Oolong tea extract (1.0% solids) (5000µg/plate)	Negative	[67]
Mouse lymphoma assay	Polyphenol mixture containing 51.4% EGCG and 4 other catechins (0-625 µg/mL in sterile water)	Not mutagenic with or without metabolic activation. Cytotoxic at ≥375 µg/mL.	[74]
Mouse lymphoma assay	Polyphenol mixture containing 51.4% EGCG and 4 other catechins (0-500 µg/mL without; 0-625 with metabolic activation in sterile water)	Mutagenic at ≥164 µg/mL without metabolic activation; mutagenic at ≥375 µg/mL with metabolic activation. Cytotoxic at ≥500 µg/mL.	[74]
Mouse lymphoma assay	EGCG (77% pure) with and without metabolic activation	Not mutagenic without metabolic activation up to 100 µg/mL; mutagenic ≥ 125 µg/mL with metabolic activation	[75]
Mouse lymphoma assay	Polyphenol mixture (0, 87, 155, 276, 492, 878, 1568, 2800, 5000 µg/mL) with and without metabolic activation	Not mutagenic with or without metabolic activation.	[72]
	In vivo		
Mouse micronucleus assay (n = 5/sex)	Polyphenol mixture containing 51.4% EGCG and 4 other catechins (0-1500 mg/kg) by gavage	Not mutagenic	[74]
Mouse micronucleus assay (n = 5/sex)	EGCG (91.9% pure) (500, 1000, 2000 mg/kg) by gavage	Not mutagenic	[75]
Big blue mutation assay Swiss-Webster mice (n = 7/sex)	Polyphenol mixture containing 51.4% EGCG and 4 other catechins (0, 500, 1000, 2000 mg/kg/d for 28 d) by gavage. Necropsied 28 days after final dose. Tissues analyzed for mutations.	No increase in cII mutant frequencies in the livers, lungs, and spleen tissues at 500 and 2000 mg/kg. Mice died during treatment in the 2000 mg/kg group and were not analyzed.	[74]
Micronucleus assay diet study using CD-1 mice (6/sex)	EGCG (80% pure) (4200, 8400, 12600 ppm in feed)	No increase in frequency of micronucleated polychromatic erythrocytes	[75]
Micronucleus assay intravenous study using Wistar rats (5/sex)	EGCG (92.6% pure) (15, 25, 50 mg/kg/d intravenously for 2 days	No increase in frequency of micronucleate polychromatic erythrocytes	[75]
Micronucleus assay intraperitoneal study using Sprague-Dawley rats (7/sex)	Polyphenol mixture (0, 8500 mg/kg). Bone marrow sampled 24 and 48 h after treatment	No increase in frequency of micronucleate polychromatic erythrocytes	[72]

Table 10. Dermal reactions to *C. sinensis* leaf (aqueous extract or dried leaves) application in ointments for dermal treatment of genital and perianal warts.[26]

DER	Very common	Common	Uncommon
≥ 1/10	Local reactions at the application site including erythema, pruritus, irritation/burning, pain, ulcer, edema, induration and vesicles		
≥1/100 – 1/10		Local reactions at the application site including exfoliation, discharge, bleeding and swelling	
≥1/1,000 - ≤100			Local reactions at the application site including discoloration, discomfort, dryness, erosion, fissure, hyperesthesia, anesthesia, scar, nodule, dermatitis, hypersensitivity, local necrosis, papules, and eczema
≥1/1,000 - ≤100			Application site infection, application site pustules, herpes simplex, infection, pyoderma, staphylococcal infection, urethritis, vaginal candidiasis, vulvovaginitis and vulvitis

DER = drug/extract ratio

Table 11. The number of published studies discovered in a PubMed search (1965-2008) for the carcinogenicity inhibitory effect of green tea extracts and its catechins in animal models.[98]

Organ/tissue	Inhibitory effect (xenograft studies)	No inhibitory effect
Lung	20 (1)	2
Oral cavity	6	0
Esophagus	4	0
Stomach	9	0
Small intestine	8	1
Colon	11 (3)	6
Skin	27 (1)	0
Prostate	4 (5)	0
Breast	10 (8)	0
Liver	7	1
Bladder	3 (1)	0
Pancreas	2 (2)	0
Thyroid	1	0

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY STUDIES OF GREEN TEA EXTRACT IN F344/NTac RATS AND B6C3F1/N MICE AND TOXICOLOGY AND CARCINOGENESIS STUDIES OF GREEN TEA EXTRACT IN WISTAR HAN[Crl:WI(Han)] RATS AND B6C3F1/N MICE

(GAVAGE STUDIES)

Scheduled Peer Review Date: May 22, 2014

NTP TR 585

NIH Publication No. 14-5927

National Toxicology Program

National Institutes of Health
Public Health Service
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

ABSTRACT

PLATE XXXIII.—*Camellia thea* (Camellia). (From Jackson: *Experimental Pharmacology and Materia Medica.*)

GREEN TEA EXTRACT

CAS No. None Available

Synonyms: Green tea catechin polyphenols; green tea; green tea polyphenols
Botanical name: *Camellia sinensis*

Dried concentrated extracts from green tea containing high amounts of catechins are a popular source for nutraceutical and medicinal uses. Green tea extracts are commonly consumed as weight loss supplements and are popular ingredients in sunblocks, cream rinses, and other cosmetics. Numerous studies in both experimental animals and clinical settings have studied the possible anticancer, anti-inflammatory, antimicrobial, and cardio- and neuroprotective properties of green tea extract. The active ingredient of green tea extract, epigallocatechin gallate (EGCG), was originally nominated by the National Cancer Institute for toxicity and carcinogenicity studies because it is the most abundant catechin in green tea extract, it is being investigated as a potential chemotherapeutic agent, and there was a lack of adequate information with regard to its toxicity. However, the NTP selected green tea extract [containing EGCG (48.4% by weight) and other green tea catechins] for study because there is more human exposure to green tea extract and to products containing a concentrated mixture of various green tea catechins. The NTP analyzed four lots of green tea extract and selected a source based on quantities of EGCG, consistency with

other products on the market, and availability in bulk quantity. Oral gavage was chosen as the route of administration because it was considered most relevant to human exposure. Male and female F344/NTac rats and B6C3F1/N mice were administered green tea extract in water by gavage for 3 months and male and female Wistar Han [Crl:WI(Han)] rats (referred to as Wistar Han rats) and B6C3F1/N mice were administered green tea extract in water by gavage for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, *Escherichia coli*, and mouse peripheral blood erythrocytes.

3-MONTH STUDY IN F344/NTAC RATS

Groups of 10 male and 10 female core study rats were administered 0, 62.5, 125, 250, 500, or 1,000 mg green tea extract/kg body weight in deionized water by gavage, 5 days per week for 14 weeks. Groups of 10 male and 10 female clinical pathology study rats were administered the same doses for 23 days. One 125 mg/kg female died during week 7. Mean body weights of males and females administered 250 mg/kg or greater were significantly less than those of the vehicle controls.

The cauda epididymis, epididymis, and testes weights of 1,000 mg/kg males were significantly less than those of the vehicle controls. Females administered 1,000 mg/kg had longer estrous cycles and spent significantly more time in extended diestrus than did the vehicle controls. These data indicate that green tea extract exhibits the potential to be a reproductive toxicant in male and female F344/NTac rats.

Several nonneoplastic liver lesions were observed in three of ten 1,000 mg/kg females. Lesions included hepatocyte necrosis, bile duct hyperplasia, oval cell hyperplasia, and mitosis. There were significant increases in the incidences of several nonneoplastic lesions in the nose of 1,000 mg/kg males and females including inflammation (females); hyperplasia in the Bowman's gland of the olfactory epithelium; nerve atrophy; and atrophy, metaplasia, and pigmentation in the olfactory epithelium; the increased incidences of inflammation (females), nerve atrophy, and olfactory epithelium metaplasia and pigmentation (males) were also significant in the 500 mg/kg groups. The incidences of histiocyte cellular infiltration in the mesenteric lymph node in 125 mg/kg or greater males were significantly increased compared to that in the vehicle control group.

3-MONTH STUDY IN MICE

Groups of 10 male and 10 female mice were administered 0, 62.5, 125, 250, 500, or 1,000 mg green tea extract/kg body weight in deionized water by gavage, 5 days per week for 14 weeks. Six males and four females administered 1,000 mg/kg died before the end of the study; early deaths were due to liver necrosis. Mean body weights of males administered 250 mg/kg or greater and females administered 125 mg/kg or greater were significantly less than those of the vehicle controls. Clinical findings included lethargy, abnormal breathing, and ataxia in females that died early.

A significantly decreased spermatid per testis count was observed in 500 mg/kg males. Females administered 500 mg/kg spent significantly more time in extended diestrus than did the vehicle controls. These data indicate that green tea extract exhibits the potential to be a reproductive toxicant in male and female mice.

In the liver, the incidences of glycogen depletion were significantly increased in 250 and 500 mg/kg males and 500 and 1,000 mg/kg females. In addition, the incidences of centrilobular necrosis were significantly increased in 1,000 mg/kg males and females, and the incidence of karyomegaly was significantly increased in 1,000 mg/kg females. The incidences of nerve atrophy, olfactory epithelium atrophy, and olfactory epithelium metaplasia of the nose were significantly increased in males administered 250 mg/kg or greater and in 500 and 1,000 mg/kg females; the incidence of olfactory epithelium necrosis was significantly increased in 1,000 mg/kg females. The incidences of lymphoid atrophy in the spleen were significantly increased in 500 and 1,000 mg/kg females. The incidences of atrophy of the mandibular lymph node and thymus were significantly increased in 1,000 mg/kg males and females.

2-YEAR STUDY IN WISTAR HAN RATS

Groups of 60 male and 60 female rats were administered 0 or 1,000 mg green tea extract/kg body weight and groups of 50 male and 50 female rats were administered 100 or 300 mg/kg in deionized water by gavage, 5 days per week for up to 105 weeks. Ten male and 10 female rats randomly selected from the vehicle control and 1,000 mg/kg groups were evaluated at 3 months; no significant increases in mortality or nonneoplastic lesion incidences were observed at 3 months. In the 2-year study, there were significant decreases in survival in 1,000 mg/kg males and

females compared to the vehicle control groups. Mean body weights of 300 and 1,000 mg/kg males were at least 10% less than those of the vehicle control groups after weeks 41 and 9 of the study, respectively; mean body weights of dosed groups of female rats were at least 10% less after weeks 65 (100 mg/kg), 61 (300 mg/kg), and 57 (1,000 mg/kg).

No increases in the incidences of neoplasms in male or female rats were attributed to the administration of green tea extract.

At 2 years, the incidences of hepatic necrosis were significantly increased in 1,000 mg/kg males and females, and the incidence of oval cell hyperplasia was significantly increased in 1,000 mg/kg females.

In the glandular stomach of 1,000 mg/kg males and 300 and 1,000 mg/kg females at 2 years, the incidences of mucosa necrosis were significantly greater than the vehicle control incidences. At 2 years, the incidences of mucosa necrosis in all segments of the small intestine were significantly increased in 1,000 mg/kg males and females.

In the nose at 3 months, the incidences of nerve and olfactory epithelium atrophy in 1,000 mg/kg males and the incidence of pigmentation in the olfactory epithelium of 1,000 mg/kg females were significantly increased. At 2 years, the incidences of numerous nonneoplastic lesions of the nose were generally significantly increased in all dosed groups of males and females. These lesions included mineralization and pigmentation of the lamina propria; suppurative inflammation of the nasopharyngeal duct; nerve atrophy; atrophy, respiratory metaplasia, and pigmentation of the olfactory epithelium; respiratory epithelium atrophy; and deformity and hyperostosis of the turbinate. The incidences of suppurative inflammation were significantly increased in 1,000 mg/kg males and in 300 and 1,000 mg/kg females, and the incidences of basal cell hyperplasia of the olfactory epithelium were significantly increased in males and females administered 300 or 1,000 mg/kg. Incidences of additional nonneoplastic nasal lesions were significantly increased in one or more dosed groups of males and/or females.

The incidences of suppurative inflammation in the lung and inflammation of the heart (epicardium) were significantly increased in 1,000 mg/kg males and females at 2 years.

The incidences of bone marrow hyperplasia in all dosed groups of females were significantly greater than the vehicle control incidence.

In the spleen of 1,000 mg/kg males and all dosed groups of females, the incidences of lymphoid depletion were significantly increased.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were administered 0, 30, 100, or 300 mg green tea extract/kg body weight in deionized water by gavage, 5 days per week for 105 weeks. Survival of dosed groups was similar to that of the vehicle control groups. Mean body weights of 100 and 300 mg/kg males were at least 10% less than those of the vehicle control group after weeks 89 and 65, respectively, and mean body weights of 100 and 300 mg/kg females were at least 10% less after weeks 25 and 17, respectively.

One squamous cell papilloma and one squamous cell carcinoma of the tongue were noted in 300 mg/kg females.

The incidences of hematopoietic cell proliferation and inflammation in the liver were significantly increased in 300 mg/kg males.

The incidences of numerous nonneoplastic lesions of the nose were generally significantly increased in all dosed groups. These lesions included foreign body, suppurative inflammation, nerve atrophy, atrophy and respiratory metaplasia of the olfactory epithelium, and squamous metaplasia and necrosis of the respiratory epithelium. The incidences of hyperostosis, olfactory epithelium fibrosis, septum perforation, and turbinate atrophy were significantly increased in 100 and 300 mg/kg males and females, and the incidences of respiratory epithelium hyperplasia were significantly increased in 100 and 300 mg/kg females. The incidence of nasopharyngeal duct degeneration was significantly increased in 300 mg/kg males.

The incidences of lymphoid hyperplasia and plasma cell infiltration of the mandibular lymph node were significantly increased in 100 and 300 mg/kg males and females.

The incidences of bone marrow hyperplasia were significantly increased in all dosed groups except 30 mg/kg females.

GENETIC TOXICOLOGY

Green tea extract was mutagenic in *S. typhimurium* strains TA98 and TA100 in the presence of induced rat liver S9; no mutagenicity was observed in these strains without S9 or in the *E. coli* strain WP2 *uvr*A/pKM101, with or without S9. *In vivo*, no increases in the frequencies of micronucleated erythrocytes were seen in peripheral blood of male or female B6C3F1/N mice in the 3-month study.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of green tea extract in male or female Wistar Han rats administered 100, 300, or 1,000 mg/kg. There was *no evidence of carcinogenic activity* of green tea extract in male B6C3F1/N mice administered 30, 100, or 300 mg/kg. There was *equivocal evidence of carcinogenic activity* of green tea extract in female B6C3F1/N mice based on occurrences of squamous cell neoplasms of the tongue.

Administration of green tea extract resulted in increased incidences of nonneoplastic lesions of the liver, glandular stomach, small intestine (duodenum, ileum, and jejunum), nose, lung, heart, and spleen in male and female rats; bone marrow of female rats; the nose, mandibular lymph node, and bone marrow of male and female mice; and the liver of male mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Green Tea Extract

	Male Wistar Han Rats	Female Wistar Han Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
Doses in water by gavage	0, 100, 300, or 1,000 mg/kg	0, 100, 300, or 1,000 mg/kg	0, 30, 100, or 300 mg/kg	0, 30, 100, or 300 mg/kg
Body weights	300 and 1,000 mg/kg group at least 10% less than vehicle control group after weeks 41 and 9, respectively	100, 300, and 1,000 mg/kg groups at least 10% less than vehicle control group after week 65, 61, and 57, respectively	100 and 300 mg/kg groups at least 10% less than vehicle control group after weeks 89 and 65, respectively	100 and 300 mg/kg groups at least 10% less than vehicle control group after weeks 25 and 17, respectively
Survival rates	35/50, 37/50, 43/50, 24/50	26/50, 28/50, 23/50, 4/50	33/50, 36/50, 33/50, 37/50	34/50, 33/50, 44/50, 39/50
Nonneoplastic effects	Liver: necrosis (1/50, 2/50, 2/50, 13/50) Stomach, glandular: mucosa necrosis (0/49, 3/50, 3/50, 21/50) Small intestine, duodenum: mucosa, necrosis (0/50, 1/47, 1/49, 10/48) Small intestine, ileum: mucosa necrosis (0/50, 1/48, 2/49, 6/45) Small intestine, jejunum: mucosa necrosis (0/49, 0/47, 2/48, 9/46) Small intestine, (duodenum, ileum, jejunum): Necrosis (0/49, 2/46, 4/48, 14/45) Nose: suppurative inflammation (11/50, 12/50, 20/50, 42/50); lamina propria, mineralization (0/50, 33/50, 34/50, 44/50); lamina propria, pigmentation (0/50, 4/50, 11/50, 25/50); nasopharyngeal duct, suppurative inflammation (0/50, 6/50, 8/50, 20/50); nerve, atrophy (0/50, 33/50, 44/50, 44/50); olfactory epithelium, atrophy (1/50, 38/50, 41/50, 41/50); olfactory epithelium, hyperplasia, basal cell (0/50, 1/50, 9/50, 28/50); olfactory epithelium, metaplasia, respiratory (4/50, 40/50, 43/50, 47/50); olfactory epithelium, necrosis (1/50, 3/50, 0/50, 12/50); olfactory epithelium, pigmentation (6/50, 18/50, 12/50, 21/50); respiratory epithelium, atrophy (0/50, 2/50, 5/50, 6/50)	Liver: necrosis (3/50, 2/48, 5/49, 24/46); oval cell hyperplasia (1/50, 2/48, 3/49, 16/46) Stomach, glandular: mucosa necrosis (0/50, 1/49, 7/49, 20/44) Small intestine, duodenum: mucosa, necrosis (0/47, 0/48, 1/48, 5/39) Small intestine, ileum: mucosa necrosis (0/45, 0/46, 0/47, 5/36) Small intestine, jejunum: mucosa necrosis (0/45, 0/43, 1/45, 6/40) Small intestine, (duodenum, ileum, jejunum): Necrosis (0/44, 1/42, 2/44, 10/33) Nose: foreign body (3/49, 2/49, 4/50, 8/49); suppurative inflammation (5/49, 3/49, 17/50, 35/49); epithelium, nasopharyngeal duct, necrosis (0/49, 1/49, 2/50, 7/49); epithelium, nasopharyngeal duct, regeneration (0/49, 0/49, 0/50, 8/49); lamina propria, mineralization (3/49, 23/49, 30/50, 22/49); lamina propria, pigmentation (1/49, 0/49, 6/50, 14/49); nasopharyngeal duct, suppurative inflammation (0/49, 2/49, 5/50, 15/49); nerve, atrophy (0/49, 38/49, 41/50, 38/49); olfactory epithelium, atrophy (2/49, 35/49, 42/50, 34/49); olfactory epithelium, hyperplasia, basal cell (0/49, 0/49, 8/50, 20/49); olfactory epithelium, metaplasia, respiratory (1/49, 42/49, 43/50, 36/49); olfactory epithelium, necrosis (0/49, 3/49, 1/50, 18/49)	Liver: hematopoietic cell proliferation (2/50, 2/50, 6/50, 10/50); inflammation (4/50, 1/50, 5/50, 12/50) Nose: foreign body (1/50, 10/49, 16/50, 25/50); hyperostosis (0/50, 0/49, 28/50, 46/50); suppurative inflammation (14/50, 40/49, 49/50, 48/50); nasopharyngeal duct, degeneration (0/50, 0/49, 4/50, 9/50); nerve, atrophy (0/50, 26/49, 49/50, 50/50); olfactory epithelium, atrophy (4/50, 24/49, 28/50, 3/50); olfactory epithelium, fibrosis (0/50, 4/49, 37/50, 43/50); olfactory epithelium, metaplasia, respiratory (11/50, 45/49, 49/50, 49/50); respiratory epithelium, metaplasia, squamous (0/50, 14/49, 39/50, 46/50); respiratory epithelium, necrosis (0/50, 7/49, 16/50, 27/50); septum, perforation (1/50, 0/49, 26/50, 37/50); turbínate, atrophy (0/50, 0/49, 41/50, 50/50) Mandibular lymph node: lymphoid hyperplasia (0/50, 1/50, 31/50, 37/50); plasma cell infiltration (1/50, 1/50, 24/50, 41/50) Bone marrow: hyperplasia (5/50, 42/50, 38/50, 46/50)	Nose: foreign body (4/48, 8/48, 13/50, 17/50); hyperostosis (0/48, 0/48, 21/50, 48/50); suppurative inflammation (4/48, 24/48, 44/50, 47/50); nerve, atrophy (0/48, 13/48, 47/50, 48/50); olfactory epithelium atrophy (0/48, 18/48, 26/50, 17/50); olfactory epithelium, fibrosis (0/48, 1/48, 39/50, 43/50); olfactory epithelium, metaplasia, respiratory (2/48, 36/48, 49/50, 48/50); respiratory epithelium, hyperplasia (1/48, 1/48, 22/50, 15/50); respiratory epithelium, metaplasia, squamous (0/48, 8/48, 42/50, 42/50); respiratory epithelium, necrosis (0/48, 4/48, 28/50, 32/50); septum, perforation (0/48, 0/48, 38/50, 42/50); turbinate, atrophy (0/48, 0/48, 40/50, 48/50) Mandibular lymph node: lymphoid hyperplasia (0/50, 1/48, 8/49, 12/48); plasma cell infiltration (0/50, 0/48, 31/49, 18/48) Bone marrow: hyperplasia (6/50, 11/50, 41/50, 34/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Green Tea Extract

	Male Wistar Han Rats	Female Wistar Han Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
Nonneoplastic effects (continued)	Nose (continued): respiratory epithelium, metaplasia, squamous (0/50, 1/50, 3/50, 7/50); turbinate, deformity (0/50, 16/50, 22/50, 35/50); turbinate, hyperostosis (0/50, 18/50, 27/50, 40/50) Lung: suppurative inflammation (0/50, 1/50, 3/50, 10/50) Heart (epicardium): inflammation (0/50, 0/50, 1/50, 5/50) Spleen: lymphoid depletion (1/50, 2/50, 1/50, 13/50)	Nose (continued): olfactory epithelium, pigmentation (0/49, 11/49, 7/50, 5/49); respiratory epithelium, atrophy (0/49, 8/49, 9/50, 3/49); respiratory epithelium, necrosis (0/49, 1/49, 2/50, 17/49); respiratory epithelium, pigmentation (0/49, 1/49, 5/50, 5/49); turbinate, deformity (0/49, 6/49, 20/50, 15/49); turbinate, hyperostosis (0/49, 18/49, 32/50, 36/49) Lung: suppurative inflammation (1/50, 3/49, 2/50, 9/48) Heart (epicardium): inflammation (0/50, 2/48, 2/50, 4/48) Bone marrow: hyperplasia (6/50, 14/50, 16/50, 13/50) Spleen: lymphoid depletion (0/50, 7/49, 5/48, 17/43)		
Neoplastic effects	None	None	None	None
Equivocal findings	None	None	None	Tongue: squamous cell papilloma or squamous cell carcinoma, (0/50, 0/50, 0/50, 2/50)
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	Equivocal evidence
Genetic toxicology				
Bacterial gene mutations:		Positive in *S. typhimurium* strains TA98 and TA100 with S9, negative in TA98 and TA100 without S9, and negative in *E. coli* with or without S9		
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:		Negative		

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)
CIR Expert Panel Members
Liaison Members of the CIR Expert Panel

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: April 30, 2014

SUBJECT: Comments Concerning the Conclusion of the Tentative Report: Safety Assessment of *Camellia sinensis*-Derived Ingredients as Used in Cosmetics

The CIR Science and Support Committee (CIR SSC) of the Personal Care Products Council appreciates the opportunity to comment on the Tentative Report: Safety Assessment of *Camellia sinensis*-Derived Ingredients as Used in Cosmetics.

We are especially concerned about the "safe as used" conclusion for Camellia Sinensis Catechins. This conclusion is difficult to justify when there are no reported uses or concentrations of use for this ingredient presented in the report. Camellia Sinensis Catechins should be included with the ingredients with insufficient data conclusions.

The guinea pig sensitization studies summarized in the CIR report suggest that catechins may be sensitizing. Perhaps, the CIR Expert Panel should include catechins among the constituents of concern for these ingredients. Currently, the subsection Constituents of Concern is not clear as to which compounds are of concern to the CIR Expert Panel, compared to other compounds, such as caffeine and stearic acid, that may also be present.

The CIR Expert Panel should also consider revising the conclusion for the leaf extract. As the composition of Camellia Sinensis Leaf Extract can be variable depending on how the leaves are treated before extraction, e.g., green, black, oolong, as well as the extraction solvent and extraction conditions, relying on two HRIPTs of products containing 0.86% of a black tea extract to set a concentration limit for all tea leaf extracts does not seem appropriate. The Discussion of the report should be expanded to note the RIFM review of tea leaf absolute that uses a dose of 480 $\mu g/cm^2$ as the weight of evidence (WoE) No Expected Sensitization Induction Level (NESIL) for calculating the IFRA standards, as well the negative animal and human studies on various other Camellia Sinensis Leaf Extracts summarized in the CIR report. Based on the information in the report, safe when formulated to be non-sensitizing would be a more appropriate conclusion for Camellia Sinensis Leaf Extract. When the

"non-sensitizing" limitation is used in a conclusion for plant-derived ingredients, the Discussion of the CIR report should clearly state the constituents of the plants that are known sensitizers.

The composition of *Camellia sinensis* leaves is well-described in the CIR report and other ingredients derived from the leaves, e.g., Camellia Sinensis Leaf, Camellia Sinensis Leaf Oil, Camellia Sinensis Leaf Powder and Camellia Sinensis Leaf Water, are expected to contain similar constituents as the leaf extracts. Therefore, the CIR Expert Panel should consider extending a conclusion of "safe when formulated to be non-sensitizing" to other leaf-derived ingredients. The conclusion for ingredients derived from other plant parts should remain as insufficient data.

Personal Care Products Council
Committed to Safety, Quality & Innovation

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: April 24, 2014

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

The company that provided the studies containing 0.86% Camellia Sinensis Leaf Extract has indicated that it is an extract of black tea.

Key Issue

The Carcinogenicity section should at least mention that NTP has completed a 2 year oral study on green tea extract (peer review is scheduled for May 22, 2014).

Additional Comments

p.2 - The Introduction should note that Camellia Sinensis Seed Oil is not included in this report.

p.3 - What are the constituents of concern in *Camellia sinensis*-derived ingredients? The current section titled Constituents of Concern mentions theanine, standard α-amino acids, caffeine and stearic acid. Are these substances all constituents of concern? The following sentence is presented in the Constituents section and the section on Constituents of Concern. It is not necessary to have it twice on the same page. "Constituents reported predominantly in *C. sinensis* seeds include caffeine, glucothea saponin, stearic acid, theasponin, and theobromine."

p.5 - As Camellia Sinensis Seed Oil is no longer in the report, the information on the manufacture of triglyceride oils in the Method of Manufacture section (last 5 paragraphs) should be deleted. Information from the Dictionary concerning the manufacture of essential oils and waters should be added to this section.

p.6 - The product containing 50% Camellia Sinensis Leaf Powder should be called a professional face and neck product that is diluted with water before use, rather than a "leave-on" product.

p.7 - Polyethylene glycol 400 (average MW 400) is PEG-8 or PEG 400. It should not be called PEG-400 (average number of moles of ethylene oxide 400).

p.8 - As saponins are not the same as catechins, the study on saponins extracted from *C. sinensis* leaf should not be presented under the heading Camellia Sinensis Catechins.

p.8 - The study on Korean green tea (reference 64) should be presented under the subheading Camellia Sinensis Leaf Extract.

p.9 - The In Vitro subheading under Genotoxicity should be deleted as there are also *in vivo* studies (micronucleus) studies summarized in this section.

p.9 - What concentration of catechins "have been shown to have preventive and treatment effects in cancer cell lines related to cancers of the prostate, lung, skin, pancreas, breast, and ovaries"?

p.12 - Rather than saying that the oolong tea extract was not irritating in the guinea pig study, it should state that it was not sensitizing in the guinea pig study.

p.12 - In the description of the IFRA standard, it should also state that based on animal data, it was concluded that tea leaf absolute was a moderate sensitizer.

p.13 - The CIR report should also state that the 480 $\mu g/cm^2$ dose was the weight of evidence (WoE) NESIL used to develop the IFRA standard based on a QRA for sensitization.

p.14 - The discussion of the IFRA standard should state that the endpoint on which it is based is sensitization.

p.14 - In the last paragraph of the "Other Reviews" section, it is not clear what is meant by "this topic".

p.14-15 - In the Summary, please note the FDA product categories associated with the reported use concentrations.

p.14 - As the product is diluted before use, it is not appropriate to state "it was used up to 50%".

p.15 - In what species was the inhalation study of tea catechins conducted?

p.15 - The Summary should also mention the negative HRIPT of a black tea extract (1% solids) that was completed in 100 subjects.

p.15-16 - The following sentence is misleading: "Linalool is a dermal sensitizer that has been found to be safe up to 4.3%." The RIFM review actually concluded that at use concentrations (maximum 4.3% (20% in a consumer fragrance)) linalool presented no significant risk of sensitization. The 4.3% concentration was a use level, not a limit based on sensitization. It should also be noted that oxidation products of linalool are thought to be sensitizers, rather than linalool itself.

p.18, Table 3 - If it not explained elsewhere, the basis for the RIFM limit on linalool should be explained in this table. It was not based on sensitization. It was based on the reported highest use levels which were considered safe.

p.20, Table 3 (should be Table 7) - Camellia Sinensis Leaf Extract: The low concentration for eye area products should be 0.00002% not 0.0002%.

In the most recent concentration of use information, there is no spray product containing 3% Camellia Sinensis Leaf Extract.

In the Council survey results, the products containing 0.00008% Camellia Sinensis Leaf Extract and 50% Camellia Sinensis Leaf Powder are marked as not spray; therefore, these

products should not be presented in the incidental inhalation spray row with a footnote Not aerosol product(s).

Exposure from aerosol compared to pump sprays are different. Therefore, the pump spray hair spray containing 0.0005% Camellia Sinensis Leaf Extract should not have a footnote indicating that it is an aerosol product.

p.21, Table 8 - Please add "rats" after "Sprague-Dawley" (second row under oral).

p.27, Reference 87 - Although the Council may have brought the IFRA standard to the attention of CIR, the standard is publically available on IFRA's website http://www.ifraorg.org/en-us/standards#.U07XtU1OX5o . Therefore, it should be cited to IFRA's website. It is not correct to state: "Unpublished data submitted by the Personal Care Products Council.

p.28, Reference 97 - Please correct: "*Drub Safety*"