Safety Assessment of *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients as Used in Cosmetics

Status:	Draft Final Report for Panel Review
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The 2018 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. 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

Cosmetic Ingredient Review

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MEMORANDUM

To: CIR Expert Panel and Liaisons
From: Lillian C. Becker, M.S.
Scientific Analyst and Writer
Date: May 11, 2018
Subject: Safety Assessment of *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients As Used In Cosmetics

Attached is the Draft Final Report of *Eucalyptus globulus* (Eucalyptus)-derived ingredients as used in cosmetics. [*eucaly062018rep*] The source for all of these ingredients is the leaf of the plant; one ingredient is obtained from the twigs as well.

In March 2018, the Panel issued a Tentative Report with the conclusion that these 6 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing.

No new data have been discovered or submitted since the Tentative Report was announced. The data that were submitted in Wave 2 and Wave 3 prior to the March 2018 meeting have been incorporated into the report and highlighted in yellow. This includes data on Eucalyptus Globulus Leaf Extract (characterization, method of manufacture, and chemical/physical properties), Eucalyptus Globulus Leaf Oil (animal and human dermal irritation, human ocular irritation, and human sensitization), and eucalyptol (acute dermal toxicity and dermal irritation in rabbits). ADME data on eucalyptol from the rosemary report were also added.

Also included in this Panel book are the flow chart [*eucaly062018flow*] history of this report [*eucaly062018hist*], the data profile [*eucaly062018prof*], the search strategy [*eucaly062018strat*], transcripts [*eucaly062018min*], FDA's VCRP data [*eucaly062018FDA*], and Council comments [*eucaly062018pcpc_1,2*].

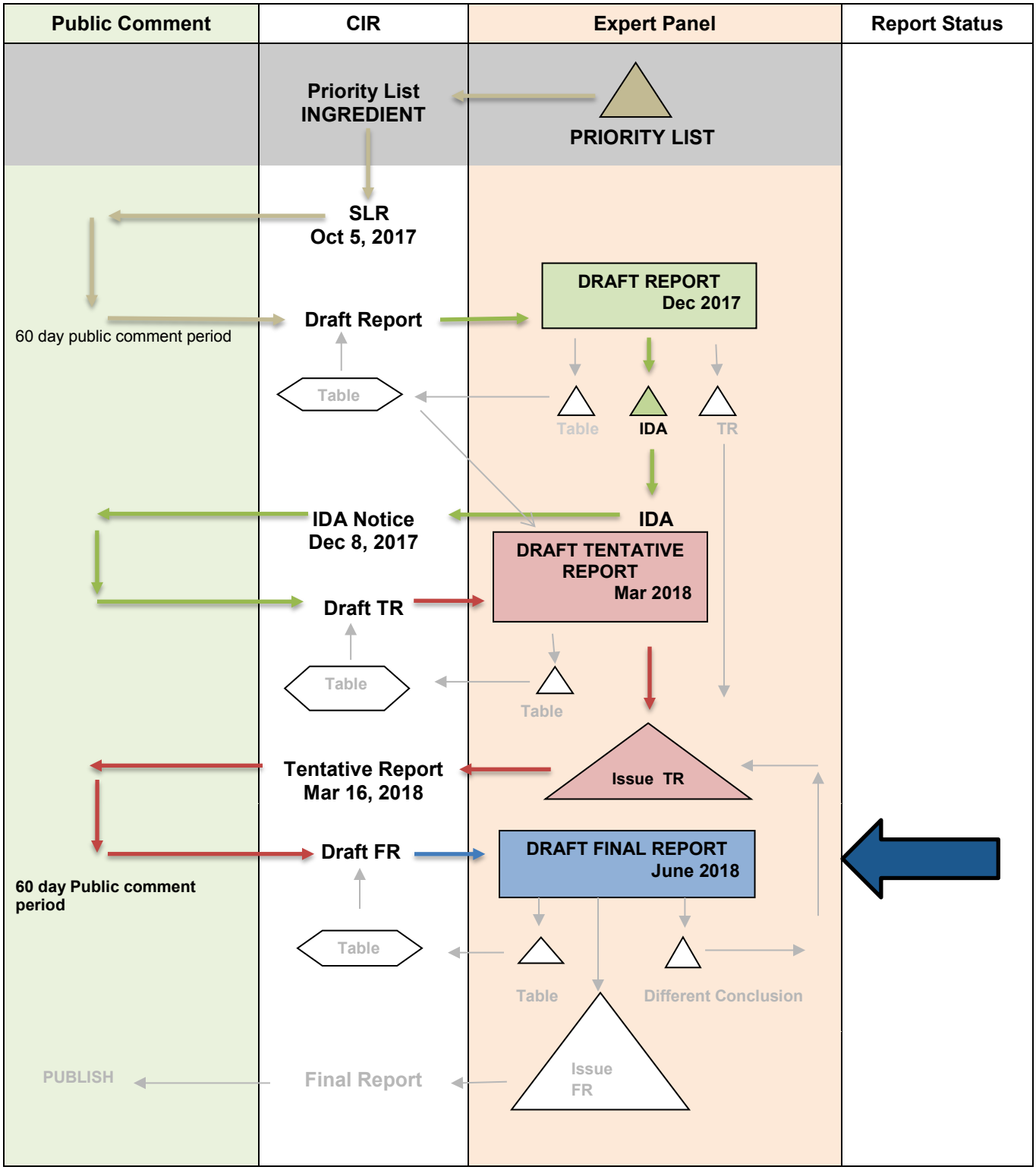
The Panel should carefully review the Abstract, Discussion, and Conclusion of this report. If these are satisfactory, the Panel should issue a Final Report.

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

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Eucalyptus globulus* (Eucalyptus) -derived ingredients

MEETING June 2018



HISTORY – *Eucalyptus globulus*-Derived Ingredients

2016 – *Eucalyptus globulus* added to the priority list.

October, 2017 – SLR posted with the following data request:

The CIR is seeking, at a minimum, the following information on *Eucalyptus globulus*-derived cosmetic ingredients for use in the resulting safety assessment:

1. dermal irritation and sensitization data on *Eucalyptus globulus*-derived ingredients, for which such data were not available;
2. because these ingredients are botanicals and composition and extraction methods vary, specific chemical composition data, as well as the extraction solvent used for each cosmetic product being tested, should be included with all data that are submitted;
3. clarification of the definition of Eucalyptus Globulus Leaf Oil, which states that the oil may be sourced from other *Eucalyptus* species [Eucalyptus Globulus Leaf Oil is the volatile oil obtained from the leaves of *Eucalyptus globulus* and other species of *Eucalyptus*.]

December, 2017 – The Panel examined the Draft Report and issued an IDA.
The data needs were:

- Sensitization on Eucalyptus Globulus Leaf Oil at 5.5% or greater
- Impurity data on all ingredients
- Margin of safety (MOS) calculations for inhalation and dermal exposure using the Eucalyptus Globulus Leaf Oil and/or the major constituent, eucalyptol (1,8-cineole)

The Panel decided not to add Eucalyptol to the report but to add the information that was supplied in the December Memo to the report as supporting information.

March, 2018 – Impurity data and an HRIPT at 0.5% Eucalyptus Globulus Leaf Oil were submitted. The other data needs have not been addressed. Does the supporting information on Eucalyptol and the new data meet the Panel's needs?

Wave 2 - The Council updated the concentration of use data. The maximum use concentration of Eucalyptus Globulus Leaf Oil in body and hand preparations (not spray) was corrected from 5.5% to 0.1%. Therefore, the highest maximum concentration for leave-on use (with dermal contact) is now 0.4%.

The Panel reviewed the report and come to the conclusion that these Eucalyptus-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing and issued a Tentative Report.

June, 2018 – Wave 2 and 3 data from March were incorporated into the report.

The Panel should review the report and review the Abstract, Discussion, and Introduction to ensure that they reflect the Panel's thinking. The Panel should issue a Final Report.

***Eucalyptus globulus*-Derived Ingredients** Data Profile for ***June* 2018**. Writer – Lillian Becker																					
		ADME		Acute toxicity			Repeated dose toxicity			Irritation					Sensitization						
	Use	Log K_{ow}	Dermal Penetration	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Animal	Ocular In Vitro	Dermal Animal	Dermal Human	Dermal In Vitro	Animal	Human	In Vitro	Repro/Devel	Genotoxicity	Carcinogenicity	Phototoxicity
Eucalyptus Globulus Leaf Oil	X			X	X	X	X			X		X	X			X		X	X		X
Eucalyptus Globulus Leaf	X																				
Eucalyptus Globulus Leaf Extract	X						X												X		
Eucalyptus Globulus Leaf Powder	X																				
Eucalyptus Globulus Leaf/Twig Oil						X															
Eucalyptus Globulus Leaf Water	X																				
Eucalyptol	x			x	x	x	x				x	x	x	x	x	x			x	x	

Eucalyptus globulus-Derived Ingredients

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Eucalyptus Globulus Leaf Oil	8000-48-4	Y	12/3	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	Y
Eucalyptus Globulus Leaf		Y	0	Y	Y	Y	Y	N	N	N	N	N	N	N	Y	Y	Y	Y
Eucalyptus Globulus Leaf Extract	84625-32-1	Y	0	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	Y
Eucalyptus Globulus Leaf Powder		Y	0	Y	Y	N	Y	N	N	N	N	N	N	N	N	N	N	Y
Eucalyptus Globulus Leaf/Twig Oil		Y	0	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	Y
Eucalyptus Globulus Leaf Water		Y	0	Y	Y	N	Y	n	N	N	N	N	N	N	N	N	N	Y

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
Eucalyptus Globulus Leaf Oil	8000-48-4	Y	N	N	N	N	N
Eucalyptus Globulus Leaf		Y	N	N	N	N	N
Eucalyptus Globulus Leaf Extract	84625-32-1	N	N	N	N	N	N
Eucalyptus Globulus Leaf Powder		N	N	N	N	N	N
Eucalyptus Globulus Leaf/Twig Oil		Y	N	N	N	N	N
Eucalyptus Globulus Leaf Water		N	N	N	N	N	N

Search Strategy

PUBMED

"Eucalyptus Globulus" OR "8000-48-4" OR "84625-32-1"

555 hits. Culled "AND tox*" – 48 (3 possibly useful); AND "geno*" – 0; AND repro* - 4 not useful; AND sensit* - 17 not useful; AND Irritat* - 0; AND carc* - 140 – 4 possibly useful.

SciFinder

"Eucalyptus Globulus", INCI names, and CAS Nos. 13 hits. None useful.

Transcripts – *Eucalyptus globulus*-Derived Ingredients

March, 2018

Dr. Marks' Team

DR. MARKS: Next is eucalyptus. We have a draft tentative report dated February 9th of this year. In December of last year, the panel issued an insufficient data announcement on Lillian's memo. The three needs were elucidated sensitization, impurity, and margin of safety calculations, which Ron Hill wanted. I just wanted to confirm, Lillian, that on wave two we now have that the highest concentration is 0.4 percent for the leaf oil?

MS. BECKER: Correct.

DR. MARKS: Okay. Ron and Tom, do you prefer to comment before you're influenced by Ron Shank, or do you want me to read Ron Shank's comments first?

DR. SLAGA: Well, we have some data. If we followed suite like we have done on some other botanicals, I could go with being formulated to be non-sensitizing.

DR. MARKS: That's what I have. Safe when formulated to be non-sensitizing. And we have this safety for sensitization now since the highest concentration of leaf oil is 0.4. We, in wave two, got more method of manufacture and impurities data. It looks like Ron Shank agrees with that.

The bottom line -- well, he said conclusion -- four possible conclusions. He didn't commit. He did have safe when formulated to be non-sensitizing. He had some comments on page 25 in the middle. Lillian, this will probably be -- and Carol -- directed at you. Is eucalyptol listed in the cosmetic ingredient dictionary? It is a component of the oil, but is it an ingredient unto itself?

DR. EISENMANN: Yes.

DR. MARKS: It is? We discussed that, that we don't put specific chemicals when we do botanicals in here, and this is a specific ingredient, but okay. The new data on eucalyptol was the alpha-2U-globulin seen in both males and females. So, we wondered about is that both males and females. I'm not sure what he would do with that.

And the end of paragraph two -- and Lillian you can address that, you'll be getting a copy of this. Then why is the panel asking for sensitization data oil at the 5.5 percent concentration? We aren't asking for that any longer; we have data that support the 0.4 percent in the leaf oil.

Ron Hill, I think you were commenting about the margin of safety. How do you want to move? Do you want to go onto a safe when formulated to be non-sensitizing?

DR. HILL: I was more concerned about the effects of eucalyptol itself, other than sensitizing. I was hoping that we would end up with some information in here about ADME or at least dermal penetration for eucalyptol, and I don't see that anything new popped up.

We have some penetration enhancement, but then it says, the leaf oil is readily absorbed and then that's weird because what component of the oil. That's what we have written on page 30. I still don't feel like we have any sense of eucalyptol absorption dermal root in humans. How do you get a margin of safety if we don't have any info? Or did we just simply still not capture it? That's what I'm driving at.

DR. MARKS: Ron, do you have difficulty with that, moving with a tentative report with a conclusion of safe?

DR. HILL: What's our highest concentration of leave on use and in what, now?

DR. MARKS: The leaf oil is 0.4 percent.

DR. HILL: Leaf extract -- I've got a number of comments written, but I was revisiting --

DR. EISENMANN: For the leaf water, it's 1.4 percent in face and neck products; and I did the rough calculation using a 95th percentile amount for face cream. And it's .931 milligrams per

kilogram per day.

DR. HILL: 0.93, so a little shy of one milligram per kilogram per day.

DR. EISENMANN: And that's the water, which would have less.

DR. HILL: That would be with 100 percent absorption?

DR. EISENMANN: Yes.

DR. HILL: Well, it's not 100, but it should be a substantial fraction because this is a compound that --

DR. EISENMANN: Since we didn't know anything, I just -- what would be exposed -- I'm looking at exposure, not dose.

DR. HILL: That's a good safe way. So, then the question is, can we get -- what I was looking for is if we -- what does that one -- roughly one milligram per kilogram per day, what does that -- that's estimated?

DR. EISENMANN: What is permitted in a drug is 1.2 to 1.3 percent eucalyptus oil. The anti-cough drugs that you rub on. That's 1.2 to 1.3 percent.

DR. HILL: 1.2 to 1.3 percent as those are drug products and not cosmetic ingredients.

DR. EISENMANN: Correct, which is for comparison.

DR. HILL: What flagged my attention on them is the ingredient -- honestly, working backwards from that one case study, it was the one where it was over a large body area and then they covered it in plastic. But there were other indications that in some cases we were seeing toxicity show up -- this is what happens when you read a lot of reports in a short span of time, which is why I took notes. So, hang on.

DR. MARKS: Carol, did you say that was leaf water?

DR. EISENMANN: 1.4, yes, leaf water.

DR. HILL: The other question I had, actually this came up in the -- I asked my wife about this. Informal consultant. Do we have cold creams not in the leave on category? We have them in rinse off, because we have 1.2 percent leaf extract, 1 percent leaf powder in cold creams. Do we consider those --

DR. EISENMANN: There are some creams that they do put in rinse offs, yes.

DR. HILL: Well, cold creams in particular. I asked my wife how does she use a cold cream, and she says in general anything that is cold cream is going to stay on. But I think it's showing up in our rinse off or --

DR. EISENMANN: Well, there is a skin cleansing group that they consider rinse off and I think that -- you have to remember that these product categories were created in the '70's or '80's, something like that. They were as they were then. Sometimes companies have to tell me whether they're rinse off or leave on and I put it down.

DR. HILL: This came into play here, again, because of trying to come up with -- I did a back of an envelope margin of safety calculation. What product would be being smeared on with this stuff in it, over what body surface area, and perhaps what kind of skin?

But mostly -- so face, how much surface area? How much eucalyptol? I was hoping we'd get some penetration coefficient type information. Something to indicate how fast this stuff goes into the skin. I think we can agree it would be absorbed based on -- I can just look at the structure and say, it would be absorbed.

So, using 100 percent absorption would be a good conservative number. The question is if we can tolerate one milligram per kilogram per day, how much stuff at 1.2 percent, over what fraction of our skin, do we have to put on to get to that? That's what I was looking for is, let's do the kind of calculation that you see RIFM do, that we see SCCS do, that we sometimes do. Say how much of the body surface area would we have to cover if we make a conservative estimate to get --

DR. EISENMANN: I didn't know what you would want to compare it with, that's the thing. I can do a rough exposure value for you, but I can't -- I'm not sure what the effect --

DR. HILL: Well, we can get a rough idea from the combination of case studies and other information in the previous report to see just about exactly where that cutoff is. It corresponds to about three mills [mils?] -- swallowing 3 to 3.5 mills of eucalyptol could potentially be fatal. That's what I calculated from the information we had.

So, the question is, if it's eucalyptol and that's the bad actor, how much do we have to put on how much of our skin, and what product, before we have a problem. Since fatality is the endpoint, I think we need to pay attention.

DR. KAPAL: Regarding the question about the cold cream, it depends upon the intended use. If the intended use is to apply and wash and depending upon -- then that cream probably is a wash off. Now, if it says to leave on, apply and leave it on, then that would be a leave on. So, it depends upon what's the intended use of that cold cream.

DR. HILL: Okay. So, what we'd hope is that the people responding to the surveys are responding according to how they think their product should be being used per the labeled instructions. Because what you said pretty well accords with what my wife said.

DR. MARKS: I think first of all, I'll go back and clarify about Ron Shank. He didn't mention, in his notes, any of those concerns. Of his four options -- and I mentioned the safe when formulated to be non-sensitizing. The other three options were all referenced to sensitivity and before we got the wave two data which clarified it. In point of fact, I think Ron also would be safe when formulated to be non-sensitizing. I'll second that conclusion tomorrow in a tentative report presumably.

Ron Hill, probably either I'll ask you directly, or maybe Wilma when she asks for comments, you can mention your comment about margin of safety and your concern about the amount of eucalyptol that potentially could be absorbed, or should I say the amount which could be systemically exposed. Am I interpreting that right, Ron?

DR. HILL: Yes.

DR. MARKS: That's where your concern is?

DR. HILL: Yes, indeed.

DR. MARKS: We'll have that discussion tomorrow. We have a tentative report, so we'll have more time to go over it and we'll see tomorrow whether or not -- and we can see what more we flush out in terms of -- in the discussion it would be what the margin of safety, and I'll address that.

Any other comments?

DR. HELDRETH: I just wanted to clarify that the non-sensitizing caveat that we're using in conclusion, that is specifically just for the potential cumulative effect of using multiple products that have the same constituent, correct?

DR. MARKS: Yes.

DR. HELDRETH: Okay.

DR. MARKS: Absolutely.

DR. HILL: Yes, because I wasn't clear that it was written that way. Maybe it wasn't this report where that was an issue, but there was at least one -- our boiler plate language needs to be adapted, depending on the particular ingredient under consideration. That's what struck me in reading one of those other reports. The reason for why it's there needs to be added invariably.

DR. MARKS: That actually appears -- there's the boilerplate as you mentioned, Ron -- that appears in the discussion; but Bart, thanks for clarifying. I guess for the record, every time we come to that conclusion, in the panel meeting, we should reiterate that, that it's really the reason that's in.

So, that if you have sensitizers, which most of these botanicals do, even though they're at a low level in this particular ingredient in its use -- and we're not worried about, say, sensitization and the use concentration with this ingredient alone. It's the combination, this with other botanicals that have this same sensitizing chemical that the additive effect may take it over the threshold.

DR. HELDRETH: Historically, for botanicals, we've only used this non-sensitizing caveat in this way. But for discrete chemicals, if it's the actual ingredient that we're having concern for, we

typically say, formulated to be non-sensitizing, which may be determined by a QRA or something.

DR. HILL: One other comment I was going to make before we move on is that on that -- because I feel like I picked on Wilbur -- that page 29 ADME data that's there is coming out of an INCHEM report, so that's a second source. And my comment was -- and I think I dropped this on the document -- is, is there any way we can get access to the original sources that they used of that information?

I don't know if those are listed and we can get those papers or not, but in the INCHEM -- that's the I-N-C-H-E-M -- I'm sorry, Lillian.

Dr. Belsito's Team

DR. BELSITO: Okie-doke. Eucalyptus, Lillian, Curt, passed something out. This comes from fragrance, raw material monograph.

At the December meeting we issued an insufficient data for sensitization at maximum concentration, which was the globulus leaf oil at 5.5 impurity [percent?] on all ingredients. Margin of safety calculation for inhalation and dermal exposure of eucalyptus globulus leaf oil and/or the major constituent, eucalyptol. We got some stuff, material safety data sheet, an HRIPT on a lipstick with the leaf oil at .5. Wave two data was brought in.

DR. SNYDER: The leaf oil use dropped from 5.5 down to 1. So, now our new maximum concentration use is .4.

DR. BELSITO: Right.

DR. SNYDER: We have data for sensitization at that level.

DR. BELSITO: Yeah, it's now .4, you're right. We have one HRIPT at .2. I think we're okay for the HRIPT. And I thought we could go safe as used.

DR. LIEBLER: When formulated to be nonsensitizing?

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah. Yeah. I agree.

DR. SNYDER: I had a question. In the abstract you mentioned with eucalyptus globulus-deriving ingredients, the panel was concerned about presence of geraniol and oxidation products of linalool in cosmetics. But there's also some other things that should also be of concern, that are constituents of concern, I think. Besides that, right?

DR. BELSITO: Yeah.

DR. SNYDER: Because there's carcinogens and genotoxic constituents listed below in the impurities. We probably shouldn't just pull out the two sensitizers, although there's also limonene also is a sensitizer, right?

DR. BELSITO: Right.

DR. SNYDER: We need to capture all those.

MS. BECKER: In the abstract?

DR. SNYDER: Yeah.

MS. BECKER: Not just the discussion.

DR. SNYDER: Constituents of concerns, yeah.

DR. BELSITO: I mean, if we're limited in the abstracts -- I mean, I think the constituents of concerns during the discussion. And in the abstract just say limit constituents of concern without pointing them out.

DR. SNYDER: Specific ones. Okay. That'll be fine.

DR. BELSITO: Otherwise, just putting those two in makes it seems like those are the only two we're concerned about, and they're not.

DR. LIEBLER: Or that they're unusually high in eucalyptus.

DR. BELSITO: Right. Because there's also quercetin that's reported in there, we don't deal with that.

DR. SNYDER: Right. And it is a penetration enhancer, right? Leaf oil.

MS. BECKER: Yes. PDF Page 29.

DR. SNYDER: Page 29, okay.

DR. BELSITO: Is there anything in the current discussion that needs to be further developed? Obviously, the new data range for eucalyptus globulus oil that needs to be updated there. In fact, that whole paragraph now can actually be eliminated.

DR. SNYDER: Yup.

DR. BELSITO: That's the top of 39.

DR. LIEBLER: Yeah. I think it's fine. I don't see anything else that we need to emphasize. I didn't have any notes on the discussion.

DR. SNYDER: That next paragraph, Don. Is that one now going to be because we're saying if we going to have -- when formulated to be nonsensitizing. Because now we talk about the possibility, the presence of sensitizers and below the level of toxicologic concern. Lack of dermal irritation -- lack of sensitization --

DR. BELSITO: Yeah. I understand. But I think that that's all good to be put there. And then to say, because we have this issue with botanicals being added into the same final product, that when formulated to be nonsensitizing, cover that. And just point out that there are sensitization issues here, potentially, but not specifically at the range that these are used in.

DR. SNYDER: Okay.

DR. BELSITO: Now, we don't say anything about quercetin here?

MS. BECKER: I don't think so.

DR. BELSITO: Do we need to?

DR. SNYDER: I didn't have that on my list of concern. But is it in the impurity section?

DR. BELSITO: It's in the composition section.

DR. SNYDER: Is it in the new data, or is it in here already? I usually pull it out.

MS. BECKER: Table 9.

DR. SNYDER: Oh, Table 9, okay.

DR. BELSITO: It's a pretty low amount.

DR. SNYDER: Okay. Yup.

DR. BELSITO: Do we mention it at all, or?

DR. SNYDER: No. I think it's captured.

DR. LIEBLER: Or you could add it to the sentence that has the others, which is in the middle of that paragraph. I mean, you could just add it. If you want to mention it, that the place.

DR. KLAASSEN: I guess I'm not -- quercetin isn't that -- I mean, that's a huge food additive that they use by the gallons. I guess I'm not very concerned about it, to the best of my knowledge.

DR. BELSITO: Okay. So, we don't need to bring it up in the discussion.

DR. KLAASSEN: No.

DR. BELSITO: Okay. Safe as used when formulated to be nonsensitizing. And what did you want us to see in this? We didn't look at it.

MS. BECKER: Just some additional sensitization data.

DR. KLAASSEN: It says it's safe.

DR. SNYDER: It's all the same. All negative.

DR. BELSITO: Okay. So, this will be added in or?

MS. BECKER: Yes. It's already in the next draft.

DR. BELSITO: Okay.

DR. KLAASSEN: I got a couple of small comments that you can read and change English-wise, what have you.

MS. BECKER: Okay.

DR. BELSITO: Were they done in German? Or just Kansan?

DR. KLAASSEN: I'll just go ahead and put them into Kansan. And we weren't even working on sunflower.

Day Two

DR. BELSITO: Yes. In December, insufficient data announcement. We wanted sensitization and maximum concentration of use, which at that time we were told was 5.5 percent; we're now told it's 0.4 percent. We want impurity data on all the ingredients, margin of safety for inhalation and dermal exposure, using eucalyptus globulus leaf oil and/or the major constituent that seem to be the issue, eucalyptol or 1,8-cineole.

We got quite a bit of information in Wave two. We got some information that was handed out, in Wave three, yesterday morning. We thought we could go with safe as used when formulated to be nonsensitizing.

DR. MARKS: And this will be a tentative report. Our team seconds that motion.

DR. BERGFELD: Any further discussion? Ron Hill?

DR. HILL: Just to clarify this. The concern about sensitization is because we aren't sure? Or is this just a boilerplate botanical concern?

DR. BELSITO: It's simply because there are other constituents within it that can sensitize, and it's the usual combination with other --

DR. HILL: That's what I think we discussed and clarified yesterday. I just wanted to make sure I was clear.

DR. BERGFELD: Any other comments? Call to question then? All those in favor of insufficient? Unanimous. Okay. Thank you very much. Moving on to the parabens. Dr. Marks?

December, 2017

Dr. Belsito's Team

DR. BELSITO: We are going to start here. We are looking at eucalyptus twig and this is the first time we're looking at it. We have method of manufacturing composition for the -- extensively for the leaf oil. What we don't have anything on is the leaf twig oil, but I didn't really think we needed it. I can't imagine that it would be significantly different, but anyone feel that that's an insufficiency that we don't have information on the leaf twig?

DR. LIEBLER: Yeah, I didn't have any concern about that. There was a note about adding eucalyptol, I agreed with that, to the report -- adding eucalyptol to the report. So we're good with that. I thought the supporting data for composition and constituent's concern is very good.

DR. BELSITO: Now, in your short-term toxicity, this is PDF page 18, you state that it's on eucalyptus globulus leaf extract, but that study is the same one you use in the DART. In the DART study it says it's the leaf oil, so one is wrong. So this is page 18 of the PDF just above see developmental and reproductive toxicity DART. The first line of that paragraph it says that this data is on eucalyptus leaf extract and then the DART study is -- it says it's the leaf oil. That's on PDF 20. One or the other is incorrect.

MS. BECKER: I'm pulling up the original just to see. It is the oil.

DR. BELSITO: So that needs to be corrected.

MS. BECKER: Yes.

DR. BELSITO: Then on PDF page 27, you list the constituents of concern. This almost seems to be a boilerplate. Except for limonene, I didn't see any of these other ingredients listed as part of the composition of eucalyptus oil.
MS. BECKER: We originally had a full list from Duke in here and we pulled that out so that the constituents that were listed in there aren't listed now. We removed that now, but we should have looked at that to make sure that somehow got addressed when we took that table out --
DR. LIEBLER: Yes, limonene and alpha pinene are in the table immediately preceding.
DR. BELSITO: Right. But most of the other ingredients that are listed as being constituents of concern were not told at all that they're present in eucalyptus. It just to me looks foolish to say it's a constituent of concern when we have no data in the report that indicates that geraniol or phellandrene or quercetin are even in eucalyptus oil.
MS. BECKER: We got that in the comments actually from the council, and I've already started the next version of this and I've added that to the constituents of concerns section in the text --
DR. BELSITO: What have you added --
MS. BECKER: That they're there from the David -- from the Duke information, because we took out that table. I didn't pull that information out and put it in the text, and I'm doing that now.
DR. BELSITO: So you're going to summarize it in a text?
MS. BECKER: Right.
DR. BELSITO: So in the Duke phyto botanical logo database, those are listed as potential constituents?
MS. BECKER: Right.
DR. LIEBLER: Do we really need that as a table, table 9, if you've already got in text and you've got a lot of these listed in the tables immediately preceding, although they're not labeled as constituents of concern? I'm just wondering what you guys think. Do we need that table 9 there on top of whatever is mentioned in the text?
MS. BECKER: Well, do you want something to point to easily for the discussion?
DR. BELSITO: I don't mind the table. What bothered me was that they weren't listed in any place as being constituents.
DR. LIEBLER: Yeah, so anything in this table, table 9, needs to appear in table 8, table 7, table 6, and/or --
DR. BELSITO: That was my point. I don't mind table 9. I mind the fact they're not listed in any of the other tables and then the same thing with table 10. There's no mention of citronellol or carbone or any of these. I mean, we don't need to give RIFM and IFRA a boost by telling every time what ingredients they have restrictions on, only those which are present in the botanicals we're looking at. So if these are in fact in the Duke database, then they need to be mentioned.
MS. BECKER: Right.
DR. ANSELL: I think we would --
DR. LIEBLER: Go ahead and use (inaudible).
DR. ANSELL: I think we would have -- recommend that table 9, at least to the extent that the concerns are identified, be deleted, not so much identified. But some of these would seem to have essentially no relevance to the presence at low concentrations as part of a -- as part of a botanical there, the effects associated with dosing the material meet at concentrations which are not relevant to cosmetics.
DR. BELSITO: So then having said all that, I was betwixt in between how to go with a conclusion as to whether it was insufficient or not, because there are ingredients of concern which are sensitizers, so we're going to use the standard botanical boilerplate when formulating to be non-sensitizing. The oil is used in (inaudible) [a leave-on] up to 5.5 percent. The best we have for sensitization is 0.1 percent. So do we say we want sensitization data at 5.5? Even if that's negative, we're still going to say when formulated to be non-sensitizing, because it has sensitizers; or do we simply say we're going to put that in our conclusion, so why ask for data that's not going to change what we think.
DR. LIEBLER: I think this is a draft report; right?
DR. BELSITO: It's the first time we're seeing it.
DR. LIEBLER: So we typically ask for the data (talk over) get it. We had this discussion last time about something else. I remember you and Jim talking about it. We know we're going to get to safe as used when formulated to be non-sensitizing, but we should ask for the data. I found that reasonable. It does go -- it does formulate -- it does contribute -- or figure prominently in the

discussion, because on the one hand we can say -- the discussion kind of fine tunes the argument and we can say if we had negative sensitization at five percent, let's say, then we can point that out and say that data supported these in high use concentration for sensitization. However, formulation with other botanicals could create a problem. So I think it makes sense to ask for it.

DR. BELSITO: So basically discussion we need to start formulating penetration enhancement and the usual plan, inhalation boilerplates and the typical when combined with other botanicals in terms of sensitization. We'll go insufficient for sensitization of the oil at 5.5. Dan, you said you're okay not having method of manufacturer composition impurities of the leaf twig oil; is that correct?

DR. LIEBLER: Correct, because the data are so extensive and the procedures are really pretty will established for these types of preparations so that I think we can reasonably cover the leaf twig oil.

DR. BELSITO: I think most of what we'd be concerned about is going to be in the leaf, not in the twig.

DR. LIEBLER: Right. If it were like root or nut or something like that, then it would be different.

DR. BELSITO: Right. Okay.

MS. FIUME: I just wanted to reiterate as Dan said. Because with the botanicals, it's important to emphasize whether or not the ingredients themselves are sensitizers and know that versus that when formulated to be non-sensitizing, which takes all botanicals into consideration when in formulation, because there's a difference. That's why I have a question about the table 9, about removing some of the information because they might not be a cosmetic use based on these ingredients. Knowing that we look at botanicals as a whole formulation, would there be any reason to leave those constituents of concern in because you're looking at it with other botanicals and formulation?

DR. BELSITO: No, I like table 9. I thought we decided to keep it in after the discussion.

DR. ANSELL: I think it was the reference to the concern that was my problem, that looking at, what is it, phellandrene as a secondary potential carsi tumor promoter following a treatment with a polyaromatic hydrocarbon wouldn't necessarily be particularly relevant. Some of the sensitizers that might be more relevant, I think the inclusion of these without any assessment is going to be more confusing than clarifying. Are we really concerned that eucalyptus is a -- to a [tumor] promoter because an ingredient had in effect followed a long-term treatment with a benzanthrene?

DR. BELSITO: Well, I mean, are we concerned, no. Could we be criticized by a party for -- who says, well, you guys ruled on this and weren't aware of this data, I think possibly. Anything is possible, so I don't have an objection to listing it there. If it concerns you, Jay, I also don't have an objection to in the discussion saying that this type of data is irrelevant, because no one's going to put a tumor promoter or a carcinogen like DMBA into a cosmetic product.

DR. LIEBLER: But the table includes references and the references point to that -- the literature that is -- includes the scenarios in that middle column on the table; right?

DR. BELSITO: Right.

DR. LIEBLER: So if you deleted the middle column on the table and still had the references -- the identification of constituents of concern, I think you've done sufficient exposition of what they are and that we are aware of the literature on these.

DR. ANSELL: We have no issue with the inclusion of constituents. Perhaps elevating them to constituents of concern goes a bit far, but then to include this data point, do we want to do a full-blown tox assessment on phellandrene to determine whether it's safe or not as a constituent? I think the safety assessment is done on eucalyptus, and identifying materials within these other tables are simply included as constituents.

DR. BELSITO: Would you be more comfortable, Jay, retitling that as constituents of potential concern?

MS. BECKER: It's also pointing out that this is the plant, not in the ingredient.

DR. ANSELL: Well, are they the only constituents of -- that we want to pay attention to? I mean, the camphor isn't there. I guess my question is: Are these truly constituents of concern?

DR. BELSITO: Well, I mean, they're -- you're right. The constituents that we're concerned about after having signed off on the safety of botanical ingredient are the dermal sensitizers that could be added in from other botanicals. I don't have a problem with getting rid of phellandrene and saying constituents of potential concern for sensitization and just listing those. Because when and if we sign off on this, it will be when formulated to be non-sensitizing. I think it is nice to have a list of what we identified as the potential sensitizing ingredients. So I would relabel table 9 constituents of potential concern for skin sensitization in eucalyptus globulus leaf and oil and simply list those ingredients that are potential sensitizers, (inaudible), limonene, geraniol.

DR. ANSELL: That aligns perfectly with the boilerplate that these materials may be constituents of other botanicals and they're potential sensitizers and you need to pay attention to them.
DR. BELSITO: I don't have a problem with that.
DR. LIEBLER: Problem solved.
DR. BELSITO: What I would do with --
DR. BERGFELD: There are four in that table that you're going to delete. What would you do with those? Would you just put them in the text and reference them?
DR. BELSITO: Yeah, we've done that before with -- quercetin has come up with a number of botanicals where we just simply mention that, you know, it -- it will -- if it's going to be here, it should be listed as a constituent some place like beta-phellandrene at.3. In the discussion, use the same issues in terms of saying that the same language we've used for quercetin before, that levels are really below the threshold of toxicologic concern essentially.
MS. BECKER: So if you're taking it out of the table, put it in the text?
DR. BELSITO: No, it needs to be in a table of constituents of the ingredients. So the phellandrene is listed in table as a constituent of globulus leaf oil. I don't see where the quercetin was listed thuja -- there's thugene.
MS. BECKER: Let's just list it in table 9, that was when we reduced the size of the report and took out the table from Dr. Duke's.
DR. BELSITO: Then I think at some point you need to mention quercetin. Then in the discussion, you can use that same type of language that we've used to dismiss quercetin and thugone and other toxins like those based upon threshold of toxicologic concern. What we want to do with the constituents of concern are those constituents of concern for sensitization to really hit back and say, okay, when you're -- when you're looking at formulating this with another botanical, there's a similar table there that shows you what the sensitization concerns were. IFRA has standards for these. You better make sure that when you're formulating your product and mixing these botanicals, that they stay within the range of the IFRA restrictions and that they're formulated not to be sensitizing.
DR. KLAASSEN: If one looks at table 7, you know -- so our main constituent is this --
DR. BELSITO: Cineole.
DR. KLAASSEN: -- 1,8 cineole. But if you go to the top chemical -- or the top listed chemicals, the second highest concentration, which is a forth of alpha pinene and then if we go down to table 9 and look at alpha pinene, it supposedly causes cancer in urinary bladders of mice. So I guess we don't have a carcinogenicity study, should we be -- any concern about this alpha pinene?
DR. BELSITO: Well, it's at 1.2 percent of the oil and then the oil is a max of 5.5. So that gets to.05 percent possible maximum in leave-on product.
DR. KLAASSEN: I don't even know what the structure of alpha pinene. I don't suspect that's given in here, is it?
DR. BELSITO: It's terpene now.
DR. LIEBLER: Well, we got negative Ames and mammalian genotox on the leaf oil extract.
DR. BELSITO: Right.
DR. LIEBLER: So we don't have carcinogenicity, but we do have --
DR. KLAASSEN: Genotox.
DR. LIEBLER: -- Genotox data stuff that's pretty strong.
DR. KLAASSEN: Okay.
DR. BELSITO: Anything else? So we have part of our discussions set up there, penetration enhancer, usual plant inhalation boilerplates, the individual constituents of concern for sensitization, the individual constituents of concern for other toxicity end points being below the threshold of toxicologic concern, negative Genotox data, and we're going insufficient for sensitization of the oil of 5.5 percent.
DR. SNYDER: Sort of a general discussion issue maybe. Monice elicited to it a minute ago. So as I was reading through these reports and the minutes, and I know Ron has strong feelings about us using this when formulated to be non-sensitizing. I think we have transgressed from what we originally used that statement for was specifically for botanicals that had sensitizers as impurities that we recognize, so we said because you may -- you may formulate with multiple botanicals that contain this same sensitizer, that you need to be careful that you don't -- that you formulate to be non-sensitizing. Somehow that has translated over into us saying that for an ingredient, we're saying now to not be sensitizing without an absence of any data. Whereas previously, we would

either ask for sensitization data at the maximum concentration of use or we would use a clinical data that suggested there were no problems with sensitization. So have we in fact directed to where now we're --

DR. BELSITO: No, that's why we decided insufficient --

DR. SNYDER: No, I'm talking more globally for -- because we had used when formulated to be non-sensitizing for non-botanicals, haven't we?

DR. BELSITO: Well, we did that because of the impurities in cocamidopropyl betaine where --

DR. SNYDER: I just want to make sure that we haven't drifted to where we're -- because I know I read that in the minutes from at least --

(Talk over)

DR. BELSITO: We did that with methylisothiazolinone because we know that the limit for sensitization will depend upon product use. So for instance in underarms and wet wipes is where methyliso caused the huge epidemic by sensitizing.

DR. SNYDER: But in this case as an example, we're using -- the highest concentration used is 5.5 percent and requesting sensitization of 5.5 percent irrespective of the presence of the impurities that cause sensitization?

DR. BELSITO: Right. We're asking for that, because otherwise what we're saying is that this could be safely used at 5.5 percent without really having the data and that the formulating to be non-sensitizing was based off the fact that we think 5.5 percent alone is okay in this instance, but we don't know what would happen if you put it in with rosemary extract and also -- or lemon oil that will also have a lot of limonene and linalool. So when you're doing that, you need to be careful.

DR. LIEBLER: I think it's a good distinction to make, Paul. I think that while I agree it to be a good distinction to make, I don't think we've drifted into doing that in lieu of asking for data that we should ask for, but it's something we need to emphasize from time to time.

DR. BERGFELD: I think that we have --

SPEAKER: (Unintelligible)

DR. BERGFELD: A full discussion on that is really good for the minutes as well as to re-examine what we do, because I've seen us go both ways on botanicals and other...

DR. SNYDER: So maybe then in our conclusion, we should say that it should be formulated to be non-sensitizing based upon the presence of impurities that are non-sensitizers or something, not because --

DR. BELSITO: Well, they're not impurities, they're actually constituents.

DR. SNYDER: But they're not the main ingredient.

DR. BELSITO: Right.

DR. SNYDER: We're not saying -- I think there's two very different issues. I mean, I want to make sure we're very clear in the message we're sending.

DR. BELSITO: I think in this case, I sort of agree because basically this cineol. We don't know the sensitizing capacity of cineol. It may be the goods and we're having a reported use of 5.5 percent, so we -- this is the first time we're seeing it, so let's ask for the data, let's see what we got.

DR. SNYDER: But if we don't get the data on cineol, then we can't -- then I don't think it's valid to say --

DR. BELSITO: Right. At 5.5 percent, not cineol. We don't get the data --

DR. SNYDER: But I don't think it's valid. It doesn't say safe as used when formulated to be non-sensitizing if we don't have non-sensitizing data at 5.5 percent, because we would still use --

DR. BELSITO: ...insufficient.

DR. SNYDER: But we still use that caveat, because we have the constituents of concern?

DR. BELSITO: Right.

DR. KLAASSEN: I agree.

DR. BELSITO: Essentially I think that's where we came around when I said --

DR. SNYDER: Well, I think it's clear on this report, but I think on other ones I'm not certain we've done that quite to that level.

DR. BELSITO: Yeah, you may be right.

DR. LIEBLER: Every one of these situations has its own complicating factors. I think as Wilma said, we've kind of tended to go one way or another, but it's not because -- I really don't think it's because we're sort of inconsistent. I think it's because the body of data that we consider for each of these is a little bit different.

DR. BERGFELD: But once we found -- once we had that caveat, we began to use it more and more and

more when we were stuck.
DR. LIEBLER: So we got somebody who's going to keep us honest.
DR. KLAASSEN: Yes.
DR. SNYDER: I mean, (inaudible) of money.
MS. FIUME: The text of the report does point the concern for sensitization in both the abstract and the discussion to reaching levels of constituents that could be hazardous or that could lead to sensitization, so both the abstract and discussion does lead the botanicals to constituents. I think the panel does a very good job when it is a discrete chemical where you're concerned about sensitization that in the conclusion many times we put based on the results of QRA, so we sort of distinguish where the concern is, and that is specifically for the ingredient and you're referring the industry to a QRA?
DR. BELSITO: Right. Any other issues?

Dr. Marks' Team

DR. MARKS: And what's the origin of that one, Dr. Shank? Eucalyptus to live ingredients. Let me see, so, another draft report from Lillian at the September meeting.
MS. BECKER: That's the first time I've [you've] seen this.
DR. MARKS: Yes, that was the scientific literature review in September, thank you. Usually, I put first review. So, the first thing is, are the ingredients okay? And then I think that's a no brainer, but I still --
DR. SHANK: Yes.
DR. MARKS: -- will not.
DR. SHANK: Okay.
DR. MARKS: And the next is, what needs do we have?
DR. SHANK: Skin sensitization on the oil and [at] use concentration 5-1/2 percent. (Inaudible). Can I have one of those glasses?
DR. MARKS: I think I actually drank out of both of them because the others was here from before.
DR. SHANK: Okay, that's right.
SPEAKER: I'll get some.
DR. MARKS: You got it?
DR. SHANK: (Inaudible)
DR. MARKS: Maybe oil at 5 percent.
MS. BECKER: 5 and a half
DR. SHANK: That's okay.
DR. MARKS: You keep it. Now, so Ron, I'm going to be the devil's advocate because I was there with you also. But then when we had the conclusion, Sappho [safe when] formulated it to be non-sensitizing.
DR. SHANK: There goes the knee.
DR. MARKS: Yeah, so, it's a little contradictory. I guess we could say --
DR. SHANK: Well, I had sent formulated data, did I?
DR. MARKS: No.
DR. SHANK: Not yet.
DR. MARKS: Not yet, by the way you're going. So, I guess one could issue a tentative report and we could put that in our wish list, but that would inhibit us from going forward.
DR. SHANK: Right.
DR. MARKS: The sensitization for the leaf extract and our wave two was okay. The remainder, we have no sensitization data. Now, one of the --
DR. SHANK: We have two -- we have two.
DR. MARKS: Huh?
DR. SHANK: We have two.
DR. MARKS: Yeah, that's what I said, wave two for that leaf extract, but the remainder, we don't have any sensitization data. So you picked out the oil, but I guess what I -- reassuring to me was when we look at the clinical experience and there were several studies showing -- indicating patch test clinics less than one percent and positive reactions to eucalyptus.

DR. SHANK: That's usually 5-1/2 percent.
DR. MARKS: No, when I said one, less than one percent -- I'm sorry, less than one percent of the population tested had positive reaction. So, it had a low rate of positive patch testing in patch test clinics. So --
DR. SHANK: What was the concentration of use?
DR. MARKS: I have to look at that. Really, that -- it's more concerning in terms of that they aren't patching with the irritating concentrations which they are not.
DR. SHANK: Okay.
DR. MARKS: So, I actually would say go on to a tentative report that safe and formulatedly [when] non-sensitizing.
DR. SHANK: Can you -- not only an ask should be include the data on eucalyptol and I think it adds support.
DR. MARKS: Sure, okay.
DR. SHANK: So, yes.
MS. BECKER: You want to add the ingredient eucalyptol.
DR. HILL: Yes.
DR. EISENMANN: But you haven't traditionally done that before.
MS. BECKER: Eucalyptol is in eucalyptus oil at 54 to --
DR. HILL: Ninety.
DR. SHANK: Large, large percentage.
DR. HILL: A vast majority of eucalyptus oil is eucalyptol.
DR. EISENMANN: I mean, menthol's in the dictionary. I didn't add it.
DR. HELDRETH: Just historically, we haven't mixed botanicals with discreet chemicals.
DR. EISENMANN: Right.
DR. HILL: In fact, if we think back to the rosemary example. We took rosemarinic acid and --
DR. SHANK: I didn't mean add it as an ingredient.
DR. HILL: No, I did.
DR. SHANK: Just add the data from the (inaudible) [eucalypot] - -
DR. HELDRETH: I think that's great, thank you.
DR. SHANK: -- to support the ingredients.
MS. BECKER: For licorice, we took hallucinogenic [glycyrrhizic] acid and licorice were separate reports, so --
DR. MARKS: So just to include it in the discussion, you were saying, Ron Shank?
DR. SHANK: Well, we got some information on the toxicology data on eucalyptol. We got some major constituent --
DR. MARKS: Of the oil?
DR. SHANK: -- of the eucalyptus oil. So that being the -- I think are important --
DR. MARKS: I agree.
DR. SHANK: -- to add to the to report, but not as a --
DR. MARKS: An ingredient.
DR. SHANK: -- an ingredient.
DR. MARKS: Yeah. Does that mean it can come up tomorrow as a discussion or at the beginning of, with this the first --?
MS. BECKER: Yes.
DR. MARKS: Oh, you already know, Lillian, I'm going to second it if they'll see that between us and mention it, Ron, you can mention it. I had a question, Mark, about inhalation, so (inaudible). Was there any concern, Ron Shank, about any inhalation toxicity?
DR. SHANK: Um.
DR. MARKS: And let me say -- I didn't put a page number so I'm sorry I can't --
DR. SHANK: I don't, but let me look at it again.
DR. MARKS: While you're looking at that I'll bring up one other thing that I, again, this is relevant to RIFREM [RIFM] and we don't know the answer to this and one thing. We can get it, is the leaf twig oil and the leaf water at the fragrance use only. And so the question here comes if RIFREM [RIFM] is not going to be evaluating these in the near future, we would use the same reasoning we would include in this report so perhaps we can ask RIFREM if they're reviewing it?
MS. BECKER: We did.

DR. MARKS: Oh, you did, and they are?
MS. BECKER: Yes, it's in your, it's in wave two.
DR. MARKS: Oh, it is in wave.
DR. HILL: Since they had asked any --
DR. MARKS: Okay.
DR. HILL: -- they're not doing it.
DR. MARKS: Okay. Somehow, I think I (inaudible) sensitization and wave two, but I didn't get that. Okay, so, that answers that question. Thanks Lillian.
MS. BECKER: You're welcome.
DR. SHANK: You asked about inhalation.
DR. MARKS: Yes.
MS. BECKER: Seventeen [in the PDF].
DR. SHANK: It says there's not very much information -- inhalation toxicology on the oil, but it is used medicinally; approved. I guess you call it a drug.
DR. MARKS: That's probably why I questioned the inhalation; there's not much there. So do we handle that in the discussion or do we just say that there's not much information and move forward?
DR. HILL: So, if it's gone through some pre-market approval for that use then somewhere there's some information one might guess. What do you need to do to get it?
DR. MARKS: Well, Lillian's already done getting. I guess you could do more getting.
MS. BECKER: Yeah.
DR. MARKS: Would you respond?
MS. BECKER. This is one of those things like Witch Hazel; that it's been around forever and all the studies are really old and a lot of them are not online.
DR. SHANK: Folk -- folk (inaudible) [medicine].
MS. BECKER: Yes. Yeah, the folk use for eucalyptus is a lot longer than the approved use.
DR. HILL: Well, if there's one product that had pre-market approval somewhere in the world; ideally in this country, then there should be something that's happened in the last 25 to 40 years.
MS. BECKER: Except if it's under herbal uses in which case they don't have to -- they just have to say it's in there, they don't have to claim it does anything.
DR. HILL: Yeah.
DR. SHANK: I don't think you need to put that in the discussion.
DR. MARKS: Would you change the literature in relation to the toxicity in humans for the leaflet or scarce; that makes sense? Following as a summary or do you like the way it's, Lillian has it worded here? Since I brought it up, I just want to make sure the inhalation of the oil, either it's a liquid or an aerosol may result in pneumonitis. Inhalation of vapor may be used medicinally and there's no data available on toxicity by this group. However, the respiratory problems include bronchial spasm to kidney or pulmonary edema, yeah, that's the reason why I had inhalation question mark because --
DR. HILL: Well, because it's clearly a threshold because there's, there were deaths described in the case reports --
MS. BECKER: Right.
DR. HILL: -- if I'm not mistaken --
DR. MARKS: So, I --
DR. HILL: -- when you receive that threshold.
DR. MARKS: Yeah, so that's why I put inhalation as an issue it needs --
DR. HILL: But I don't think it was from breathing it, it was from swallowing it, wasn't it or normal aspiration?
DR. EISENMANN: It says aspiration.
DR. MARKS: Well, here it says inhalation and of the oil result in pneumonitis. Even if it's inhalation, it's obviously not swallowing --
DR. HILL: No.
DR. MARKS: -- so, either that or it's not correct.
DR. HILL: Right above our new discussions where there was oral exposure --
DR. MARKS: Yeah.
DR. HILL: -- stemming to --
DR. MARKS: Yep.
DR. HILL: -- toasting.

MS. BECKER: Are you looking at the case reports on page 15?
DR. MARKS: No, I'm looking at page 17 under inhalation. It's the heading and then it has the eucalyptus leaf oil; that's what I read, it's all about the oil and the significant toxicity; respiratory toxicity from it. I would just reference 10.
MS. BECKER: Okay and this is another one of those things where all the references refer to each other? And sorting out where it began is just nuts.
DR. MARKS: I don't know. Ron, Ron, Tom, he had a way out of that? Obviously, when I read it I was concerned that whenever I read pneumonitis attack a coronary a pulmonary edema, I get concerned and I wasn't even considering death. And I didn't, I should look at the use. Is there uses in aerosol products?
MS. BECKER: Yes, for hairsprays, ties [tonics], dressings, face and neck products, night products.
DR. HILL: Is there referenced to him that has the setback handbook of use of essential oils this is that, that reference. I think it is. International program, that's in- count [INCHEM], okay. Yeah.
DR. MARKS: Ron Shank. They could always extend the conclusion when formulated to be non-sensitizing and non-toxic when it failed.
DR. EISENMANN: You know, the products that are listed as the concentrations that I got and the products that are listed as incidental inhalation, the maximum use concentration is .74 percent.
DR. SLAGA: You could say safe if not applied to the skin.
DR. MARKS: So, .74 is a maximum concentration so that we know that?
DR. HILL: Okay, an in-count [INCHEM] report is -- I haven't looked at it directly that I have to say that's.17. So, maybe we can get some more information about what's actually in it with that. If there's anything to get a better sense of the threshold.
MS. BECKER: I'm just reminding myself, I'm looking at the in-count [INCHEM] and they're pretty much just referring to all reports in 1910 and 1911.
DR. HILL: Well, can we get them? I mean, just because they done in 1910, we know we don't have HPOC studies, correct?
MS. BECKER: Mm-hmm.
DR. EISENMANN: Tom has brought up the MEA [BIBRA] summary and they say (inaudible) 1991; that's probably another view, but there's a couple of inhalation studies in here. Sixty- three human subjects exposed for eight hours, chrome mixture contained 1.7 eucalyptol placed in a hot steam vaporizer. Liver and kidney function test in 25 new subjects reveal no (inaudible) effects; no further details reported. Here's another 10 minute study --
DR. MARKS: Hold on a second. What was the number that was exposed?
DR. EISENMANN: Sixty-three.
DR. MARKS: And how many reported no effect?
DR. EISENMANN: They just did liver and kidney function testing in 25.
DR. MARKS: Oh, okay.
DR. EISENMANN: So, it doesn't --
MR. JOHNSON: (Inaudible)
DR. EISENMANN: -- and then there were no effects, they don't know what they did with the other subjects. But, it was 1.7 percent. This could be in a vaporizer, I mean, so there are --
DR. MARKS: Oh, yeah.
MR. JOHNSON: It is, it's --
DR. EISENMANN: -- right.
MR. JOHNSON: You buy this --
DR. EISENMANN: Mix.
MR. JOHNSON: -- oil. You put it in that machine that heats the water and goes through the vaporizer.
DR. EISENMANN: But, I mean, even other medicinal products, I think, can contain --
DR. SLAGA: Some of the lozenges at least.
DR. MARKS: Well, I guess one could put out an insufficient data and ask for inhalation toxicity and if we put a tentative report for site and formulate in the non- sensitizing, I still think we have the inhalation toxicity in limbo, I guess. I don't know, how do you all feel?
DR. HILL: I agree. When you get through a couple of different sections in the report, you can get a pretty clear picture of the acute dermal threshold as well as the acute oral because those case reports give it pretty clearly. If you integrate them together and then they'll appear, but I don't think we have any good data on them. Unless, if there's a long history of use in vaporizers, certainly. So we

have anything from that long history of use I suspect that there's a problem.
DR. EISENMANN: But inhalation data on eucalyptol would be (inaudible).
DR. HILL: Yeah.
DR EISENMANN: Okay.
DR. MARKS: Tom, what do you feel; a tentative report or insufficient data? What was your analysis?
DR. SLAGA: I initially said in insufficient study.
DR. MARKS: Oh, you did?
DR. SLAGA: Yeah, (inaudible).
DR. MARKS: What did you, what was your insufficient data?
DR. SLAGA: Well, inhalation.
DR. MARKS: Okay.
DR. HILL: So, mine was there are no impurities data on non-constituent purity. You got data on the substances, but not other impurities.
DR. MARKS: Okay, so, let me see. We're eventually going to end up with safe and formulated to be non- sensitizing, probably.
DR. SLAGA: Yeah, but that's where I think it's going.
DR. MARKS: But we would like our needs for the insufficient data announcement would be inhalation toxicity clarify that and then, you mentioned, Ron, you would --
DR. SHANK: Is that on just the oil?
DR. MARKS: I think it's just - why don't we put --
DR. HILL: I put that for, if you're talking about the non-constituent impurities; I put that for all of them. We don't have any impurities information.
DR. MARKS: Yeah, usually we want that, so, impurities for all. Do we want the inhalation toxicity for all or do we want to just limit it to the oil? I'd say, get whatever we can. What do you think, Ron? You think if we got the oil, we'd feel -- you'd be comfortable in all the rest?
MS. BECKER: Well, if you get the oil it's a sub, I would guess, it's a subset, I believe, extract. So, and that's -- highest concentration is 0.4.
DR. HILL: No oil comes from the extract; the leaf extract contains the oil?
MS. BECKER: My guess is the oil would also be included in the extract.
DR. HILL: Okay.
MS. BECKER: So --
DR. EISENMANN: Depends on how extract is made.
MS. BECKER: Yeah, that's true.
DR. MARKS: Why don't we just ask for inhalation toxicity and impurities for all the ingredients and see and go from there?
DR. SLAGA: See what we get.
DR. SHANK: Yeah.
DR. MARKS: Okay.
DR. HILL: I got a couple of other things; one, which was, number one, I'm not sure that I'm clear on actual cosmetic uses for other impurities. We said two were just reported to be pregnant -- pregnancies, right?
DR. MARKS: Yes.
DR. HILL: What else have we got?
MS. BECKER: Well, I'm not sure what the question is.
DR. HILL: The question is what are the cosmetic uses of these? I don't get any sense of clarity of, let's see, in the table -- it's table one.
MS. BECKER: Table one on 24.
DR. HILL: Yeah, okay, so obviously the covers embrace, so that one's clear and two more in fragrance. So, then what we have is skin conditioning miscellaneous, right?
MS. BECKER: Correct.
DR. HILL: Okay. Let's just see, leaf oil, the leaf and the leaf extract. But it's interesting because the leaf/twig oil which is listed as the only a fragrance ingredient appears to be pretty much the same stuff as the leaf oil.
DR. MARKS: And just remember those cosmetic functions are --
DR. HILL: I know that.
DR. MARKS: -- not vetted.

DR. HILL: The other thing I have is I wondered if we couldn't get a durable exposure margin of safety calculation because we have a pretty good idea where those thresholds are and I was looking at table 15, page two. And then the essential oils book has a maximum 20 percent recommendation. Two spots it's referenced, I think. So, it would be awful nice to know if we could get a margin of safety calculation, what that would look like. Because in the case reports, deaths are described and we get much above that threshold. Dermal exposure leading to deaths or severe incidents.
DR. MARKS: So, inhalation impurities and then the third thing would be --
MS. BECKER: Dermal sensitization.
DR. MARKS: Well, we -- dermal sensitization isn't an issue because it's going to be eventually safe and formulated in sensitizing. We had sensitization for the leaf extract. But, you're talking about dermal exposure margin of safety?
DR. HILL: Yeah, I guess, because the oil is used up to five -- the cosmetic uses is reported up to five percent. And we're looking at pretty significant problems above 20 percent.
DR. MARKS: And where are you?
DR. HILL: Are you talking about --?
DR. MARKS [SHANK]: Where you said people dying.
DR. HILL: Yeah, table 15, there's some case reports; a long listing of case reports and some of them are dermal and then there's, some of them oral and they're not in the main text. At least some of them are not in the main text. So, it starts on PDF page --
MS. BECKER: Thirty-three.
DR. HILL: Thirty-two and then -- 32 is where the dermal starts and continues on to 33. The one I had to start was the first one on the top of page 33. No, yeah, that was - -
DR. MARKS: That just, I think, no this is patch test of case reports. Yeah, I guess, let's see.
DR. HILL: All right, actually, with the dermal ones I don't think there's any deaths associated with those. There are some significant events. The deaths show up in the oral exposures.
DR. MARKS: Now, where are the deaths, it's on table 15?
DR. HILL: Let's see, yeah, table 15 under the oral ones.
DR. MARKS: They say I'm installing the case reports here --of (inaudible) okay, I see where you are now.
DR. HILL: Yeah, there's one, two, three, four, five, six, there's a 10-year-old boy. One, two, three, four, five, six, seven -- seventh one down. Of course, he took a big slug of this stuff.
DR. MARKS: Well, it's still though -- when you look at it. The first ones, of course, a teaspoonful. So that can be anywhere from 15 to 20 millimeters and he ends up with gasping for breath, restlessness, convulsive movements, vomiting.
DR. HILL: Like I said, with that in combination with this information that was in the main report, get a pretty clear sense of where the thresholds are. We got an oral lethal dose of.05 mils to.5 mil per kilogram and I did the calculations so, basically in a 70 kilogram person, 3.5 millimeters of the oil can be fatal.
DR. MARKS: So, how would you --
DR. HILL: I don't know if there's enough information to do the dermal on it or not, but --
DR. MARKS: That was 33 was it?
DR. HILL: That's tables, where it has the case reports for dermal exposure.
DR. MARKS: That's okay, that's their sunrise system [summarized sysinctly] there. What -- Ron Shank, what's your, or Tom, what's your response to that (inaudible)?
DR. SLAGA: I didn't think you needed (inaudible).
DR. SHANK: I just took all these as basically (inaudible) [poisoning] cases.
DR. MARKS: Yeah.
DR. HILL: Well, they are.
DR. MARKS: And the exposure we had on the cosmetic when you can approach that.
DR. HILL: We owe 5-1/2 percent. If you got case reports describing the incidents from dermal exposure and you got a highest concentration of use of 5-1/2 percent, but put that on a skin area, you might have issue. And that's, I guess, that's what I'm driving at is -- I mean, I can do that calculation myself back at the (inaudible) [envelope], but I wondered if somebody was interested enough to try a little harder than that.
DR. SHANK: Well, a normal [the oral] dose is bogus [bolus].
DR. HILL: Yes.
DR. SHANK: Blood concentration would be much higher. We need anything that would reach from skin

a application.
DR. MARKS: So, that would you put one in if you have Lillian put that in the discussion? My concern with the world [oral] toxicity you mentioned in that table, I know what, Ron, your answer is.
DR. HILL: I'm looking at the first --
DR. MARKS: You raised the issue.
DR. HILL: Yeah, I'm looking at the first entry on page 33 where the six-year old girl; they did some home remedy where they were giving her 80 to 85 percent eucalyptol which is a single [?] oil and she wasn't doing okay, but didn't getting better. And then they doubled the dose and now she, a slurred speech, unsteady gait and nausea, vomiting and after a night in the hospital, her symptoms have resolved.
DR. HILL: So, that was the limit, grant you it's one case, but the details were quite clear.
DR. SLAGA: The problem is it's one case.
DR. HILL: But, the details were very clear and within reason. So, you're right, there's not --
DR. MARKS: So, it's something that in effect, Ron Shank, you would say we can put it in the discussion that the oil toxicity, when you have oral exposure to the oil, it's much greater and other toxicity or oral exposure to the oil is much greater than what you'd expect the cosmetics, makes this cosmetic safe.
DR. SHANK: The blood concentration would be very high compared to application of the product containing eucalyptus oil to the skin. Could be fortification, but it'll be much slower absorption through the (inaudible).
DR. MARKS: Yeah. You know this is just --
DR. SHANK: And there could have been aspiration, you know --
DR. MARKS: Yeah.
DR. SHANK: -- if they're vomiting right away, gasping, they could dismiss aspirating into the lungs.
DR. MARKS: And discussion, okay. Do you know if --
DR. SHANK: I think they're a lot --
DR. MARKS: -- it sounds --
DR. SHANK: -- of ingredients that if you --
DR. MARKS: -- it sounds -- is this eucalyptus oil available?
DR. SHANK: I have no idea.
DR. MARKS: And it's really interesting because where I think of it being used now, just off the top of my head, and I didn't do any research, would be in a massage therapist using eucalyptus and massages or on you -- and I don't know what the concentration would be, but --
DR. EISENMANN: Well, with that book, the essential oil safety handbook, is written by an aroma therapist and he recommends maximum concentration of 20 percent.
DR. MARKS: Yeah.
DR. EISENMANN: That's what he recommends. And but, yes, you can buy little vials of pure essential oil; eucalyptus that are for diffuser type things or they're intended to dilute with other like olive oil or something like that.
DR. MARKS: Right.
DR. HILL: I can assure you that, Carol, eucalyptol works wonderfully well. I had a tooth meltdown and I, to a distant past -- actually this summer, and it did dandy. And then I looked for the product again recently and I couldn't find it again.
MS. BECKER: I have 100 percent pure eucalyptus, in a 4 ounce bottle for 7.99.
DR. MARKS: Four ounces? So, we had no difficulty getting a large teaspoon, tablespoonful of that stuff? Okay, well, I think -- because it sounds --
MS. BECKER: Because it's not a cosmetic product.
DR. MARKS: -- Ron Hill, we're going to be seeing this again, but I think at this point, maybe mention that in the discussion. What do you think, Ron Shank, or would you just leave that table exist?
DR. SHANK: I think that if you drink a tablespoon of peppermint oil, you'll get pretty sick. I don't think these are interesting reports, but they're not indicative of masking [risk] cosmetic use.
DR. HILL: What is, yeah, what's weird is, now grant you, they had a home remedy that had a mixture of things which I think included something dermally penetrate -- to enhance penetration, which was --
DR. MARKS: So, Ron --
DR. SHANK: We'll bring it up tomorrow (inaudible) - -
DR. MARKS: Yeah, I'll bring it up, but kind of going forward then, Ron, if these are not relevant to

cosmetic use, should they even be included in the report? Because now, we can see with Ron Hill it raised a red flag and we've spent the last whatever; 15, 20 minutes discussing it --
DR. SHANK: Well, we've always included case reports.
DR. MARKS: Yes, exactly.
DR. SHANK: Or it's cosmetic ingredients.
DR. MARKS: Well, that's -- so, I think that being alert is worth mentioning in the discussion; maybe a sentence or two.
DR. SHANK: Since there are human deaths.
DR. MARKS: Yes.
DR. SHANK: Yes, I can put it in the discussion and explain --
DR. MARKS: Yes, just what you said, yeah, that the oral exposure in this situation leads --
DR. SHANK: Would lead to a rapid high concentration in the blood which would not be obtained through cosmetic use.
DR. MARKS: Yep, okay.
DR. HILL: So, it appears that they included 100 milliliters of the oil and the 400 mil concoction and put it on her limbs and her trunk and then put it on the plastic wrap. And within -- with the doubled-up dose and within a few minutes; 10, 15 minutes she was intoxicated. So, that's a huge whopping dose.
MR. STEINBERG: Was that in Minnesota?
DR. HILL: I don't know, it might have been in Minnesota.
MR. STEINBERG: (Inaudible).
DR. HILL: Yeah.
MR. STEINBERG: With Ben-gay?
DR. HILL: I don't know.
SPEAKER: The incidental ingestion is maxes at .74 for the leaf oil.
DR. HILL: Yeah, so I think, it's just the oil anyway that's any concern.
DR. MARKS: Okay, so I think we'll see how it goes tomorrow; our team and I will be seconding a motion, hopefully, for insufficient data announcement and what we would like is more inhalation toxicity and the impurities for all ingredients. And we'll see what we get. Does that sound good?
DR. MARKS: Ron Shank, I see a --
DR. SHANK: Okay.
DR. MARKS: -- hesitation. You want to go with safe when formulated they're non-sensitizing?
DR. SHANK: Yes, well, but, I'm not going to push it.
DR. MARKS: Oh, no, that's okay.
DR. SLAGA: Well, we'll see tomorrow. It's not yours is it?
DR. MARKS: Oh, that doesn't matter.
DR. SLAGA: I know, but I'm just --
DR. MARKS: I'm still going to, I'm still --
MS. BECKER: No.
DR. MARKS: -- no matter what the other team says, I'm going to still -- our position, other than Ron Shank's, is that he's not going push it, but I hear you. Obviously, Ron Hill disagrees with the team at times and I don't feel strongly; I just brought up the inhalation toxicity because of the red flags I saw there.
DR. SHANK: No, it should certainly be discussed.
DR. MARKS: Yeah. I don't know how to discuss it once we get (inaudible).
DR. SHANK: It's also used medicinally via the respiratory tract.
DR. HILL: I have a long history of that; a long history. Who knows how long?
DR. MARKS: So, that can be handled in the discussion?
DR. SHANK: So we'll both go into the (inaudible).
DR. MARKS: And then how about the impurities? Ron Hill, how strongly do you feel about that?
DR. HILL: I feel like that's our due diligence that we do for everything.
DR. MARKS: Yep, yep, I agree also. Okay, well, Ron Shank, don't -- I shouldn't have to say this to you, but don't hesitate to speak up tomorrow.
DR. SHANK: Me?
DR. MARKS: That's what I say. That's why I say that tongue-in-cheek, but at least that's what I'm going to present tomorrow and then we'll go from there, if that's okay, Ron Shank?

DR. HILL: Yes.
DR. SLAGA: How early in the morning does this come up?
DR. MARKS: For you, it's probably about 4:00 a.m., I don't know, 5:00 a.m.
MS. BURNETT: It's later in the morning, later in the morning.
DR. MARKS: Okay. That was fun.

Day Two

DR. BERGFELD: Okay. The next ingredient is eucalyptus, Dr. Belsito.
DR. BELSITO: Yes. So this is the first time we're looking at the six eucalyptus globalized [globulus] ingredients and we had quite a bit of information on these including composition, method of manufacturing, etc. except for the what was it -- leaf, twig, but we didn't think that the leaf and the little bit of the twig that was stuck to the leaf would significantly change the composition. However, we did notice that we had sensitization data only at 0.1 percent and that the oil is used up to 5.5 percent in product. So we will go insufficient with this group for sensitization at the highest concentration of use, which is 5.5.
DR. BERGFELD: 5.5 -- Dr. Marks?
DR. MARKS: Yes. We second the insufficient data announcement. We had other needs, our team. We are concerned about the possibility of inhalation toxicity and we wanted more data about that as eucalyptus [is] being inhaled in cosmetics, so that data need -- we wanted impurities for all the ingredients and then we wanted toxicity when oral exposure was much greater than skin exposure. So there is concern about could we get toxicity when we are in that setting. So those were our three needs to add on to your sensitivity. I think ultimately we will be doing what we do in all the biologics. We didn't highlight sensitization because we have a conclusion, which usually is safe when formulated to be non sensitizing, but I like that done to get that data.
DR. BELSITO: We discussed that and it was a work around for sensitization. However, we usually do that because we have data that suggests that at 5.5 percent or whatever concentration that particular ingredient is non sensitizing. However it contains substances such as limonene or limonool that might be in other botanicals that added together could be sensitizing. Since it is a difference of 50 fold between what we are saying would be safe and what we have data on we wanted that data.
I guess I am a little bit confused why you are asking for inhalation and oral toxicity. We have a huge number of case reports of people swigging down tablespoons of this and developing neurologic problems and inhaling it and developing inhalation problems. So exactly what were you looking for in terms of oral toxin, respiratory toxin?
DR. MARKS: Ron Shank, would you?
DR. HILL: I had just made the comment that it would be nice to have a better indication of a margin of safety for dermal exposure to actually do for the oil where we know if you swallow enough there is problem up to including fatality. That we had a calculation that showed the margin of safety would be huge even if something was smeared on a large portion of the body. In particular, there was one case report where that is exactly what happened and when you got enough on a large portion of the body there were systemic effects. That is an aberration because there was a large amount and the circumstances under which it was used and the probability that they are penetration enhancers in that "formulation" that these people were doing as a home remedy. But the point is if we can just -- it shouldn't be that hard to do. I would probably do something reasonable, but some kind of margin of safety calculation. The consumer is assured and we have some information in there as to don't smear it in this over 100 percent of your body and cover it in plastic wrap or something like that.
DR. BELSITO: Actually, what you're asking for is add me [ADMA] data because we don't have that. We don't have any data on what is absorption. And we're not going to be able to do that calculation without that data.
DR. BERGFELD: Are you adding that to the list as well?
DR. BELSITO: Well, if they want to calculate a margin of exposure we need to know what the absorption is and we don't have any of that absorption distribution of data information in the report.
DR. HILL: Then the question is if we had that for eucalyptol would we consider since that is a major

component be sufficient or do we have any reason to believe there is combination effects? I would think eucalyptol would be the major player.

DR. BELSITO: I think that's I mean I think that's what's driving what we've seen, so yes. I mean that --

DR. BERGFELD: Are you adding that in addition to the inhalation? I just want to make it clear what you are adding. You are adding it to a list.

DR. BELSITO: I am saying that if the other team feels that we need to look at margins of exposure then we need absorption and I would agree with Ron Hill that it is going to be difficult to -- I mean it depends upon the eucalyptus oil -- I mean the eucalyptol in the individual ingredient would be the best to look for that data because it is probably -- it is not probably it is almost certainly what is driving any toxicity that is seen.

DR. HILL: That data if you capture the eucalyptol data we talked about adding it actually might already in there, I'm not sure. It might be.

DR. LIEBLER: So well the -- the cover memo raised the issue of whether we should add eucalyptol. We didn't mention that explicitly, but I supported adding eucalyptol to the report. PDF page three gives a brief synopsis of available data for eucalyptol. It doesn't explicitly indicate a dermal absorption data. However, we do have a summary of data for oral administration to brush tail possums, which is a first in my professional experience. Just wanted to note that for the record.

DR. MARKS: Our team discussed again, doing a specific ingredient including it in this report the eucalyptol. We felt since it's botanical based setting a new precedent we usually don't include a specific ingredient along with the botanicals. Bart, do you want to comment on that?

DR. HELDRETH: It's up to the panel whether you want to do it. I just wanted to remind the panel that in the past they have often deleted ingredients from a botanical review that were discreet chemicals for instance, the rosemary derived ingredients report we removed rosemarinic acid. But that doesn't mean that you can't do that here. It's up to the panel.

DR. LIEBLER: The reason I piped up is because it is a possible solution to the problem of assessing absorption and that gives us something we could also use a eucalyptus oil and measure eucalyptol or somebody could try and do that. I don't know if that's going to happen.

We talked about adding the data but not adding the ingredient. I don't know if that makes sense or not but that is what we talked about or maybe adding selected data.

DR. BELSITO: We've done that before. I could go either way, but in response to your idea about when added with penetration enhancers I would just point out that eucalyptus oil has been reported to be a penetration enhancer.

DR. BERGFELD: So --

DR. LIEBLER: The policy sometimes is poor substitute for good judgment. I think the issue of whether or not to have individual chemical species in a report that is largely or otherwise entirely botanicals often there is a good reason to adopt that posture, but it doesn't mean that needs to be a barrier to including it when it makes sense. If it helps us solve a problem then it makes sense. So that is why I kind of lean towards including it. I forgot about the rosemarinic acid example and I don't remember the circumstances there. Anyway, that's my two cents.

DR. BERGFELD: Jim, do you want to relook at your needs that you are going to be requesting on this insufficient?

DR. MARKS: I think the first thing is we going to do the single ingredient eucalyptol in --

DR. HILL: Yes.

DR. MARKS: Yes. Okay, so we --

DR. KLAASSEN: What you are really going to do -- what experiment are you expecting to be done with the dermal absorption?

DR. HILL: I wasn't asking for dermal absorption. I was saying we have a pretty good idea what the oral threshold is probably even in humans based on at least this -- I don't know if it is good, hard clinical research of course. We do use in toxicology accidental exposures. I think we have a pretty good idea exactly how much eucalyptol delivered orally. Enough to be able to do a margin of safety calculation without any new data I believe. I just wanted the calculation done and then say well, if we have dermal exposure I think we do have information about dermal exposure of eucalyptol. I bet you anything that data is out there in the literature if we look to find it. If we don't find it then we have to decide what to do about that. But I think we have enough -- I bet we find that information without -- it's not really a new data request. It's a literature search request.

DR. MARKS: I guess when I read the report there is certain end points like pneumonitis, pulmonary

edema, death and such and so that raised alert and for me, some of it was inhalation as it was oral and so the question is how do we handle those in terms of the cosmetic? Do we say the concentration is so low we are not worried about it? So that's why I brought up like the inhalation toxicity and also why Ron Hill brought up the issue of how there is a total body application compared with an oral ingestion.

DR. BERGFELD: Well we have -- we have a motion to go on the table that was insufficient, which it seems that both teams agree upon. And the sensitization request both teams agree on. What we are not agreeing on is the other things that have been asked. The margin of safety can it be calculated as Ron Hill suggests?

DR. BELSITO: That's not my area of expertise. I mean I don't know. But I think that the cleanest thing to do is regardless of whether we bring eucalyptol into the report or not is to go out and see what is available for that in terms of dermal absorption and respiratory toxicity looking for a NOEL or NOAL.

DR. BERGFELD: So your needs assessment in an insufficient would include the specific ingredient about 40 percent of all product or --

DR. MARKS: Yea, we are going to include that as an ingredient.

DR. BERGFELD: And it needs to be under that particular ingredient.

DR. BELSITO: We can't say eucalyptol is insufficient we determine whether we are bringing that into the report.

DR. BERGFELD: Well, it's in the announcement. You don't have it so you are going to ask for it.

DR. BELSITO: No. Are we bringing it -- we are going to ask for data on eucalyptol to drive a margin of exposure with this oil, but are we actually adding eucalyptol to the report? Because then it is not insufficient for data on eucalyptol. It's insufficient for margin of exposure for dermal and respiratory and the panel feels that could be calculated based on data from eucalyptol.

DR. BERGFELD: Jay, do you have something?

DR. ANSELL: Yea, we would not recommend adding every ingredient within a botanical to the name of the report to the extent that eucalyptol could be a marker to address the toxicity questions surrounding eucalyptus. I think that's fine. But then to go through and then add all of the components as being safe or reviewed would just open you know, it would be a very, very difficult task. I mean where would you even draw the line?

DR. BERGFELD: Bart?

DR. HILL: I think what's unique about this situation is that eucalyptus oil is up to 90 percent eucalyptol invariably above [45] or 50 percent eucalyptol, was we haven't seen that in very many botanical situations. This is pretty unique.

DR. BERGFELD: Bart, oh you make a suggestion?

DR. BELSITO: Certainly. I would just point out that cineole was a huge component too of one of the botanicals. So I mean I agree with Jay's point. Let's keep it as the full material and not bring in individual ingredients but use the data for eucalyptol to support toxicity or to refute that there would be toxicity.

DR. SNYDER: I think regarding inhalation the oral study you are worried about was the oral human study -- was that under the oral human? You mentioned about wanting inhalation data or dermal exposure related --

DR. BELSITO: Dermal [margin of] exposure.

DR. SNYDER: Dermal exposure. Well -- because the we have inhalation data that suggests that it's definitely irritating but the concentration of use is very, very low for inhalation that we have. And then I thought you were worried about the oral human inhalation. I think those patients they aspirated the stuff because they had vomiting and stuff like that. And so that pneumonitis and stuff was all probably related to aspiration of the stuff from vomit. It's not from oral ingestion causing pneumonitis.

DR. HELDRETH: Just to your comment on cineole -- that is eucalyptol. They are one and the same. It's all --

DR. BELSITO: Right.

DR. BERGFELD: Don, do you want to make a conclusion of what we should do at this point in time?

DR. BELSITO: I think we are going insufficient for sensitization of the oil at 5.5 percent and asking for a calculation of a margin of exposure for inhalation and dermal toxicity based upon data that can be generated either from the whole plant, the eucalyptus leaf oil or generated on the ingredient eucalyptol.

DR. BERGFELD: I think that's nicely stated.
DR. MARKS: Right. And the only other thing we wanted to maybe it's there -- but we didn't' see impurities for the ingredients. We'd like to have that also.
DR. BELSITO: Fine.
DR. BERGFELD: All right, so that's added.
DR. MARKS: It sounds like we landed on Dan, want you to comment, that we aren't going to include the ingredient eucalyptol despite I like the way you phrased it when you proposed the argument why to include it.
DR. LIEBLER: So I'm -- I will -- I think the wisdom of the group prevails and I am happy to go along. So not including eucalyptol.
DR. BERGFELD: However, it's been mentioned in the needs assessment that the documentation or information on eucalyptol would be acceptable. So it is very possible after another review of this when these materials come in that we might act.
DR. BELSITO: I don't think so.
DR. BERGFELD: You don't think so? Okay. It's a possibility.
DR. HILL: I might make a separate report if you have done the review you can consider doing that. I mean it's not on the list, but.
DR. BERGFELD: All right. Is there any other discussion? I think that Don has outlined specifically the specific needs. It is going insufficient and we have added the impurities to that list. Any other? We are going to call the question. All those in favor then. Insufficient data announcement. Thank you. Unanimous.

(MOTION PASSES UNANIMOUSLY)

Safety Assessment of *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients as Used in Cosmetics

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The 2018 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. 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

This is a safety assessment of 6 *Eucalyptus globulus* (eucalyptus)-derived ingredients as used in cosmetics. The reported functions of the *Eucalyptus globulus* (eucalyptus)-derived ingredients include abrasive, fragrance ingredient, and skin-conditioning agent (miscellaneous and occlusive). The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the relevant data on these ingredients. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Industry should use good manufacturing practices to limit impurities. The Panel concluded that *Eucalyptus globulus* (eucalyptus)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing.

INTRODUCTION

This is a review of the safety of 6 *Eucalyptus globulus* (eucalyptus)-derived ingredients as used in cosmetics. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*), the reported functions of the *Eucalyptus globulus* (eucalyptus)-derived ingredients listed below include abrasive, fragrance ingredient, and skin-conditioning agent (miscellaneous and occlusive; Table 1).[1]

Eucalyptus Globulus Leaf
Eucalyptus Globulus Leaf Extract
Eucalyptus Globulus Leaf Oil
Eucalyptus Globulus Leaf Powder
Eucalyptus Globulus Leaf/Twig Oil
Eucalyptus Globulus Leaf Water

To avoid redundancy of effort, CIR may exclude from review ingredients that are known to exclusively function as fragrance ingredients when the ingredient has been or will be evaluated by the Research Institute for Fragrance Materials (RIFM). According to the wINCI *Dictionary*, Eucalyptus Globulus Leaf/Twig Oil and Eucalyptus Globulus Leaf Water are only reported to function as fragrance ingredients.[1] However, communications with RIFM in November 2017 revealed that these ingredients have neither been assessed for safety by the RIFM Expert Panel, nor are these ingredients on RIFM's prioritized agenda to be reviewed in the foreseeable future. Thus, CIR is reviewing the safety of these ingredients as part of this assessment.

Plant-derived cosmetic ingredients, such as *Eucalyptus globulus* (eucalyptus)-derived ingredients, may contain hundreds of constituents, some of which have the potential to cause toxic effects. For example, geraniol is reported to be a potential dermal senisitzer.[2-6] In this safety assessment, the Panel is reviewing information available to evaluate the potential toxicity of each of the *Eucalyptus globulus*-derived ingredients as whole, complex mixtures. Except for specific constituents of concern, CIR is not reviewing information that may be available to assess the potential toxicity of the individual constituents derived from *Eucalyptus globulus*. However, Eucalyptus Globulus Leaf Oil consists of not less than 70% (w/w) eucalyptol (also known as cineol, cineole, or 1,8-cineole), a cosmetic ingredient that has not been reviewed by CIR.[1,7] Since the content of eucalyptol is so high, it is appropriate to include relevant toxicity data on eucalyptol as supporting information for the *Eucalyptus globulus* (eucalyptus)-derived ingredients. Representative data are summarized in the relevant sections in this safety assessment. While the data are being considered in evaluating the safety of *Eucalyptus globulus* (eucalyptus)-derived ingredients, the safety of eucalyptol as used in cosmetics is not being assessed in this report.

The Panel has reported on related ingredients that can be used to support the safety of the *Eucalyptus globulus*-derived ingredients. Phytosterols were found in chloroform and methanol extracts of *Eucalyptus globulus* leaves.[8] The Panel reviewed the safety of phytosterols, which are plant-derived sterols, in 2013 and concluded that the phytosterol cosmetic ingredients are safe as used.[9]

The names of the cosmetic ingredients in this report are written in accordance with the International Nomenclature Cosmetic Ingredient (INCI) naming conventions as shown above, i.e., capitalized without italics and without abbreviations. When referring to the plant from which these ingredients are derived, the standard taxonomic practice of using *italics* is followed (e.g., *Eucalyptus globulus*). Often in the published literature, the information provided is not sufficient to determine how well the tested substance represents the cosmetic ingredient. Therefore, the taxonomic name is used or it is noted that the similarity could not be determined, unless it is clear that the test substance is similar to cosmetic ingredients. If the tested substance is a cosmetic ingredient, then the INCI name is used.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics and chemicals industries, as well as by other interested parties.

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA)[10] and the International Program of Chemical Safety (INCHEM)[11] websites. In this safety assessment, ECHA and INCHEM are cited as the references for summaries of information obtained from these websites. Also referenced in this safety assessment are summary data found in reports made publically available by the World Health Organization (WHO)[7] and the European

Medicines Agency (EMA) Products Committee on Herbal Medicinal Products (HMPC).[12]

CHEMISTRY

Definition

The definitions of the ingredients in this safety assessment are provided in Table 1. The genus *Eucalyptus* contains more than 750 species (i.e., *Eucalyptus cordata*, *Eucalyptus diversifolia*, *Eucalyptus gigantea*, *Eucalyptus glauca*, and *Eucalyptus pulverulenta*, etc.) and the term "eucalyptus" in the literature can refer to any or all of these.[13] There are four subspecies of *Eucalyptus globulus*: bicostata, globulus, maidenii, and pseudoglobulus.[14] It is not known if only one or all of these are used in cosmetics. This review cites studies where it can be reasonably certain that the test substance is *Eucalyptus globulus*. However, because the wINCI *Dictionary* defines Eucalyptus Globulus Leaf Oil as the volatile oil obtained from the leaves of *Eucalyptus globulus* and other species of *Eucalyptus*, data on other species may be included where deemed appropriate. "Eucalyptus oil" may be extracted from any *Eucalyptus* species that is rich in eucalyptol.[7] The other main species that *Eucalyptus* essential oil is extracted from are *Eucalyptus polybractea* and *Eucalyptus smithii*, which contain a minimum of 70% eucalyptol.[15]

In addition, according to the wINCI *Dictionary*, the CAS number that is associated with Eucalyptus Globulus Leaf Oil (defined above) is 8000-48-4. However, according to the Chemical Abstracts Service (CAS) database, the substance associated with CAS number 8000-48-4 is defined as "extractives and their physically modified derivatives of *Eucalyptus*, Myrtaceae." Also, according to the wINCI *Dictionary*, CAS number 84625-32-1 is associated with Eucalyptus Globulus Leaf Extract, which is defined as the extract of the leaves of *Eucalyptus globulus*. However, according to the CAS database, the substance associated with this CAS number is defined as "extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from *Eucalyptus globulus*, Myrtaceae."

Plant Identification

Eucalyptus globulus, also referred to as blue gum or Tasmanian blue gum tree, is a member of the Myrtaceae family. These plants are evergreens that are indigenous to Tasmania and southeastern Australia, and are cultivated in subtropical regions of the world including Africa, South America, Asia, southern Europe (Spain and the Black Sea region) and the U.S.[7,12]

Eucalyptus globulus is a large tree with smooth, very pale or ash-grey bark, which grows up to 20 m high.[7,12,16,17,17-20] The bark types vary with plant age, and include: stringy bark, ironbark, tessellated bark, box, and ribbon. The bark cells are able to photosynthesize in the absence of foliage, giving the plant an increased ability to re-fix internal carbon dioxide following partial defoliation. This allows the tree to grow in less-than-ideal climates. Branchlets are quadrangular or glaucous. Eucalyptus leaves are ensiform (shaped like a sword blade; long and narrow with sharp edges and a pointed tip), usually ranging from 15 to 30 cm, and possibly up to 40 cm, long and 5 cm wide. The leaves, which are bluish-green in hue, alternate and are vertical. The leaves are studded with brown lenticels and colorless glands containing fragrant volatile oil. Younger leaves tend to have higher oil content than mature ones; however, eucalyptol content is higher in mature leaves. The flowers, which are present most of the year, have very short pedicels, mostly umbellate, sometimes 2 to 3 in a fascicle. The flowers consist of several white fluffy stamens (12 mm long), which are numerous, threadlike, white anthers opening in broad slits with round gland. The fruit has numerous small seeds and is enclosed by a cup-shaped receptacle. The root system grows rapidly and uses large quantities of water; it consists of a strong taproot, at least 6 ft (1.8 m) in length, and lateral roots that can spread up to 100 ft (30.5 m).

Physical and Chemical Properties

Physical and chemical properties are presented in Table 2. The odor of rectified Eucalyptus Globulus Leaf Oil changes over time as it is exposed to air.[21] In the first 15 min, the odor is described as terpene-like, harsh, and conifer-like. At 15 min to 1 h, the odor is fresh, characteristic of eucalyptol, minty, and camphoraceous. At 2 to 8 h, the odor is hay- and cumic-like, similar to rosemary. At 5 to 20 h, the odor is woody, dusty, and powdery. The specific gravity of Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf/Twig Oil increases as the eucalyptol content increases (0.9005 to 0.930).[21]

Method of Manufacture

The definitions of several of the *Eucalyptus globulus*-derived ingredients in this safety assessment give insight into possible methods of manufacture. For example, the definition of Eucalyptus Globulus Leaf Water states that this ingredient is an aqueous solution of the steam distillate obtained from the leaves of *Eucalyptus globulus*.[1]

Methods of manufacture from the literature of Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf Extract are presented in Table 3.

Composition/Constituents

The reference substances that are used to identify the legal entity composition of Eucalyptus Globulus Leaf Extract, Eucalyptus Globulus Leaf Oil, and/or Eucalyptus Globulus Leaf/Twig Oil in Europe were reported to ECHA (Table 4).[10] The constituents in these ingredients include eucalyptol, pin-2(10)-ene, dipentene, and (*R*)-*p*-mentha-1,8-diene. Eucalyptol, the

most common constituent, with the highest concentration, is shown in Figure 1.

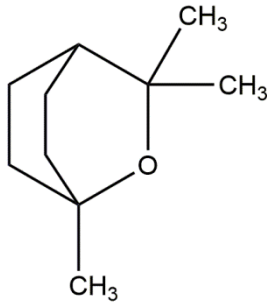

Figure 1. Reported primary component of *Eucalyptus*, eucalyptol

Reported concentrations of *Eucalyptus globulus* essential oil and its constituents vary in the literature. *Eucalyptus globulus* leaves contain not less than 2% (v/w) essential oil, consisting of not less than 70% (w/w) eucalyptol.[7] Another report states that fresh leaves of *Eucalyptus globulus* contained 54% to 61% eucalyptol, 19.5% to 24.3% α-pinene, 6.7% to 9.1% limonene, 2.1% to 5.4% α-terpinyl acetate, and 3.6% to 7.7% sesquiterpenes.[12] The author attributed the differences observed among the different preparation methods to potential hydrolyses during steam distillation. Another author reported that fresh leaves of *Eucalyptus globulus* contain only 1.87% volatile oil with 35.7% eucalyptol.[12]

Phytosterols were found in chloroform and methanol extracts of *Eucalyptus globulus* leaves but not in petroleum ether or aqueous extracts.[8] Table 5 shows the major constituent groups found by using different extract media.

Eucalyptus Globulus Leaf Extract

A supplier reports that the aqueous Eucalyptus Globulus Leaf Extract contains no eucalyptol.[22]

Eucalyptus Globulus Leaf Oil

A supplier reported the constituents of Eucalyptus Globulus Leaf Oil, which included eucalyptol at 78.8% (Table 6). Another source reported on the concentration ranges of the constituents of Eucalyptus Globulus Leaf Oil (essential oil; Table 7). As shown in Table 8, gas chromatography-mass spectrometry (GC-MS) analyses demonstrates the variation in constituents of Eucalyptus Globulus Leaf Oil collected by steam distillation with geographic source location.[20,23,24]

Eucalyptus Globulus Leaf/Twig Oil

In general, the major constituent of Eucalyptus Globulus Leaf/Twig Oil is eucalyptol (54% to 95%).[7] In addition, there are reported to be moderate amounts of α-pinene (2.6%), *p*-cymene (2.7%), aromadendrene, cuminaldehyde, globulol and pinocarveol. Eucalyptus Globulus Leaf/Twig Oil for medicinal use contains not less than 70% (w/w) eucalyptol. Eucalyptus Globulus Leaf/Twig Oil also contains monoterpenes such as β-pinene, limonene, geraniol and camphene.[12]

Constituents of Concern

Constituents of the *Eucalyptus globulus* plant that may be of concern are listed in Table 9.

Potential sensitizers include geraniol[2-6] (found in the essential oil) and the hydroperoxides of limonene[2,6,25] (leaf essential oil) and linalool[2,26] (leaf and leaf essential oil).[27]

Other constituents of concern found in the *Eucalyptus globulus* plant are myrcene (leaf essential oil), pinene (essential oil, leaf, and leaf essential oil) and quercetin (leaf and stem bark).[27] These constituents are potential carcinogens or are genotoxic.[28-30,30-33]

The International Fragrance Association (IFRA) publishes restrictions for fragrance ingredients, which form the basis for the globally accepted and recognized risk management system for the safe use of fragrance ingredients.[34] Constituents of *Eucalyptus globulus* leaves and oil that have restrictions established by the International Fragrance Association Standards are listed in Table 10.

Impurities

A supplier reported specifications for a trade name mixture containing 10% Eucalyptus Globulus Leaf Extract include a total bacterial count limit of < 100 colony forming units (cfu)/g.[35] This supplier also reported specifications for this same trade name mixture that certain allergens, including eugenol, geraniol, and linalool, are not detected (limit of detection 0.001%; Table 11).[36]

Another supplier reported specifications for another trade name mixture containing Eucalyptus Globulus Leaf Extract (concentration not specified; Table 11).[37] This mixture was also reported to not contain allergens and not to contain antimony (detection limit 0.021 gm/l), arsenic (0.055 mg/l), cadmium (0.004 mg/l), chromium (0.010 mg/l) iron (0.087 mg/l), lead (0.015 mg/l), mercury (0.0002 mg/l) or nickel (0.016 mg/l). There were no residual pesticides detected and a total

bacterial count limit of < 100 organisms/g (opg).

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetic industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentration by product category.

According to VCRP survey data received in 2018, Eucalyptus Globulus Leaf Oil is reported to be used in 433 formulations (214 leave-on formulations, 160 rinse-off formulations, and 59 formulations that are diluted for the bath).[38] Eucalyptus Globulus Leaf Extract is reported to be used in 77 formulations and Eucalyptus Globulus Leaf Powder is reported to be used in 2 formulations. The VCRP included ingredients with the non-INCI name "eucalyptus" (42 reported uses) and "eucalyptus extract" (11 reported uses; Table 12).

The results of the concentration of use surveys conducted by the Council in 2017 and 2018 indicate Eucalyptus Globulus Leaf Water is used at up to 1.4%, with the maximum use reported in face and neck products.[39] The rest of the ingredients with reported concentrations of use are used at a maximum of 0.4% in leave-on products or 1.2% in rinse-off products.

In some cases, no uses were reported in the VCRP, but concentration of use data were received from industry. For instance, although Eucalyptus Globulus Leaf Water has concentrations of use reported in several categories, there are no reported uses in the VCRP. It should be presumed there is at least one use in every category for which a concentration is reported.

One *Eucalyptus globulus*-derived ingredient, Eucalyptus Globulus Leaf/Twig Oil, had no uses reported in the VCRP or industry survey.

Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf Extract are reported to be used in products that are used near the eyes (e.g., eye lotions at up to 0.038% Eucalyptus Globulus Leaf Oil), and in products that may be ingested and come in contact with mucus membranes (e.g., mouthwashes and breath fresheners at up to 0.74% Eucalyptus Globulus Leaf Oil). Eucalyptus Globulus Leaf Oil is reported to be used in baby products (e.g., lotions, oils, powders, and creams at up to 0.00067%).

Additionally, some of the *Eucalyptus globulus*-derived ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Eucalyptus Globulus Leaf Oil is reported to be used in fragrance products at up to 0.4% and hair sprays at up to 0.002%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[40,41] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[42,43]

The cosmetic ingredient SD alcohol 38-B may be denatured with any of several essential oils, including *Eucalyptus globulus* oil.[1] Essential oils used as a denaturant must meet National Formulary (NF) specifications. [27 CFR 21.92] Specifications for eucalyptol (there are no specific standards for *Eucalyptus globulus* oil) include a specific gravity between 0.921 and 0.924, congealing temperature ≥ 0, distilling temperature range between 174 and 177°C, and no detectable phenols.[44]

The FDA lists "Eucalyptus globulus" as a non-traditional preservative for cosmetics in its Compliance Program Guidance Manual.[45]

None of the *Eucalyptus globulus*-derived ingredients named in the report are restricted from use in any way under the rules governing cosmetic products in the European Union.[46]

Non-Cosmetic

Food

In the U.S., Eucalyptus globulus is not generally used for human food, but as an additive. *Eucalyptus globulus* (*Eucalyptus globulus* Labill) leaves are food additives permitted for direct addition to food for human consumption as a flavoring agent. [21 CFR 172.510] Australian Aborigines use the roots as a source of water, and cook and eat the roots. Dried Eucalyptus globulus leaves are fed to horses, cattle, and sheep.[17]

As a chemical residue in food, an exemption from the requirement of tolerance is established for residues of *Eucalyptus globulus* oil in or on honey, honeycomb, and honeycomb when used at 2 g or less *Eucalyptus globulus* oil per hive, where the eucalyptus oil contains 80% or more eucalyptol. [40 CFR 180.1271]

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

The European Commission Scientific Committee on Food (SCF) concluded that the available toxicological studies

of eucalyptol are limited and inadequate to derive an acceptable daily intake (ADI).[47] However, the available animal data do not indicate a cause of concern associated with the daily intake from food, estimated from the small amount of information available.

Drugs

Eucalyptus globulus oil may be used in over-the-counter (OTC) products that treat nasal decongestion (in a lozenge or mouthwash), sinusitis, dermal irritation, fever blisters/cold sores, and poison ivy, oak and sumac, and in astringent and external analgesic drug products. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses. [21 CFR 310.545]

Eucalyptus globulus oil is permitted in combinations containing a nasal decongestant (1.2 to 1.3%) and an analgesic-antipyretic. [21 CFR 341.40]

Combinations containing camphor, menthol, and *Eucalyptus globulus* oil are permitted for use as active ingredients in cold, cough, allergy, bronchodilator, and anti-asthmatic OTC drugs when so labeled. [21 CFR 341.85]

Eucalyptus globulus oil has been used in OTC smoking deterrents, but there is a lack of adequate data to establish general recognition of the safety and effectiveness. [21 CFR 310.544]

Eucalyptus Globulus Leaf/Twig Oil is used orally to treat catarrh and coughs, and dermally as a rubefacient for treatment of rheumatic complaints in traditional medicine.[7] Other traditional medicinal uses that are not supported by experimentation or clinical data are treatment of cystitis, diabetes, gastritis, kidney disease (unspecified), neuralgia, laryngitis, leucorrhoea, malaria, pimples, ringworm, sinusitis, wounds, ulcers of the skin, urethritis and vaginitis.

Daily oral dosages of eucalyptus oil obtained by steam distillation range from 0.3 to 0.6 ml essential oil or equivalent preparations.[7] Examples of oral dosages include: one capsule of 100 to 200 mg, 2 to 5 times daily; one lozenge of 0.2 to 15.0 mg dissolved slowly in the mouth, every 30 to 60 min; and a mouthwash as 20 ml of a 0.91 mg/ml solution, gargled twice daily. The dose for administration by inhalation is 12 drops *Eucalyptus globulus* oil/150 ml boiling water. For dermal use, daily dosage consists of several drops or 30 ml of the essential oil in 500 ml lukewarm water rubbed into the skin; 5% to 20% of the essential oil in liquid and semisolid preparations; or 5% to 10% in hydroalcoholic preparations. Since there are no sufficient clinical data on children, the EMA states that oral use should be restricted to adolescents over 12 years of age and the cutaneous use should be limited to children over 4 years of age.[12]

It is recommended that the maximum adult daily oral dose is 600 mg and the maximum dermal use level is 20%.[6] It is noted that essential oils high in eucalyptol can cause central nervous system (CNS) and breathing problems in young children and recommend that the essential oil not be applied to or near the face of infants or children under ten years of age.

Health Canada restricts the use of *Eucalyptus globulus* leaf essential oil to 1% to 5% for use as a massage oil (covering more than 10% of the body surface), but may be used up to 25% for a local (less than 10% of the body surface) use.[48] The oil may also be used in aromatherapy to help relieve joint/muscle pain associated with sprain/strain/rheumatoid arthritis, to help relieve headache, and to help relieve colds/cough.

<u>Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)</u>

Eucalyptol may be used in lozenges and mouthwash that act as nasal decongestants, expectorants, dandruff/ seborrheic dermatitis/psoriasis drug products, and oral care products. Based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these preparations for the specified uses. [21 CFR 310.545]

Other

Eucalyptus globulus oil may be used in the manufacture of denatured alcohol, rum, and other denatured spirits. [27 CFR 21.65; 27 CFR 21.151]

TOXICOKINETIC STUDIES

Obtaining data on the toxicokinetics of unknown, complex mixtures, such as botanicals, would be impractical. However, if the compositions are well understood, including the concentrations of constituents, such studies may be useful.

Penetration Enhancement

In Vitro

In vitro dermal penetration enhancement studies of Eucalyptus Globulus Leaf Oil are summarized in Table 13.

Generally, dermal penetration of chlorhexidine digluconate (CHG) through human skin samples over 24 h increased in a manner dependent on the concentration of Eucalyptus Globulus Leaf Oil.[49] Eucalyptus Globulus Leaf Oil (82.9% eucalyptol) at 5% facilitated greater CHG skin penetration to the deeper layers of the skin (below 300 μm) and 10% (v/v) Eucalyptus Globulus Leaf Oil enhanced CHG skin penetration in the upper 900 μm. CHG, with and without 50% Eucalyptus Globulus Leaf Oil, was detected at negligible levels in the receptor compartment over 24 h, suggesting that CHG did not permeate through the full skin thickness, and was retained within the tissue.

When the dermal penetration enhancement of Eucalyptus Globulus Leaf Oil (2.5%, 5%, or 7.5%) was tested with 2,3,5,6-tetramethylpyrazine (TMP), the enhancement ratios for human skin were 3.38, 4.47, and 4.64, respectively. [50] The

TMP flux across the human chest skin with 5% Eucalyptus Globulus Leaf Oil was 17-fold greater (346.0 mg/cm^2/h) than the flux (20.1 mg/cm^2/h) of a saturated solution of TMP without the oil. The receptor fluid was water. When the ability of Eucalyptus Globulus Leaf Oil (80% to 85% eucalyptol) to enhance the dermal penetration of ketorolac was evaluated using a dermal patch across abdominal rat skin, the enhancement ratios were 1.80, 3.04, and 3.68 for 5%, 7.5%, and 10%, respectively.[51] Eucalyptus Globulus Leaf Oil increased the dermal penetration of 5-fluorouracil (5-FU) through rat skin when using 2-chamber diffusion cells; the enhancement ratios ranged from 58.49 to 82.55, depending on temperature (100°C through 140°C). [52]

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

Oral

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol undergoes oxidation in vivo with the formation of hydroxycineole which is excreted as glucuronide.[53,54] In rats, 2-hydroxycineole, 3-hydroxycineole, and 1,8-dihydroxycineol-9-oic acid were identified as main urinary metabolites. After oral administration to brushtail possums (*Trichosurus vulpecula*), *p*-cresol, 9-hydroxycineole, and cineol-9-oic acid were found in urine. Rabbits given eucalyptol by gavage excreted 2-exo- and 2-endo-hydroxycineole as well as 3-exo- and 3-endo-hydroxycineole in the urine.

A gavage study on the metabolism of eucalyptol from rosemary oil (4 µl, 20 µl or 40 µl rosemary oil containing 39% of eucalyptol; approximately equivalent to 52, 260 and 520 mg/kg eucalyptol, respectively) was conducted in NMRI mice (n = 5).[55,56] The rosemary oil was administered in an oil/water emulsion with 10% Tween 80 (0.3 ml). Controls were administered water and Tween 80. Groups of mice were killed and blood samples were collected at intervals over 90 min. There was rapid absorption and metabolism; blood concentrations of eucalyptol reached a peak 5 min. At the 52 mg/kg dose, the blood concentration of eucalyptol peaked at approximately 4.5 nl/g and then dropped to close to undetectable over 90 min. At 260 mg/kg, blood concentrations remained constant (between 7.0 and 10.1 nl/g) over the next 90 min, while at 520 mg/kg, the peak blood concentration peaked at 18.0 nl/g and then dropped to 60% of the maximum value after 10 min and remained in that range (9.1 to 12.2 nl/g) for the following 80 min. The slowing of the metabolism of eucalyptol at higher doses suggests saturation.

Inhalation

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

An inhalation study on the metabolism of eucalyptol from rosemary oil (0.1, 0.3, 0.4, 0.5, or 0.6 ml rosemary oil containing 39% of eucalyptol; approximately equivalent to 0.039, 0.117, 0.156, 0.195, or 0.234 ml eucalyptol) was conducted in NMRI mice (n = 20 to 30).[56] The mice (5/cage) were placed into air-tight cages in which rosemary oil was applied to filter paper and allowed to evaporate over an hour. The concentrations of rosemary oil and eucalyptol in the breathing air were 35 to 40 nl/ml and 13.7 to 15.6 nl/ml, respectively. Soda lime was used to remove the CO_2 and calcium chloride was used to remove humidity. Oxygen was replaced through an opening in the cage. After an hour, the mice were killed and blood samples were collected. Immediately after exposure, eucalyptol blood concentration was approximately 4.5, 10, 10, 12, and 16 nl/g after doses of 0.039, 0.117, 0.156, 0.195, or 0.234 ml eucalyptol/cage, respectively. In a second experiment, mice (n = 5 to 10) were exposed to 0.195 ml eucalyptol/cage. The mice were killed and blood samples were collected at intervals over 120 min. The eucalyptol blood concentration peaked at 16.2 nl/g and the elimination of the eucalyptol was biphasic. The concentration of eucalyptol dropped to approximately 5 nl/g in 30 min and approximately 1.5 nl/g at 120 min; there was a short half-life of 6 min during the first 10 min and a half-life of about 45 min during a second phase.

TOXICOLOGICAL STUDIES

Acute Dose Toxicity

Acute dermal and oral toxicity studies in animals that are summarized below are presented in Table 14.

Animal

Dermal

The dermal LD_{50} of Eucalyptus Globulus Leaf Oil was > 5000 mg/kg in rabbits.[10] There were no mortalities or signs of toxicity. The dermal LD_{50} of eucalyptol was > 5000 g/kg in rabbits.[54]

Oral

Eucalyptus Globulus Leaf Oil administered to mice (n = 10) by gavage had an oral LD_{50} of 3320 mg/kg.[10] The LD_{50} of an aqueous emulsion comprising 5% Eucalyptus Globulus Leaf Oil in mice was between 3 and 3.5 ml/kg.[57] In the 3.0 and 3.5 ml/kg groups, 1 of 6 and 4 of 6 mice died within 24 h of dosing, respectively. The oral LD_{50}s of Eucalyptus Globulus Leaf Oil were 3811.5 mg/kg,[58] 2334.3 mg/kg,[59] and 4400 mg/kg[10] in three different studies in rats. Mice orally administered a single dose of eucalyptol (500 mg/kg) had an increase in liver enzyme activity.[53] Reported oral LD_{50}s of eucalyptol in rats were 2480 mg/kg and 1560 mg/kg.[53,54]

Inhalation

Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf/Twig Oil

Male and female rabbits (n = 8 to 14) were lightly anesthetized and cannulated through the trachea.[60] A second collecting tube was also installed. Water vapor from a boiling water bath, mixed with ambient air and cooled to the body temperature of the rabbits, was inhaled directly into the rabbit's trachea. Respiratory tract fluid was collected for a control period of 2 to 4 h. The collecting tracheal tube was then replaced by a new empty tube, and *Eucalyptus globulus* oil (0.4 to 19,683 mg/kg body weight in ethyl alcohol; not known if leaf or leaf/twig oil) was added to the boiling water bath; respiratory tract fluid was collected from each rabbit for a subsequent 4 to 6 h or until the rabbit died. The highest dose caused deaths and significantly augmented the output of respiratory tract fluid; lower doses had no effect on the volume of respiratory tract fluid. Doses of 729 to 19,683 mg/kg produced increasingly lower values for the specific gravity of collected respiratory tract fluid and the two highest doses augmented the concentration of total solids and insoluble mucus. Doses which are considered to be in the therapeutic range for humans (3 to 243 mg/kg) were repeated in 2 successive years and in each instance they again produced no significant change in any parameter measured. Local irritation of the respiratory tract appeared after administration of the two highest doses.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Ovalbumin (OVA)-sensitized guinea pigs were exposed to aerosolized eucalyptol for 15 min. The eucalyptol (1 mg/ml) was aerosolized using a nebulizer into a box (21 x 20 x 30 cm).[61] Approximately 3 min later, the guinea pigs were exposed to aerosolized saline for 15 min. The control group was exposed to aerosolized saline for both exposures. The guinea pigs were killed 24 h later and inflammatory parameters such as tracheal responsiveness to carbachol, cytokine levels and myeloperoxidase activity on bronchoalveolar lavage fluid, as well as mucociliary clearance were evaluated. There were no differences in the numbers of eosinophils, neutrophils, lymphocytes and macrophages in the treatment group compared to controls. Cytokine levels (IL-1, TNFα, and IL-10) were also similar between the two groups.

Human

Oral

Eucalyptus Globulus Leaf Oil

The literature on the oral toxicity in humans of Eucalyptus Globulus Leaf Oil is generally old (yrs 1900 – 1965). The following is a summary of this information. The substances are referred to as eucalyptus, eucalyptus oil, and similar names, and little or no information on source plant parts, method of manufacture, or concentration/purity is provided.

The probable oral lethal dose for adult humans is 0.05 ml to 0.5 ml/kg.[11] The oral ingestion of Eucalyptus Globulus Leaf Oil may initially result in a burning sensation in the mouth, vomiting, diarrhea, and epigastric pain. Vomiting may be delayed for periods varying from minutes up to 4 h. Permanent sequelae following recovery from the acute phase have not been reported, although symptoms such as drowsiness, ataxia, and fatigue may occasionally persist for 1 to 2 weeks. Those subjects who suffered severe gastric irritation who promptly vomited recovered better but almost all made an uneventful recovery within 24 h. Recovery may be interrupted or reversed by bronchopneumonia. Death has occurred from within 15 min to 15 h after ingestion. One patient died 40 h after taking the oil, relapsing after apparent recovery.

Oral ingestion of Eucalyptus Globulus Leaf Oil, as low as approximately 5 ml, can affect the CNS (e.g., loss of consciousness, hypoventilation, depression of reflexes and convulsions), the gastrointestinal system (e.g., abdominal pain, vomiting and diarrhea), and the respiratory system (respiratory depression, dyspnea, pneumonitis, and bronchospasm). Gastrointestinal effects are frequently the initial effects, although drowsiness may occur in a few min and coma within 10 min. Urinary tract symptoms are only occasionally mentioned, and there is little evidence of direct nephrotoxicity following doses of up to 30 ml in an adult or older child; nephritis is rare but has been recorded. The subject may vomit while drowsy or unconscious and aspiration is a major risk. Tachycardia and a weak irregular pulse have been noted. Muscle weakness and ataxia may occur. Both mydriasis and miosis (more commonly) have occurred. CNS depression or vomiting has been delayed up to 4 h. Recovery is often within 24 h.[11]

Inhalation

Eucalyptus Globulus Leaf Oil

The literature on the inhalation toxicity in humans of Eucalyptus Globulus Leaf Oil is scarce, and the following is a summary of this information. The substances are referred to in the literature as eucalyptus, eucalyptus oil, and similar names with little or no information on source plant parts, method of manufacture, or concentration/purity.

Inhalation of eucalyptus oil either as liquid or aerosol may result in pneumonitis.[11] Inhalation of vapor may be used medicinally and there are no data available on toxicity by this route. However, respiratory problems include bronchospasm, tachypnea, pulmonary edema, respiratory depression, and pneumonitis following aspiration of the oil. Eucalyptus oil inadvertently given intranasally has caused irritated nasal mucous membranes.

Short-Term Toxicity Studies

No published short-term dermal or inhalation toxicity studies were discovered and no unpublished data were

submitted.

Oral

Short-term oral toxicity studies summarized below are presented in Table 15.

Eucalyptus Globulus Leaf Extract

Aqueous Eucalyptus Globulus Leaf Extract (2000 mg/kg/d) orally administered (route not specified) to mice for 10 days caused no mortalities, but did cause general weakness and decrease in physical activity.[62] There were significant neurodegenerative changes, including a decrease in size and number of neurons in the cerebral cortex.

Aqueous Eucalyptus Globulus Leaf Extract (0, 80, 100, or 120 mg/kg) administered by gavage to rats for 7 days caused a significant increase in the level of malondialdehyde (MDA) in the liver of all treatment groups and in the serum of the 120 mg/kg group.[63] In a 42-day drinking water study in rats of an aqueous/ethanol Eucalyptus Globulus Leaf Extract (1 g/l), the rats consumed the equivalent of 130 mg dry leaves/day. Consuming the extract caused no changes in creatinine, urea, protein, or uric acid in the blood.[64]

Eucalyptus Globulus Leaf Oil

Eucalyptus Globulus Leaf Oil (0, 1.5, or 2.0 ml/kg/day), administered by gavage to mice for 12 weeks, caused no signs of toxicity and no mortalities for either treatment group; however, kidney effects (pyknosis of renal tubular epithelial cells and widening of tubular lumen) and liver effects (pyknosis, vacuolations of hepatocytes, and focal necrosis) were observed in the high-dose group at necropsy.[57]

In a combined repeated dose and reproductive/developmental study, Eucalyptus Globulus Leaf Oil (0, 100, 300, or 1000 mg/kg/day) orally administered by gavage to rats caused transient signs of reduced activity and unsteady muscle reactions, multiple changes in blood chemistry, hyaline droplet nephropathy in the kidneys of male rats, and centrilobular hepatocytic hypertrophy in the livers of male rats and an increase in glycogenic vacuolation in the livers of female rats.[10] Males were treated starting from 2 weeks before mating for at least 5 weeks; females were treated from 2 weeks before mating until lactation day 6. The no-observed-adverse-effect level (NOAEL) for males was 1000 mg/kg/day based on hyaline droplet nephropathy at all dose levels; however this response is considered to be rat specific and to have no counterpart in humans. The NOAEL for females was 300 mg/kg/day based on effects on body weight and feed consumption.

Eucalyptus Globulus Leaf Oil (100, 300, or 1000 mg/kg/day) orally administered by gavage to rats for 2 weeks caused no mortalities.[10] The lowest-observed-adverse-effect level (LOAEL) and NOAEL in female rats could be considered as 300 and 100 mg/kg/day, respectively, based on the clinical signs at 300 and 1000 mg/kg/day and increased liver weight at 1000 mg/kg/day. Since dose-related increases in liver and kidney weights were observed in males at all doses, no NOAEL could be identified for the male rats in this study. The LOAEL in male rats could be considered as 100 mg/kg/day.

Eucalyptus Globulus Leaf Oil (0 or 233 mg/kg/dose in corn oil) administered by gavage every 3 days for 30 days caused an increase in white blood cell (WBC) counts and a decrease in hemoglobin concentration and platelets count in both blood samples, and relatively moderate pathological changes in the liver as congestion of the blood vessels in the portal area associated with inflammatory infiltration.[59]

Eucalyptus Globulus Leaf Oil (0, 396, 792, and 1188 mg/kg/day) administered by gavage for 30 days caused no clinical signs, but changes to aspartate transaminase (increased), creatinine (increased), and glucose (decreased) in serum chemistry in the mid- and high-dose groups were observed.[58] In the livers of the experimental groups, the central veins were extended with hyperemia and varying degrees of vacuolar degeneration of hepatocytes were observed.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol (150, 300, 600 and 1200 mg/kg/day) administered by stomach tube or in encapsulated form in feed (600 to 5607 mg/kg/day for males and 705 to 6777 mg/kg/day for females) to mice for 28 days caused increased relative liver weights in all but the lowest dose in feed and a minimal hypertrophy of centrilobular hepatocytes in both sexes, especially in the two highest dose levels.[53]

Eucalyptol (150, 300, 600 and 1200 mg/kg) administered by stomach tube or in encapsulated form in feed (381 to 3342 mg/kg/day for males and 353 to 3516 mg/kg/day for females) to rats for 28 days caused a dose-dependent decrease of body weight gain starting at 600 mg/kg and an absence of a normal degree of hepatic centrilobular cytoplasmic vacuolization was observed in male rats.[53] Eucalyptol (0, 500, or 1000 mg/kg/day) orally administered by gavage to male rats for 28 days caused no changes in the brain, but minor focal infiltration of mononuclear cells in liver was observed in both treatment groups and a dose-related accumulation of eosinophilic protein droplets containing α_{2u}-globulin in the cytoplasm of proximal tubular epithelial cells was observed in kidneys.[53]

Subchronic Toxicity Studies

No published subchronic toxicity studies were discovered and no unpublished data were submitted.

Chronic Toxicity Studies

Oral

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

A toothpaste containing eucalyptol (0, 8 and 32 mg eucalyptol/kg/day; 1 ml toothpaste) was administered by gavage to pathogen-free CFLP mice (n = 52) 6 days/week for 80 weeks, followed by 16 and 24 weeks of rest.[53] No treatment-related effects on body weights, feed consumption, survival, weight of adrenals, kidneys, liver, lungs or spleen, on the microscopic appearance of brain, lungs, liver and kidneys, and on the tumor incidence were observed.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Oral

Eucalyptus Globulus Leaf Oil

In a combined repeated dose and reproduction/developmental study, Eucalyptus Globulus Leaf Oil (100, 300, or 1000 mg/kg/day; in corn oil) was administered by gavage to Crl:CD(SD) rats (n = 10/sex).[10] The study was conducted in accordance with Organisation of Economic Co-operation and Development Guidelines (OECD GL) 422. Males were treated starting from 2 weeks before mating for at least 5 weeks; females were treated from 2 weeks before mating until lactation day 6. The adults and offspring rats were then killed and necropsied. [For results related to short-term toxicity, see Short-Term Toxicity Studies]

There were no adverse effects detected in reproductive assessments on estrous cycles, mating performance and fertility, gestation length and parturition observations, and reproductive performance. There were no significant effects of the Eucalyptus Globulus Leaf Oil on litter size, offspring survival indices or sex ratio. The body weights of offspring of the treatment groups at birth were similar to that of the control group. However, body weight gains of male and female offspring in the 1000 mg/kg/day group were low (approximately 27% to 28% lower than the control group), and by day 4 after parturition, absolute body weights of this group were also significantly lower than that of the control group. A slightly increased incidence of "cold to touch" was observed in litters in the 1000 mg/kg/day group. At microscopic examination, there were no findings attributed to treatment for offspring that died and were examined during the experiment or were killed and examined at the end of the experiment.

Under the test condition, the NOAEL for the females was considered to be 300 mg/kg/day for systemic toxicity, based on lower body weight gain and feed consumption during gestation. The authors stated that both findings appeared to be associated with pregnancy status. It was not possible to link this effect to the taste of the substance since females had shown a significant duration of normal body weight and feed performance prior to Day 6 of gestation and after birth of the pups. These latter observations appeared to indicate recovery in females. The NOAEL for developmental toxicity was 300 mg/kg/day, which was based on lower offspring body weight gain, and clinical signs (pups cold to touch) that were only observed in the 1000 mg/kg/day group. This effect may be associated with test material entering the milk. The authors note that fat soluble test materials have a higher chance of becoming incorporated in the milk and Eucalyptus Globulus Leaf Oil is fat soluble. A NOAEL at 300 mg/kg/day was determined for systemic effects in the offspring based on the magnitude of the weight reduction, which was quite high. The effects on offspring body weight were not selective and have been observed at a dose producing maternal toxicity, and therefore the substance was not considered to be a selective reproductive toxicant. The NOAEL for reproductive toxicity was 1000 mg/kg/day, since no adverse effects were observed for any reproductive parameters.

GENOTOXICITY STUDIES

In Vitro

Genotoxicity studies are summarized in Table 16.

Eucalyptus Globulus Leaf Extract was not mutagenic, with and without metabolic activation, at up to 5000 µg/plate in an in vitro mammalian cell gene mutation test using mouse lymphoma cells.[10] Eucalyptus Globulus Leaf Oil was not genotoxic in a bacterial reverse mutation assay using *Salmonella typhimurium* and *Escherichia coli* at up to 5000 µg/plate, with and without metabolic activation.[10] Eucalyptus Globulus Leaf Oil was not genotoxic in an in vitro mammalian chromosome aberration test using human lymphocytes and an in vitro mammalian cell gene mutation test using mouse lymphoma L5178Y cells.[10] Eucalyptus Globulus Leaf Oil at 0.12 and 0.25 µl/ml was found to increase the mitotic instability of the original diploid strain and the number of diploid mitotic recombinants of *Aspergillus nidulans*.[12] The genotoxicity of the oil was associated with the induction of mitotic crossing-over or with oil-broken chromosomes.

Eucalyptol (concentration not specified) was not mutagenic in Ames assays, with and without metabolic activation. Eucalyptol (concentrations not specified) was not mutagenic to Chinese hamster ovary (CHO) cells in a chromosome aberration assay and a sister chromatid exchange assay, with and without metabolic activation. Eucalyptol (concentration not specified) was not mutagenic in rec assays using *Bacillus subtilis*.[53]

CARCINOGENICITY STUDIES

No published carcinogenicity studies were discovered and no unpublished data were submitted on the *Eucalyptus globulus* (eucalyptus)-derived ingredients in this safety assessment.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

A toothpaste containing eucalyptol (0, 8, or 32 mg/kg/day) was administered by gavage to male pathogen-free CFLP mice (n = 52) for 80 weeks.[65] The controls were administered nothing (n = 52) or the toothpaste base (n = 260). The mice were observed daily, and were weighted weekly for the first 6 weeks of the study then every 2 weeks. Mice found dead were necropsied. At week 80, the mice were killed and organ weights for the kidneys, adrenals, lungs, liver, and spleen were examined. All macroscopically identified tumors were examined histopathologically. Tissues from the kidneys, liver, lungs, and brain were also examined histopathologically. All of the mice in the low-dose group and 47 of the mice in the high-dose group were necropsied. There were no differences between the test groups and the control and vehicle control groups in the incidence or severity of tumors of the organs or the presence of malignant lymphoma.

Tumor Promotion

Dermal

Eucalyptus Globulus Leaf Oil

Eucalyptus Globulus Leaf Oil (neat; 0.25 ml) was tested for tumor promotion in mice.[29] A single application of 9,10-dimethyl-1,2-benzanthracene (DMBA) was administered to the clipped backs of 8-week-old mice (n = 14). The dose of DMBA (225 µg; 2 ml in acetone) was described as being sufficient to initiate skin tumor formation but, generally, inadequate for complete carcinogenesis. After three weeks, Eucalyptus Globulus Leaf Oil was administered to the backs of the mice once per week for 33 weeks. Dorsal hair was removed as necessary. The control group (n = 13) received the DMBA treatment alone. Papillomas were observed on 4 of 14 mice in the treatment group and 0 of 13 in the control group.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation and sensitization studies are summarized in Table 17.

Irritation

Eucalyptol (100%) was predicted to be a dermal non-irritant in an EpiSkin™ assay.[66] Eucalyptus Globulus Leaf Oil (neat) was not dermally irritating to hairless mice,[67] but was slightly (neat; 5000 mg/kg) or moderately (intact and abraded skin) irritating to rabbits.[10,67] In an open mouse ear assay of eucalyptol using albino mice (n = 10), the irritant dose in 50% of test individuals (ID_{50}) was 1.008 g/5 l acetone (0.0202%).[10] Eucalyptol (100%) administered to intact and abraded skin of rabbits for 24 h under occlusion was not irritating.[54] Eucalyptus Globulus Leaf Oil (10% in petrolatum)[67] and eucalyptol (16% in petrolatum) were not irritating to human subjects (n = 25).[54]

Sensitization

Eucalyptol (25% and 50% v/v) tested in a local lymph node assay (LLNA) using female mice (n = 5) was considered to be a sensitizer at 100%, but not at 25% and 50%.[66] In a Draize test using Harley albino guinea pigs (n = 10), eucalyptol (0.25%; 0.1 ml) was not irritating or sensitizing.[68]

In multiple human repeated insult patch tests (HRIPT), cosmetic formulations containing Eucalyptus Globulus Leaf Oil (up to 0.5%) were found to be non-irritating.[69,70] In a maximization assay in human subjects (n = 25), Eucalyptus Globulus Leaf Oil (10% in petrolatum) produced no sensitization reactions.[67]

PHOTOSENSITIZATION/PHOTOTOXICITY

In Vitro

Eucalyptus Globulus Leaf Oil

An in vitro photohemolysis test (human erythrocyte suspensions) was used to evaluate the phototoxicity of Eucalyptus Globulus Leaf Oil (0.001%, 0.01%, or 0.1% in alcohol).[71] The ultraviolet A (UVA)-rich light source was a UVASUN 5000 lamp (320 to 460 nm; 42 mW/cm^2) and the ultraviolet B (UVB)-rich light source was a lamp with TL 20 W/12 light bulbs (between 275 and 365 nm; 1 mW/cm^2 [UVB] and 0.4 mW/cm^2 [UVA]). There was no hemolysis observed under the test conditions. The authors concluded that the test substance is not expected to be photosensitizing.

Human

In the Draize-Shelanski HRIPT (n = 52) described earlier of a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%; no dose specified), the backs of subjects were exposed to an UV light (wavelength included 3600°) at a distance of 12" (30.48 cm) for 1 min. These exposures were after the first, fourth, seventh, and tenth induction patches and the challenge patch were read.[69] The test sites were read 48 h after each application. Induction applications were rotated between three sites on the back of each subject; therefore, irradiation was administered to the same test site every third patch. The challenge was administered to a naïve site. There were no signs of photosensitization in any subject at any reading. [See Sensitization section for sensitization data.]

In the Schwartz-Peck prophetic patch test described earlier for a skin cream containing Eucalyptus Globulus Leaf Oil (0.1%) (n = 101), photosensitization potential was evaluated at the occlusive patch sites.[69] The test sites were exposed to an UV light (wavelength included 3600°, at a distance of 12" (30.48 cm) for 1 min) 48 h after the second patch was administered. The test sites were read 48 h after the UV exposure. There were no signs of photosensitization in any subject.

[See Sensitization section for sensitization data.]

OCULAR IRRITATION STUDIES

In Vitro

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol (100%; 0.75 ml) was tested in a bovine corneal opacity and permeability assay.[66] Eucalyptol was not considered to be an ocular corrosive or severe irritant.

Animal

Eucalyptus Globulus Leaf Oil

In an eye irritation study performed in accordance with OECD GL 405 (acute eye irritation/corrosion), undiluted Eucalyptus Globulus Leaf Oil (0.1 ml) was instilled into the right eye of a single New Zealand White (Hsdlf:NZW) rabbit.[10] After consideration of the ocular responses produced in the first treated animal, two additional animals were treated. The eyes were not rinsed after administration. The left eye of each rabbit served as control. Animals were observed 1, 24, 48, and 72 h after dosing under a light source from a standard ophthalmoscope. The reactions in the conjunctiva (redness, chemosis and discharge), the iris and the cornea (opacity and area involved) were scored according to the Draize scale. No corneal or iridial effects were observed during the study. Moderate conjunctival irritation was noted in all treated eyes 1 h after treatment with minimal conjunctival irritation noted at the 24- and 48-h observations. All treated eyes appeared normal at 72 h. Mean scores calculated for each rabbit over 24, 48, and 72 h were 0.0/0.0/0.0 for cornea opacity, 0.0/0.0/0.0 for iris lesions, 0.7/1.0/0.7 for redness of the conjunctivae, and 0.7/0.7/0.7 for chemosis. One rabbit had no body weight gain and two rabbits showed expected gain in body weight during the study.

CLINICAL STUDIES

Retrospective and Multicenter Studies

Dermal

Dermal retrospective and multicenter studies of Eucalyptus Globulus Leaf Oil are summarized in Table 18.

In a retrospective study of dermatologic patients during the years 2010 to 2015, 1 of 22 subjects was sensitized with Eucalyptus Globulus Leaf Oil.[2] In a retrospective study of dermatologic patients during the years 2000 to 2007, 4 of 679 (0.6%) had positive results in sensitization studies with Eucalyptus Globulus Leaf Oil (2%). Two of the subjects were scored with a +/- reaction, 2 with a + reaction, and 1 with a ++ reaction. In a retrospective study of dermatologic patients during the years 2000 to 2009, of the 6680 subjects that were tested for sensitization to Eucalyptus Globulus Leaf Oil, 0.24% had positive reactions.[72] In a cross-sectional study conducted in Belgium (2000 to 2009) of 301 subjects having had reactions to fragrance mixes, a reaction was confirmed to “eucalyptus oil” in 1 of 23 bath and shower products and 1 in 88 skin care products.[73]

In sensitization tests (method not reported) of patients (n = 5315) in London with dermatitis, 1 subject had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified).[74] In patch tests of subjects (n = 96) with dermatitis and/or eczema, 5 subjects had positive reactions (2 scored with a +/- reaction, 2 with a + reaction, and 1 with a ++ reaction) to Eucalyptus Globulus Leaf Oil (2% in petrolatum).[75]

In sensitization tests (method not clear) of patients (n = 200) in Poland with dermatitis, 3 subjects had positive reactions to Eucalyptus Globulus Leaf Oil (concentration not specified).[76] When this study was continued on additional patients (n = 450) with dermatitis, 5 subjects had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified).[77]

Oral

In a respective study of accidental ingestion of Eucalyptus Globulus Leaf Oil by children in Australia (n = 109), 41% had no effects, 30% resulted in minor poisoning, 25% resulted in moderate poisoning, and 3% resulted in severe and life threatening poisoning.[78] Of those where the volume was known, 17 ingested 100% oil and 10 ingested inhalation preparations. All of those children who had been given Eucalyptus Globulus Leaf Oil by a parent or guardian by mistake ingested a mean volume of 2.2 mL (range, 0.2 - 7.5ml). There were no deaths. Adverse effects included vomiting, depression of conscious state, ataxia, pulmonary disease, miosis, and abdominal pain.

Case Reports

Case reports of adverse reactions to dermal, oral, and inhalation exposure to Eucalyptus Globulus Leaf Oil are presented in Table 19.

Dermal effects ranged from none to eczema, erythematous macular lesions, papules and vesicles, and/or pruritus.[79-84] Oral effects included esophageal pain, gasping for breath, restlessness, dyspnea, weak pulse, vomiting, drowsiness, and convulsions.[11,83,85-88] Inhalation effects included strong characteristic smell on the breath, coughing, chest tightness, dyspnea, hoarseness, and wheezing.[83,89]

In children, inhalation effects included nasal and epigastric burning, nausea, vomiting, dizziness, muscular

weakness, miosis, tachycardia, and a feeling of suffocation. Cyanosis, delirium, and convulsions may be exhibited, especially in infants.[90]

SUMMARY

This is a review of the safety of 6 *Eucalyptus globulus*-derived ingredients as used in cosmetics. According to the wINCI *Dictionary*, the reported functions of the *Eucalyptus globulus*-derived ingredients include abrasive, fragrance ingredient, and skin-conditioning agent (miscellaneous and occlusive). Eucalyptus Globulus Leaf/Twig Oil and Eucalyptus Globulus Leaf Water are reported to function only as fragrance ingredients.

Because Eucalyptus Globulus Leaf Oil consists of not less than 70% (w/w) eucalyptol, relevant toxicity data on eucalyptol are included as supporting information in this safety assessment. Other reported main components of Eucalyptus Globulus Leaf Oil include α-pinene (9.22% to 24.6%), globulol (0.819% to 2.817%), and β-pinene (0.217% to 1.237%), depending on the origin of the plant.

According to VCRP survey data received in 2018, Eucalyptus Globulus Leaf Oil is reported to be used in 433 formulations (214 leave-on formulations, 160 rinse-off formulations, and 59 formulations that are diluted for the bath). Eucalyptus Globulus Leaf Extract is reported to be used in 77 formulations and Eucalyptus Globulus Leaf Powder is reported to be used in 2 formulations. The VCRP included ingredients with the non-INCI name "eucalyptus" (42 reported uses) and "eucalyptus extract" (11 reported uses). The results of the concentration of use survey conducted by the Council in 2017 and 2018 indicate Eucalyptus Globulus Leaf Water is used at up to 1.4% in face and neck products. The rest of the ingredients with reported concentrations of use are used at 1.2% or less. There were no uses reported to the VCRP or industry survey for Eucalyptus Globulus Leaf/Twig Oil.

In in vitro studies, Eucalyptus Globulus Leaf Oil has been shown to increase the dermal penetration of CHG, TMP, ketorolac, and 5-FU.

Orally administered eucalyptol undergoes oxidation in vivo with the formation of hydroxycineole which is excreted as glucuronide. In rats, urinary metabolites were 2-hydroxycineole, 3-hydroxycineole, and 1,8-dihydroxycineol-9-oic acid. In mice, eucalyptol is rapidly absorbed and metabolized; when inhaled, elimination was biphasic.

The dermal LD50 for Eucalyptus Globulus Leaf Oil and eucalyptol was > 5000 mg/kg in rabbits. The oral LD_{50} for Eucalyptus Globulus Leaf Oil was 3320 mg/kg in male mice. At doses at and above 2.5 ml/kg, toxic effects were observed; the clinical signs disappeared in surviving mice. In rats, the oral LD_{50} for Eucalyptus Globulus Leaf Oil was reported as 3811.5 mg/kg in one study and 4400 mg/kg in another study. Reported oral LD_{50}s of eucalyptol in rats were 2480 mg/kg and 1560 mg/kg.

Rabbits inhaling water vapor containing Eucalyptus Globulus Leaf Oil died; the output of respiratory tract fluid was significantly augmented at 19,683 mg/kg. OVA-sensitized guinea pigs exposed to aerosolized eucalyptol for 15 min showed no pulmonary effects.

The probable oral lethal dose of Eucalyptus Globulus Leaf Oil for adult humans is 0.05 ml to 0.5 ml/kg. The oral ingestion of Eucalyptus Globulus Leaf Oil may initially result in a burning sensation in the mouth, vomiting, diarrhea, and epigastric pain. In humans, inhalation of Eucalyptus Globulus Leaf Oil, either as liquid or aerosol, may result in pneumonitis.

An aqueous Eucalyptus Globulus Leaf Extract (2000 mg/kg/d) orally administered to mice for 10 days caused no adverse effects. In short-term oral toxicity studies, Eucalyptus Globulus Leaf Extract administered to rats showed hepatic effects in some studies (starting at 100 mg/kg) and none in another (1 g/l in drinking water for 42 days).

In short-term oral toxicity studies, Eucalyptus Globulus Leaf Oil and eucalyptol caused hepatic effects in both mice and rats. Oral administration of Eucalyptus Globulus Leaf Oil for 12 weeks caused renal and hepatic effects at 2.0 ml/kg/day in mice, but not at 1.5 ml/kg/day. In rats, hepatic effects were observed starting at 233 mg/kg Eucalyptus Globulus Leaf Oil. Eucalyptol (150 to 1200 mg/kg/day) administered by stomach tube or in feed (600 to 5607 mg/kg/day for males and 705 to 6777 mg/kg/day for females) to mice for 28 days caused increased relative liver weights in all but the lowest dose in feed. Eucalyptol (500 or 1000 mg/kg/day) orally administered for 28 days to rats caused minor focal infiltration of mononuclear cells in livers in both treatment groups. There were no treatment-related effects in mice orally administered a toothpaste containing up to 32 mg eucalyptol/kg/day for 80 weeks.

In a reproduction/developmental study of Eucalyptus Globulus Leaf Extract administered to rats, the NOAEL for the females was 300 mg/kg/day for systemic toxicity, based on lower body weight gain and feed consumption during gestation. The NOAEL for developmental toxicity was 300 mg/kg/day, which was based on lower offspring body weight gain, and clinical signs that were only observed in the 1000 mg/kg/day group. However, a NOAEL at 300 mg/kg/day was determined for systemic effect in the offspring based on the magnitude of the weight reduction. The NOAEL for reproductive toxicity was 1000 mg/kg/day, since no adverse effects were observed.

Eucalyptus Globulus Leaf Extract was not mutagenic, with and without metabolic activation, at up to 5000 µg/plate in an in vitro mammalian cell gene mutation test. Eucalyptus Globulus Leaf Oil was not genotoxic in a bacterial reverse mutation assay (up to 5000 µg/plate), in an in vitro mammalian chromosome aberration test (up to1000 µg/ml) and an in vitro mammalian cell gene mutation test using mouse lymphoma L5178Y cells (up to 300 µg/ml). However, Eucalyptus Globulus Leaf Oil at 0.12 µl/ml was found to increase the mitotic instability of the original diploid strain and the number of diploid mitotic recombinants of *A. nidulans.* Eucalyptol was not mutagenic in Ames assays, to CHO cells in a chromosome aberration assay, a sister chromatid exchange assay, and in rec assays using *B. subtilis*.

There were no differences between the test groups and the untreated control and vehicle control groups in the incidence or severity of tumors of the organs or the presence of malignant lymphoma in male mice administered a toothpaste containing eucalyptol (0, 8, or 32 mg/kg/day) for 80 days. In mice first treated with a single dermal dose of DMBA then dermally administered 0.25 ml Eucalyptus Globulus Leaf Oil (neat) weekly for 33 weeks, papillomas were observed in 4 of 14 mice. None of the 13 control mice had papillomas.

Eucalyptol (100%) was predicted to be a non-irritant in an EpiSkin™ assay. Eucalyptus Globulus Leaf Oil (neat) was not dermally irritating to hairless mice, but was slightly (neat; 5000 mg/kg) or moderately (intact and abraded skin) irritating to rabbits. In an open mouse ear assay of eucalyptol using albino mice (n = 10), the ID_{50} was 1.008 g/5 l acetone (0.0202%). Eucalyptol (100%) administered to intact and abraded skin of rabbits for 24 h under occlusion was not irritating. Eucalyptus Globulus Leaf Oil (10% in petrolatum) and eucalyptol (16% in petrolatum) were not irritating to human subjects.

Eucalyptol tested in an LLNA using female mice (n = 5) had an EC3 of 65.90%, thus was predicted to be a sensitizer at 100%, but not at 50%. In a Draize test using Harley albino guinea pigs (n = 10), eucalyptol (0.25%; 0.1 ml) was not irritating or sensitizing. In multiple HRIPTs, cosmetic formulations containing Eucalyptus Globulus Leaf Oil (up to 0.5%) were found to be non-irritating. In a maximization assay in human subjects (n = 25), Eucalyptus Globulus Leaf Oil (10% in petrolatum) produced no sensitization reactions.

In an in vitro photohemolysis test, Eucalyptus Globulus Leaf Oil (neat) was not predicted to be photosensitizing. In combined sensitization and photosensitization tests, there were no signs of photosensitization in two photosensitization patch tests of a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%).

Eucalyptol (100%) was not considered to be an ocular corrosive or severe irritant when tested in a bovine corneal opacity and permeability assay. In rabbits, Eucalyptus Globulus Leaf Oil (1 ml) caused moderate conjunctival irritation in all treated eyes 1 h after treatment. Conjunctival irritation was minimal at 24- and 48-h and all treated eyes appeared normal at 72 h.

In a retrospective study of dermatologic patients during the years 2010 to 2015, of the 22 subjects that were tested for sensitization to Eucalyptus Globulus Leaf Oil, 1 tested positive. In a retrospective study of dermatologic patients during the years 2000 to 2007, 4 of 679 (0.6%) had positive results for Eucalyptus Globulus Leaf Oil (2%). In a retrospective study of dermatologic patients during the years 2000 to 2009, of the 6680 subjects that were tested for sensitization to Eucalyptus Globulus Leaf Oil, 0.24% had positive reactions. In a cross-sectional study conducted in Belgium (2000 to 2009) of 301 subjects having had reactions to fragrance mixes, a reaction was confirmed to "eucalyptus oil" in 1 of 23 bath and shower products and 1 in 88 skin care products. In sensitization tests of patients (n = 5315) in London with dermatitis, 1 subject had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified).

In a respective study of accidental ingestion of Eucalyptus Globulus Leaf Oil by children, adverse effects included vomiting, depression of conscious state, ataxia, pulmonary disease, miosis, and abdominal pain. In case reports of exposure to Eucalyptus Globulus Leaf Oil, dermal effects ranged from none to eczema, erythematous macular lesions, papules and vesicles, and/or pruritus. Oral effects included esophageal pain, gasping for breath, dyspnea, weak pulse, vomiting, drowsiness, and convulsions. Inhalation effects included coughing, chest tightness, dyspnea, hoarseness, and wheezing. In children, inhalation effects included nasal and epigastric burning, nausea, vomiting, dizziness, muscular weakness, miosis, tachycardia, and a feeling of suffocation. Cyanosis, delirium, and convulsions may be exhibited, especially in infants.

DISCUSSION

The Panel examined the data on oral, dermal and inhalation toxicity, ocular and dermal irritation, sensitization, reproduction, genotoxicity, and phototoxicity. The Panel also considered toxicity data on eucalyptol, a large component of Eucalyptus Globulus Leaf Oil and Eucalyptus Globulus Leaf/Twig Oil. The Panel noted the lack of toxicity and the lack of irritation and sensitization at relevant concentrations of these ingredients. The genotoxicity studies and the carcinogenicity study on eucalyptol were negative and gave no cause for concern.

Case studies described adverse effects following both oral and dermal administration. Instances were reported in which persons who consumed *Eucalyptus globulus* oil became very ill following oral ingestion, with respiratory difficulties (e.g., pneumonitis, pulmonary edema, and bronchopneumonia) reported. The Panel noted that these incidents resulted from bolus doses and exposure was much greater than that expected with cosmetic use. Also, the Panel believes that the cause of the respiratory difficulties was aspiration of vomitus and not directly caused by *Eucalyptus globulus* oil. The adverse effects in the dermal case studies resulted from administration of *Eucalyptus globulus* oil at far greater concentrations than that found in cosmetics. Oral ingestion, and the circumstances of the dermal administration of *Eucalyptus globulus* oil, would lead to a rapidly increased concentration of the oil in the blood that would far exceed what would result from the use of cosmetic formulations containing Eucalyptus Globulus Leaf Oil. These high concentrations in the blood could not be obtained through cosmetic use.

The composition data are robust for Eucalyptus Globulus Leaf Extract and Eucalyptus Globulus Leaf Oil. The data on these two ingredients provide substantial insight into the other ingredients for which composition data are not as robust, and enable consideration of the entire group.

The sensitization data on Eucalyptus Globulus Leaf Oil at 10% and eucalyptol at 16% in humans provided evidence that sensitization at reported concentrations (maximum of 1.4%) of use should not be expected. This is supported by a LLNA and a Draize test in guinea pigs.

There is the possibility of the presence of potential sensitizers in the *Eucalyptus globulus*-derived ingredients because these constituents exist in the plant. However, if these constituents were to be present in a cosmetic formulation, the concentrations would be far below the level of toxicological concern. The impurity specifications of trade name mixtures containing Eucalyptus Globulus Leaf Extract, the lack of dermal irritation in human patch testing, the lack of sensitization in HRIPTs, and the small proportion of positive results in retrospective studies involving relatively large numbers of individuals assured the Panel that dermal irritation and sensitization from these constituents is not a significant concern in the cosmetic use of *Eucalyptus globulus*-derived ingredients. Relevant data on eucalyptol supported this supposition. However, because final product formulations may contain multiple botanicals, each possibly containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For *Eucalyptus globulus*-derived ingredients, the Panel was concerned about the presence of geraniol, limonene, and linalool in cosmetics, which could result in sensitization. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects. The Panel noted that IFRA standards have been developed, and published, so as to prevent adverse effects for several such constituents (Table 10).

The Panel expressed concern about pesticide residues, heavy metals, and substances from plants of other species (weeds) that may be present in botanical ingredients. To address these concerns, the cosmetics industry should continue to use current good manufacturing practices (cGMP) to limit impurities.

The Panel recognized that Eucalyptus Globulus Leaf Oil can enhance the penetration of other ingredients through the skin (e.g., chlorhexidine). The Panel cautioned that care should be taken in formulating cosmetic products that may contain this ingredient in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

The Panel discussed the issue of incidental inhalation exposure from formulations that may be aerosolized (e.g., colognes and toilet waters at up to 0.4%). The acute inhalation data and historic case studies available suggest potential respiratory effects at doses much greater than would be used in cosmetics. The Expert Panel believes that the sizes of a substantial majority of the particles of aerosol and other spray products are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation, and thus, droplets/particles from cosmetic products would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for *Eucalyptus globulus*-derived ingredients to cause systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, and genotoxicity. They noted the lack of systemic toxicity at high doses in acute oral exposure studies (in contrast to old case reports), minimal or no irritation or sensitization in tests of dermal exposure at relevant concentrations, and the absence of genotoxicity in multiple assays. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

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

Eucalyptus Globulus Leaf
Eucalyptus Globulus Leaf Extract
Eucalyptus Globulus Leaf Oil
Eucalyptus Globulus Leaf Powder
Eucalyptus Globulus Leaf/Twig Oil*
Eucalyptus Globulus Leaf Water

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

TABLES

Table 1. Definitions and functions of *Eucalyptus globulus*-derived ingredients in this safety assessment.[1]

Ingredient	Definition	Function(s)
Eucalyptus Globulus Leaf Oil 8000-48-4	Eucalyptus Globulus Leaf Oil is the volatile oil obtained from the leaves of *Eucalyptus globulus* and other species of *Eucalyptus.*	Fragrance ingredient; skin-conditioning agent - miscellaneous
Eucalyptus Globulus Leaf	Eucalyptus Globulus Leaf [is] the leaves of *Eucalyptus globulus.*	Skin-conditioning agent - miscellaneous
Eucalyptus Globulus Leaf Extract 84625-32-1	Eucalyptus Globulus Leaf Extract is the extract of the leaves of *Eucalyptus globulus.*	Skin-conditioning agent – miscellaneous, Skin-conditioning agent - occlusive
Eucalyptus Globulus Leaf Powder	Eucalyptus Globulus Leaf Powder is the powder obtained from the dried, ground leaves of *Eucalyptus globulus.*	Abrasive
Eucalyptus Globulus Leaf/Twig Oil	Eucalyptus Globulus Leaf/Twig Oil is the volatile oil obtained from the leaves and twigs of *Eucalyptus globulus.*	Fragrance ingredient
Eucalyptus Globulus Leaf Water	Eucalyptus Globulus Leaf Water is an aqueous solution of the steam distillate obtained from the leaves of *Eucalyptus globulus.*	Fragrance ingredient

Table 2. Chemical and physical properties of *Eucalyptus globulus*-derived ingredients.

Property	Value	Reference
Eucalyptus Globulus Leaf		
Odor	Aromatic, camphoric	7
Eucalyptus Globulus Leaf Extract		
Physical Form	Liquid	37
Color	Light to medium amber	37
Odor	Characteristic	37
Specific Gravity @ 25°C	0.99 - 1.01	37
Water Solubility	Soluble	37
Eucalyptus Globulus (Eucalyptus) Leaf Oil		
Physical Form	Liquid/oil Liquid	11 10
Color	Colorless to pale yellow Clear, yellow to pale yellow	11 10
Density @ 20°C @ 20°C	0.913 – 0.92 0.909	10 10
Melting Point °C	< -20	10
Boiling Point °C	153 – 184	10
Water Solubility	Insoluble	11
Other Solubility Alcohol (70%) Alcohol (90%)	 Soluble Miscible	 11 11
Eucalyptus Globulus Leaf/Twig Oil		
Physical Form	Liquid	7
Color	Colorless or pale yellow	7
Odor	Aromatic, camporic	7
Other Solubility Ethanol	 Soluble	7

Table 3. Methods of manufacture reported in the literature.

Ingredient	Method	Reference
Eucalyptus Globulus Leaf Oil	Freshly collected *Eucalyptus* leaves were cleaned by using distilled water and air-dried at room temperature under shade. The leaves were then chopped into small pieces and essential oil extraction accomplished by hydro-distillation in a modified Clevenger-type apparatus. The oil was filtered and concentrated using rotary evaporator.	[57]
Eucalyptus Globulus Leaf Oil	*Eucalyptus globulus* leaves were air-dried. Dried leaves (25 g) were mixed with 500 ml of water and subjected to hydro-distillation for 3 h. The resulting volatile oils were dried over anhydrous sodium sulfate and then stored in dark bottles in a refrigerator until used.	[59]
Eucalyptus Globulus Leaf Oil	Eucalyptus Globulus Leaf Oil used for medicinal purposes is manufactured from fresh leaves or fresh terminal branchlets of *Eucalyptus globulus* plants. Oil is extracted by steam distillation and retification.	[12]
Eucalyptus Globulus Leaf Extract	Freshly collected *Eucalyptus globulus* leaves were air-dried followed by milling into a powder. The powder (5 g) was mixed in 200 ml of distilled water overnight, and then filtered through cheese cloth.	[62]
Eucalyptus Globulus Leaf Extract	Freshly collected *Eucalyptus globulus* leaves were air-dried followed by milling into a powder. The powder (200 g) was then percolated in distilled water (500 ml) for 2 weeks. The percolated mixture was filtered and evaporated on a water bath.	[63]
Eucalyptus Globulus Leaf Extract	The extract was prepared by powdering *Eucalyptus globulus* leaves. The leaves were then macerated in 80% aqueous ethanol for one week with occasional shaking. The resulting extract was filtered and concentrated to a dark green residue under reduced pressure on a rotary evaporator. The yield was approximately 6%.	[64]
Eucalyptus Globulus Leaf Extract	Fresh or dried leaves are extracted with specified eluent(s) at specified temperature (not specified) to yield a concentrate. Concentrate is then blended with desired diluent(s) and preservation system to product the final product.	[37]

Table 4. Constituents of *Eucalyptus globulus*-derived ingredient reported to the ECHA database from various suppliers (concentrations were not provided).[10]

Constituent	Eucalyptus Globulus, Extract	Eucalyptus Globulus Oil, Rectified	Rectified Eucalyptus Oil	Eucalyptus Globulus Oil, Rectified	Eucalyptus Globulus Oil, Steam Distilled	Eucalyptus Globulus Oil, Rectified
(±)-2(10)-Pinen-3-one	-	-	-	-	+	-
(R)-*p*-Mentha-1,8-diene	-	-	-	-	-	+
(Z)-3,7-Dimethylocta-1,3,6,-triene	-	-	-	-	+	-
[1aR-(1aα,4aα,7α,7aβ,7bα)]-Decahydro-1,1,7-trimethyl-4-methylene-1H-cycloprop[e]azulene	-	-	-	-	+	-
7-Methyl-3-methyleneocta-1,6-diene	-	+	-	+	+	-
Bornan-2-one	-	-	-	-	-	+
Camphene	-	-	-	-	+	-
Dipentene	+	+	+	+	+	-
Eucalyptol	+	+	+	+	+	+
Isovaleric acid	-	-	-	-	+	-
p-Cymene	+	+	+	+	+	-
Pin-2(10)-ene	-	+	+	+	+	+
Pin-2(3)-ene	+	+	+	+	+	+
p-Menth-1-en-8-ol	-	+	+	+	+	-
p-Mentha-1,4-diene	+	+	+	+	+	-
p-Mentha-1,5-diene	-	+	+	+	+	+
Thuj-4(10)-ene	-	-	-	-	-	+
Unknown constituents	-	+	-	+	+	+

Table 5. Constituent groups found in *Eucalyptus globulus* leaf extracts using different extract mediums.[8]

Phytochemicals	Petroleum Ether Extract	Chloroform Extract	Methanol Extract	Aqueous Extract
Alkaloids	-	-	-	-
Carbohydrate	+	+	+	+
Flavonoids	-	-	+	-
Phenolic compounds and tannins	-	-	+	+
Phytosterols	-	+	+	-
Proteins and amino acids	-	-	-	-
Saponins	-	-	+	+
Triterpenoids	-	+	+	-

Table 6. The constituents of Eucalyptus Globulus Leaf Oil reported by a supplier.[91]

Constituent	Content (%)
Camphor	0.0
Eucalyptol	78.8
Limonene	7.7
p-Cymene	3.2
Terpinen-4-ol	0.2
α-Phellandrene	1.0
α-Pinene	1.2
α-Terpineol	0.3
β-Phellandrene	0.3
β-Pinene	0.6
γ-Terpinen	4.4

Table 7. The ranges of constituents of Eucalyptus Globulus Leaf Oil (essential oil) at 1% or greater.[6]

Constituent	Content (%)
(+)-Aromadendrene	1.2 – 3.5
(+)-Limonene	1.8 – 9.0
(*E*)-Pinocarveol	2.3 – 4.4
Eucalyptol	65.4 – 83.9
Globulol	Trace – 5.3
p-Cymene	1.2 - 3.5
Pinocarvone	Trace – 1.0
α-Pinene	3.7 – 14.7

Table 8. Comparison of chemical composition of the essential oil from *Eucalyptus globulus* leaves collected from different locations extracted by steam distillation. [20,23,24]

Compounds	Algeria (%)	China (%)	Northern Ethiopia (%)
4-Terpineol	0.178	*	*
Alloaromadendrene	*	2.47	*
Aromadendrene	*	*	0.694-2.858
Borneol	0.346	*	*
Camphene	0.117	*	0.164-0.269
Caren-4-ol	0.195	*	*
cis-Carveol	0.187	*	*
cis-Ocimene	*	*	15.923-21.331
Eucalyptol	51.083	72.71	66.283-75.361
Fenchol	0.179	*	*
Globulol	2.817	2.77	0.819-1.431
L-pinocarveol	9.987	*	*
Myrtenol	0.202	*	*
α-Campholenal	0.390	*	*
α-Pinene	24.600	9.22	*
α-Terpineol	0.486	2.54	1.505-2.256
α-Terpineol acetate	1.2	3.11	2.188-3.391
β-Myrcene	*	*	0.658-1.004
β-Pinene	0.217	*	0.957-1.237
Total identified	**92.184**	**92.82**	**89.191-109.138**

* Not found or found at <1%.

Table 9. Constituents of the *Eucalyptus globulus* plant that may be of concern.

Constituent	Concern	References
Geraniol	Potential dermal sensitizer	[2-6]
Limonene	Hydroperoxides are potential dermal sensitizers	[2,6,25]
Linalool	Hydroperoxides are potential dermal sensitizers. Safe at up to 4.3% (20% in a consumer fragrance)	[2,26]
Quercetin	Positive genotoxic effect in an Ames assay Consistently genotoxic in in vitro tests and in some in vivo studies of i.p. exposures, but was consistently non-genotoxic in oral exposure studies	[32,33]
β-Myrcene	Oral dosing for 2 years caused kidney cancers in male rats (0.25 g/kg) and liver cancer in male mice (0.25 g/kg); may be related to the occurrence of kidney tumors in female rats and liver tumors in female rats. Associated with other lesions of the kidney in rats, the liver in mice, and the nose in male rats.	[28]
α-Pinene	Potential carcinogen. Increased incidence of transitional epithelium hyperplasia of urinary bladder in male and female mice at 100 ppm or more, the severity of which increased with increasing exposure concentration.	[30,31]

Table 10. Constituents of *Eucalyptus globulus* leaves and oil that have IFRA standards.[34]

Constituent	Standard Limits
2-Phenylacetaldehyde	Limited to 0.01% - 2.9%, depending on use category due to sensitization.*
Benzyl benzoate	Limited to 2% - 42.8%, depending on use category due to sensitization.*
Butyraldehyde	Limited to 0.17% - 5%, depending on use category due to sensitization.*
Carvone	Limited to 0.08% - 5%, depending on use category due to sensitization.*
Citronellol	Limited to 0.8% - 21.4%, depending on use category due to sensitization.*
Cuminaldehyde	Limited to 0.03% - 5%, depending on use category due to sensitization.*
trans-β-Damascenone	Limited to 0.2% in fragrances and Eau de Toilette; 0.01% in other leave-on and rinse-off products; and 0.2% in non-skin, and incidental skin contact products due to carcinogenicity.
Estragol	Limited to 0.2% - 4.3%, depending on use category due to sensitization.*
Eugenol	Limited to 0.2% - 4.3%, depending on use category due to sensitization.*
Geraniol	Limited to 0.03% - 8.6%, depending on use category due to sensitization.*
Ionone (mixed isomers)	Limited to 2% - 50.72%, depending on use category due to sensitization.*
Limonene	D-, L-and DL-Limonene and natural products containing substantial amounts of it, should only be used when the level of peroxides is kept to the lowest practical level, for instance by adding antioxidants at the time of production. Such products should have a peroxide value of less than 20 mM peroxides per liter.
Linalool	Limit peroxide level to 20 mmol/L due to sensitization. Linalool and natural products known to be rich in linalool, such as bois de rose, coriander or ho wood oil, should only be used when the level of peroxides is kept to the lowest practical level. It is recommended to add antioxidants at the time of production of the raw material. The addition of 0.1% BHT or alpha-tocopherol for example has shown great efficiency. The maximum peroxide level for products in use should be 20 mmol/L.
Phenylacetaldehyde	Limited to 0.02% - 3%, depending on use category due to sensitization.*

IFRA - International Fragrance Association
* Use categories are based on types of contact (e.g., skin, lips), length of contact (e.g., leave-on, rinse-off), or type of use (e.g., mouthwash)

Table 11. Allergens[a] that are specified to not be detected in trade name mixtures containing Eucalyptus Globulus Leaf Extract (detection limit 0.001%).[36,37]

Allergen	Trade name mixture containing Eucalyptus Globulus Leaf Extract at 10%	Trade name mixture containing Eucalyptus Globulus Leaf Extract at unspecified concentration
Amyl cinnamal	Not detected	Not detected
Amyl cinnamal alcohol	Not detected	Not detected
Anise alcohol	Not detected	Not detected
Benzyl alcohol	Not detected	Not detected
Benzyl benzoate	Not detected	Not detected
Benzyl cinnamate	Not detected	Not detected
Benzyl salicylate	Not detected	Not detected
Butylphenyl metahylpropional	Not detected	Not detected
Cinnamal	Not detected	Not detected
Cinnamyl alcohol	Not detected	Not detected
Citral	Not detected	Not detected
Citronellol	Not detected	Not detected
Coumarin	Not detected	Not detected
Eugenol	Not detected	Not detected
Farnesol	Not detected	Not detected
Geraniol	Not detected	Not detected
Hexyl cinnamal	Not detected	Not detected
Hydroxycitronellal	Not detected	Not detected
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	Not detected	Not detected
Isoeugenol	Not detected	Not detected
α-Isomethyl ionone	Not detected	Not detected
Limonene	Not tested	Not detected
D-Limonene	Not detected	Not tested
Linalool	Not detected	Not detected
Methyl 2-octynoate	Not detected	Not tested
Methyl 12-octynoate	Not tested	Not detected

[a] The 26 fragrance allergens defined by the 7th Amendment of the Scientific Committee on Cosmetic and Non-Food Products (SCCNFP) Allergens Annex III

Table 12. Frequency of use according to duration and exposure of *Eucalyptus globulus*-derived ingredients.[38,39]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Eucalyptus Globulus Leaf Oil		Eucalyptus Globulus Leaf		Eucalyptus Globulus Leaf Extract		Eucalyptus Globulus Leaf Powder	
Total/range	**433**	**0.000002-0.74**	**NR**	**1.2**	**77**	**0.000006-0.41**	**2**	**1**
Duration of use[a]								
Leave-on	214	0.000002-0.4	NR	NR	52	0.000006-0.005	NR	NR
Rinse-off	160	0.00001-0.74	NR	1.2	22	0.000008-0.41	2	1
Diluted for (bath) use	59	0.13-0.2	NR	NR	3	NR	NR	NR
Exposure type								
Eye area	2	0.00001-0.038	NR	NR	2	NR	NR	NR
Incidental ingestion	7	0.008-0.74	NR	NR	1	0.058-0.41	NR	NR
Incidental Inhalation-sprays	18; 73[a]; 48[b]	0.00056-0.4; 0.00001-0.74[a]	NR	NR	16[a]; 10[b]	0.000006-0.005; 0.00005-0.058[a]	NR	NR
Incidental inhalation-powders	4[c]; 48[b]	0.001-0.27[c]	NR	NR	1; 10[b]	0.005[c]	NR	NR
Dermal contact	368	0.000002-0.4	NR	1.2	57	0.00005-0.025	2	1
Deodorant (underarm)	3[a]	NR	NR	NR	4[a]	NR	NR	NR
Hair-noncoloring	55	0.00001-0.12	NR	NR	17	0.000006-0.0087	NR	NR
Hair-coloring	1	0.005	NR	NR	NR	NR	NR	NR
Nail	2	0.0001-0.15	NR	NR	2	NR	NR	NR
Mucous Membrane	131	0.00013-0.74	NR	NR	8	0.015-0.41	NR	NR
Baby	7	0.000002-0.00067	NR	NR	NR	NR	NR	NR

	Eucalyptus Globulus Leaf Water		"Eucalyptus"		"Eucalyptus extract"[d]		
Total/range	**NR**	**0.02-1.4**	**42**	**NS**	**11**	**NS**	
Duration of use							
Leave-on	NR	1.4	32	NS	6	NS	
Rinse-off	NR	0.02-0.1	3	NS	5	NS	
Diluted for (bath) use	NR	NR	7	NS	NR	NS	
Exposure type							
Eye area	NR	NR	NR	NS	NR	NS	
Incidental ingestion	NR	NR	NR	NS	NR	NS	
Incidental Inhalation-sprays	NR	NR	10; 2[a]; 8[b]	NS	4[a]; 1[b]	NS	
Incidental inhalation-powders	NR	1.4[c]	8[b]	NS	1[b]	NS	
Dermal contact	NR	0.02-1.4	40	NS	10	NS	
Deodorant (underarm)	NR	NR	NR	NS	NR	NS	
Hair-noncoloring	NR	0.02-0.1	2	NS	1	NS	
Hair-coloring	NR	NR	NR	NS	NR	NS	
Nail	NR	NR	NR	NS	NR	NS	
Mucous Membrane	NR	NR	9	NS	3	NS	
Baby	NR	NR	NR	NS	1	NS	

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on + Diluted for Bath 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] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
[c] It is possible these products may be powders, but it is not specified whether the reported uses are powders.
[d] "Eucalyptus" and "eucalyptus extract" are not INCI names but were reported in the VCRP. It is not known if these correspond to cosmetic ingredients in this report.

Table 13. Dermal penetration enhancement studies of Eucalyptus Globulus Leaf Oil.

Ingredient/substance	Drug	Details	Results	Reference
Eucalyptus Globulus Leaf Oil (82.9% eucalyptol) tested at 0, 5%, 10%, 20%, or 50% v/v in distilled water	CHG 2% w/v	Thawed, full-thickness human breast skin from 3 donors. Skin was placed in vertical Franz diffusion cells (3.14 cm^2). Receptor cells filled with PBS. CHG (2% w/v) was also mixed with Eucalyptus Globulus Leaf Oil (5%, 10%, 20% and 50%v/v) and isopropyl alcohol (70% v/v) and distilled water. Mixtures without CHG were used as controls. Polysorbate 80 (0.1% v/v) was added to enhance solubility of oil. Test mixtures (1 ml) were spread on skin surface. Skin was removed and examined at 2 and 30 min, and 24 h. Punches of skin samples were sectioned horizontally and HPLC was used to measure the CHG in skin samples. In an additional 24-h permeation study: CHG, with and without 50% Eucalyptus Globulus Leaf Oil. Receptor fluid was sampled every 30 min for 2 h, every 60 min between 2 to 6 h, and at 8 h, 12 h and 24 h.	Eucalyptus Globulus Leaf Oil at 5% facilitated greater CHG skin penetration to the deeper layers of the skin (below 300 µm) and 10% (v/v) Eucalyptus Globulus Leaf Oil enhanced CHG skin penetration in upper 900 µm. There were no significant differences in CHG concentration measured in skin with 10% and 20% Eucalyptus Globulus Leaf Oil. Combining 10% Eucalyptus Globulus Leaf Oil and CHG in 70% isopropyl alcohol significantly enhanced CHG dermal penetration compared to CHG and isopropyl alcohol 0.121 ±0.019 vs 0.023 ± 0.007 µg/mg in upper 100 µm of skin. Eucalyptus Globulus Leaf Oil at 50% enhanced penetration of CHG into lower layers of skin within 2 min; CHG concentrations achieved at depths of 300 to 1500 µm were between 0.019 and 0.043 µg/mg tissue. At 30 min, concentration of CHG in upper 100 µm was 0.398 (±0.076) µg/mg tissue. CHG, with and without 50% Eucalyptus Globulus Leaf Oil, was detected at negligible levels in receptor compartment over 24 h. This suggested that CHG did not permeate through full skin thickness, and was retained within tissue.	[49]
Eucalyptus Globulus Leaf Oil 0, 2.5%, 5%, or 7.5%	TMP	Gels to be used in test patches were made containing TMP (15.6%), Carbopol 92P (2.5%), ethanol (5%), Eucalyptus Globulus Leaf Oil (0, 2.5%, 5%, or 7.5%), Polysorbate 80 (2.0%), glycerin (10%), and water. Tests were conducted using modified Keshary-Chien diffusion cells (3.14 cm^2) with either fresh dorsal rat skin or thawed human cadaver skin from chest area. Samples were collected at 1, 3, 5, 7, 9, 12 and 24 h.	Enhancement ratios for Eucalyptus Globulus Leaf Oil (2.5%, 5%, or 7.5%) were 3.38, 4.47, and 4.64, respectively, for rat and human skin. TMP flux across the human chest skin with 5% Globulus Leaf Oil was 17-fold greater (346.0 mg/cm^2/h) than the flux (20.1 mg/cm^2/h) of a saturated solution of TMP without the oil.	[50]
Eucalyptus Globulus Leaf Oil (80% to 85% eucalyptol) 5%, 7.5%, and 10%	Ketorolac	A reservoir type transdermal patch was fabricated with a core gel system of a non-ionic polymer, PBS, and isopropyl alcohol and applied to abdominal skin of Sprague-Dawley rats in diffusion cells.	ERs were 1.80, 3.04, and 3.68 for 5%, 7.5%, and 10%, respectively. When compared with other potential dermal penetration enhancers, the order of effectiveness was: Eucalyptus Globulus Leaf Oil > transcutol > DMSO > *d*-limonene. When a gel incorporated with crushed apricot seed was rubbed onto the skin prior to administration of patch, the ER for the addition of Globulus Leaf Oil (10%) was 5.16.	[51]
Eucalyptus Globulus Leaf Oil and fractions obtained using a rotary evaporator at 100°C, 110°C, 120°C, 130°C, and 140°C under vacuum.	5-FU	Saturation solution of 5-FU (1 ml saturated solution plus a crystal of 5-FU was placed in donor cell) with and without 150 µL Globulus Leaf Oil for 12 h using clipped abdominal skin of white male rats in a 2-cell diffusion cells (2.01 cm^2). Receptor fluid was saline.	ERs: Globulus Leaf Oil, 59.63; 100°C fraction, 58.49; 110°C fraction, 59.53; 120°C fraction, 59.16; 130°C fraction, 82.48; and 140°C fraction, 82.55. When compared with other potential dermal penetration enhancers, the order of effectiveness was: azone > Eucalyptus Globulus Leaf Oil > peppermint oil > turpentine oil	[52]

5-FU = 5-Fluorouracil; CHG = chlorhexidine digluconate; DMSO = dimethyl sulfoxide; ER = enhancement ratio; HPLC = high-performance liquid chromatography; PBS = phosphate buffered saline; TMP = 2,3,5,6-tetramethylpyrazine

Table 14. Acute dermal and oral toxicity

Ingredient	Animal (n)	Concentration	Procedure	Results	Reference
			Dermal		
Eucalyptus Globulus Leaf Oil	Rabbits (10)	5000 mg/kg	Dermally administered to rabbits in a single dose. Rabbits were observed for 14 days.	There were no mortalities or signs of toxicity. LD_{50} was > 5000 mg/kg	10
Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)	Rabbits	5000 mg/kg	Not provided.	LD_{50} was > 5000 mg/kg	54
			Oral		
Eucalyptus Globulus Leaf Oil	Male ddY mice (n = 10)	2200, 2900, 3700, or 6200 mg/kg in olive oil	Administered by gavage and observed for 7 days. There was no control group.	Mortalities were 10%, 20%, 70%, and 100% at 2200, 2900, 3700, or 6200 mg/kg, respectively. Surviving mice had reduced growth. LD_{50} was 3320 (confidence interval 2770 to 3980) mg/kg	10
Eucalyptus Globulus Leaf Oil	Female albino Swiss mice (n = 6)	an aqueous emulsion of 5% Eucalyptus Globulus Leaf Oil (with polysorbate-80 (2%) as an emulsifier; 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 3.5 ml/kg Control: the vehicle (2% polysorbate-80 and water).	Mice were fasted for 4 h prior to dosing and 2 h after dosing and observed every 30 min for 4 h, then daily for 14 days. Mice were then weighed, killed, and necropsied.	There were no signs of toxicity or mortality in mice in groups administered up to 2.0 ml/kg. At doses at and above 2.5 ml/kg, toxic effects were observed: restlessness immediately after administration followed by debilitation, reduced feed and water consumption, and gathering together and piloerection. Clinical signs disappeared in surviving mice, mostly after a day. In 3.0 and 3.5 ml/kg groups, 1 of 6 and 4 of 6 mice died within 24 h of dosing, respectively. Necropsy revealed no noticeable changes in appearance of observed internal organs (stomach, liver, and kidney) in all treatment groups. The LD_{50} of the emulsion was between 3 and 3.5 ml/kg.	57
Eucalyptus Globulus Leaf Oil	SPF Sprague-Dawley (SD) rats (n = 5/sex)	0, 2772, 3267, 3960, 4752, and 5742 mg/kg in water with polysorbate-80 and span-80 as emulsifier	Administered by gavage	50 min after dosing in 5742 mg/kg group, rats appeared to move slowly, gather together, have extreme sensitivity to noise, and have convulsions. Rats in other treatment groups showed milder symptoms. Rats that died after dosing with 0, 2772, 3267, 3960, 4752, and 5742 mg/kg were 0, 1, 3, 6, 8, and 9, respectively. At necropsy of rats that died, large amounts of undigested feed and Eucalyptus Globulus Leaf Oil was observed in stomachs, and no tissue damage was observed except in lungs and liver (details of the damage was not provided). LD_{50} was 3811.5 mg/kg (confidence interval: 3326.4 and 4306.5 mg/kg).	58
Eucalyptus Globulus Leaf Oil (Method of manufacture is presented in Table 3)	Male albino Wistar rats (n = 10)	500, 1000, 1,500, 2,000, or 2,500 mg/kg	Administered by gavage. Mortality was determined after 24 h.	The LD_{50} was 2334.3 mg/kg and the LD_{95} was 7632.13 mg/kg.	59
Eucalyptus Globulus Leaf Oil	Rats	Not specified	Administered by gavage.	Rats that were near death could not feed themselves. LD_{50} was 4400 mg/kg.	10
Eucalyptol	Mice	500 mg/kg	Administered by gavage.	An increase in liver enzyme activity was also found in mice given 500 mg/kg orally.	53
Eucalyptol	Rats	Not specified	Administered by gavage.	LD_{50} = 2480 mg/kg	53,54
Eucalyptol	Rats	Not specified	Administered by gavage.	LD_{50} =1560 mg/kg Lethal dose caused rapid cyanosis and stupor accompanied by irregular breathing, extreme sensitivity to noise, convulsions, and death from respiratory failure.	53

Table 15. Short-term oral studies

Ingredient (dose)	Animal (n)	Procedure	Results	Reference
Eucalyptus Globulus Leaf Extract (2000 mg/kg/day aqueous; 0.2 ml; method of manufacture is presented in Table 3)	Male Swiss albino mice (10)	Orally administered for 10 days. Control group was administered distilled water. Extract was made fresh daily.	There were no mortalities. Treated mice demonstrated general weakness and decrease in physical activity and had loss of body fur, ruffled fur, and changes in their white coat color. Treated mice had reduced feed intake and lost weight (-13.35%). There was a reduction in hemoglobin concentration (3.12%), PCV (3.11%), RBC (11.31%), and total WBC (20.97%), indicating severe leucopoenia. Platelet count was also reduced (15.55%). There were significant changes in enzymes demonstrating liver impairment: AST, 33.0 ± 1.0 vs. 75.0 ± 1.0 IU/l, 127.27% increase and ALT 35.0 ± 1.0 vs. 65.0 ± 1.0 IU/L, 85.71% increase. There was an increase in creatinine (1.90 ± 0.1 vs. 0.09 ± 0.1 mg/dl) and urea levels (75.0 ± 1.0 vs. 25.0 ± 1.0 mg/dl). Gross examination of treated mice showed pale livers, congestion and hemorrhages in lungs of some mice, enlarged spleens, and mild congestion in hearts in some mice. Histological examination of treated mice showed damage to hepatic cells manifested by swollen hepatocytes with vacuolated cytoplasm (very extensive in some cells). Many necrotic cells with pyknotic or karyolitic nuclei were observed. Some central veins of livers were congested and some hepatocytes had enlarged nuclei. Histological examination showed renal tubules of treated mice had mild to severe degeneration. Degenerative changes were in tubular epithelium reflecting failure of membrane ion pumps, allowing cells to accumulate fluid. Administration of Eucalyptus Globulus Leaf Extract caused significant neurodegenerative changes including a decrease in size and number of neurons in cerebral cortex. Many glial cells with dense fragmented nuclei were observed.	62
Eucalyptus Globulus Leaf Extract (0, 80, 100, or 120 mg/kg/day aqueous; 1 ml; method of manufacture is presented in Table 3)	Albino *Rattus norvegicus* rats (6)	Administered by gavage for 7 days. Controls were administered distilled water. Activities of ACP, ALP, SOD, and the level of MDA were determined in liver and serum.	ACP and ALP activities were increased in livers with no difference in their serum activities. Activity of SOD was increased in livers in 100 and 120 mg/kg groups. There was an increase in level of MDA in livers of all treatment groups and in the serum of the 120 mg/kg group. Authors stated results indicate that aqueous Eucalyptus Globulus Leaf Extract may have deleterious effects on liver membrane structure and functional integrity.	63
Eucalyptus Globulus Leaf Extract (20 ml/day; method of manufacture is presented in Table 3)	Male Wistar rats (8)	Administered in drinking water (1 g/l) for 42 days. The rats consumed the equivalent of 130 mg dry leaves/day. A control group was administered water.	There were no differences in creatinine, urea, protein, or uric acid in blood of both groups. In measurements of oxidative damage and antioxidant activities in kidneys, there were no differences in levels of peroxidation and activities, SOD, GPX, and CAT. There were no differences observed between the two groups when kidneys were examined microscopically.	64
Eucalyptus Globulus Leaf Oil (0, 1.5, or 2.0 ml/kg/day)	Female albino Swiss mice (12/sex)	Administered by gavage for 84 days (12 weeks). Control group was administered the vehicle (2% polysorbate-80 and water). After last dose, blood samples were collected. Mice were killed and livers and kidneys examined.	There were no signs of toxicity and no mortalities for either treatment group. Body weights were similar between treatment and control groups. There were no significant changes in hematological parameters in either treatment group compared to control group. General microscopic architecture of liver sections of mice in the 1.5 ml/kg group was similar to controls. Some areas of liver sections of mice in 2.0 ml/kg group showed that general hepatolobular architecture was altered in that pyknosis, clear spaces in the cytoplasm (vacuolations) of hepatocytes, and focal necrosis were observed. Kidney sections of mice in 1.5 ml/kg group showed no structural differences. Pyknosis of renal tubular epithelial cells and widening of tubular lumen was observed in sections of kidneys of mice in the 2.0 ml/kg group. Hyaline casts in renal tubules and perivascular lymphocytic infiltrations were also observed in small areas of kidney sections in the 2.0 ml/kg group.	57

Table 15. Short-term oral studies

Ingredient (dose)	Animal (n)	Procedure	Results	Reference
Eucalyptus Globulus Leaf Oil (0, 100, 300, or 1000 mg/kg/day; 4 ml/kg in corn oil)	Crl:CD(SD) rats (10/sex)	OECD GL 422 A combined repeated dose and reproduction/ developmental study. Test substance was administered by gavage. Males were treated starting from 2 weeks before mating for at least 5 weeks. Females were treated from 2 weeks before mating until lactation day 6. Rats were killed and necropsied.	One female in 1000 mg/kg/day group was found dead on Day 15 after mating, which was not attributed to treatment. During first week of dosing, both males and females in 1000 mg/kg/day group displayed transient signs of reduced activity and unsteady muscle reactions. Rats in 1000 mg/kg/day group also displayed chin rubbing and salivation; salivation was also recorded in females in 300 mg/kg/day group. Detailed physical and arena observations, sensory reactivity, grip strength or motor activity assessments of the animals did not detect any changes attributed to the test substance. Body weight gain of males in 1000 mg/kg/day group was low during week 1. During gestation, body weight gain and feed consumption was low in females in 1000 mg/kg/day group. Feed consumption remained low for females in the 1000 mg/kg/day group during lactation. Changes in hematology parameters were not considered to be adverse at level observed. Male rats at all doses had hyaline droplet nephropathy in kidneys, accompanied by tubular casts and/or tubular degeneration/regeneration. Hyaline droplet nephropathy in the kidneys of male rats is caused by accumulation of α_{2u}-globulin (produced by the liver) in the proximal tubules, which leads to subsequent damage and regeneration of tubular epithelium. Authors note that this has been reported with a number of organic chemicals, but it appears to be a male, rat-specific toxicological response that has no counterpart in humans. Absence of any tubular injury in test article treated females supports the conclusion that tubular degeneration is secondary to male specific hyaline droplet accumulation. All dose levels resulted in centrilobular hepatocytic hypertrophy in livers of males and an increase in glycogenic vacuolation in livers of females, which was considered an adaptive change likely associated with microsomal enzyme induction. A slight increase in incidence and severity of glycogenic vacuolation in livers of treated female compared with controls may be partially responsible for liver weight increase. Liver changes were not considered to be adverse. There were no microscopic correlates for decrease in spleen weight and increase in adrenal weight of high-dose females. NOAEL for males was 1000 mg/kg based on hyaline droplet nephropathy at all dose levels; however this response is considered to be rat specific and to have no counterpart in humans. NOAEL for females was 300 mg/kg based on effects on body weight and feed consumption	10
Eucalyptus Globulus Leaf Oil (100, 300, or 1000 mg/kg/day in corn oil)	Crl:CD (SD) rats (3/sex)	Administered for 2 weeks.	There were no mortalities. Clinical signs were salivation in isolated females in 300 and 1000 mg/kg/day groups, which authors considered minor and did not indicate an association with test material. Other signs were transient body weight loss and low feed consumption in males in 1000 mg/kg/day group during Days 1 to 5. Necropsy showed that liver and kidney weights increased with increasing dose level in males; in females, increased liver weights were only observed in females in 1000 mg/kg/day group. Thickening of mammary tissue was observed in 2 and 1 males in 300 and 1000 mg/kg/day groups, respectively, and 1 female in the 1000 mg/kg/day group. Under test conditions, LOAEL and NOAEL in female rats could be considered as 300 and 100 mg/kg/day, respectively, based on clinical signs at 300 and 1000 mg/kg/day and increased liver weight at 1000 mg/kg/day. Since dose-related increases in liver and kidney weights were observed in males at all doses, no NOAEL could be identified for male rats in this study. The LOAEL in male rats could be considered as 100 mg/kg bw/day.	10
Eucalyptus Globulus Leaf Oil (0 or 233 mg/kg/dose in corn oil; 1/10 LD_{50}; method of manufacture is presented in Table 3)	Male albino Wistar rats (5/sex)	Administered by gavage every 3 days for 30 days. Blood samples were collected on Days 15 (5^{th} dose) and 30 (10^{th} dose). Rats were then killed and necropsied.	There was an increase in WBC counts and a decrease in hemoglobin concentration and platelets count in both blood samples. RBC counts were below control levels at 10th dose. Activities of SGOT and SGPT enzymes were significantly increased at both 5th and 10th doses in treated rats. There were mild effects on kidney function in that there was an increase in creatinine and urea concentration at 10th dose. Histopathological studies on liver and kidney revealed relatively moderate pathological changes in liver as congestion of the blood vessels in portal area associated with inflammatory infiltration. There was also induced desquamation of epithelial cells of the renal tubules.	59

Table 15. Short-term oral studies

Ingredient (dose)	Animal (n)	Procedure	Results	Reference
Eucalyptus Globulus Leaf Oil (0, 396, 792, and 1188 mg/kg in water with polysorbate-80 and span-80 as emulsifiers)	SPF Sprague-Dawley (SD) rats (5/sex)	Administered by gavage for 30 days	There were no clinical signs during study period. In male rats, body weights of low-dose group was higher than control group; body weights of middle-dose group and high-dose group were lower than those of control group. In female rats, body weights of all of experimental groups were reduced. There were no differences in hematological parameters. Heart rates and respiratory rates were similar between groups. Serum biochemical parameters were similar between groups except that there were differences between control group and mid- and high-dose groups for: aspartate transaminase (increased), creatinine (increased), and glucose (decreased). There were no differences in organ weights. In livers of experimental groups, central venous extended with hyperemia and varying degrees of vacuolar degeneration of hepatocytes were observed. In spleens, red pulp extended with hyperemia and a large number of macrophages and Langerhans cells infiltration was observed in mid- and high-dose groups. Glomeruli (with varying degrees of hyperemia), renal tubular epithelial cells with varying degrees of granular degeneration, and narrowed renal tubes were observed in kidneys of mid- and high-dose groups. Histological examination showed that there were no differences with regard to heart, lung, stomach, intestines, testicles and ovaries.	[58]
Eucalyptol (Stomach tube: 150, 300, 600 and 1200 mg/kg/day Encapsulated form in diet: 3750, 7500, 15000 and 30000 mg/kg/day, equivalent to 600 to 5607 mg/kg/day for males and 705-6777 mg/kg/day for females.)	B6C3F1 mice (6/sex)	Administered 28 days either by stomach tube (5 days/week) or in encapsulated form with the diet	Liver weight/body weight ratio in males was increased at all but lowest dose given in encapsulated form as was brain weight/body weight ratio in females at the dose level. Microscopic examination revealed a minimal hypertrophy of centrilobular hepatocytes in mice of both sexes fed the encapsulated compound, especially at two highest dose levels.	[53]
Eucalyptol (Stomach tube: 150, 300, 600 and 1200 mg/kg/day Encapsulated form in diet: 3750, 7500, 15,000 and 30,000 mg/kg/day; 381 to 3342 mg/kg/day for males and 353 to 3516 mg/kg/day for females)	Fischer 344 rats (6/sex)	Administered for 28 days either by stomach tube (5 days/week) or in encapsulated form with the diet.	At dose levels of 600 mg/kg/day and higher, dose-related decrease of body weight gain and absence of a normal degree of hepatic centrilobular cytoplasmic vacuolization was observed in male rats. Other dose-related lesions in the liver, kidneys and parotid salivary glands were found at all dose levels in male rats fed encapsulated eucalyptol.	[53]
Eucalyptol (0, 500, or 1000 mg/kg/day)	Male Wistar rats (10)	Administered by gavage for 28 days	There were decreases in terminal body weight and increased relative liver and kidney weights in both treatment groups. Relative brain weight was increased in 1000 mg/kg/day group. No macroscopic changes were observed. Only brain, liver and kidneys were examined histopathologically. No changes in brain were observed; minor focal infiltration of mononuclear cells in liver was observed in all groups. In kidneys, a dose-related accumulation of eosinophilic protein droplets containing α_{2u}-globulin in the cytoplasm of proximal tubular epithelial cells was observed.	[53]

ACP = acid phosphatase; ALP = alkaline phosphatase; ALT = alanine aminotransferase ; AST = aspartate aminotransferase; CAT = catalase; GPX = glutathione peroxidase; IU = International units; LOAEL = lowest-observed-adverse-effect level; MDA = malondialdehyde; NOAEL = no-observed-adverse-effect level; OECD GL = Organisation of Economic Co-operation and Development Guidelines; PVC = packed cell volume; RBC = red blood cell count; SGOT = serum glutamic oxalacetic transaminase; SGPT = glutamic pyruvic transaminase; SOD = superoxide dismutase; WBC = white blood cell count

Table 16. In vitro genotoxicity studies

Ingredient/substance	Assay	Details	Results	References
Eucalyptus Globulus Leaf Extract	mammalian cell gene mutation test	OECD GL 476 using mouse lymphoma L5178Y cells. Without S9 mix (3-h exposure): 10, 100, 150, 200, 225, 250, 275 and 300 µg/ml; Without S9 mix (3-h exposure, additional test): 10, 100, 115, 130, 145, 160, 175, 190, 210, 225, 250 and 300 µg/ml in acetone; With S9 mix (3-h exposure): 10, 100, 115, 130, 145, 160, 175, 190, 210, 225, 250 and 300 µg/ml in acetone; Without S9 mix (24-h exposure): 10, 50, 100, 150, 175, 200, 225, 250, 275 and 300 µg/ml in acetone.	Not mutagenic with or without metabolic activation	[10]
Eucalyptus Globulus Leaf Oil	Bacterial reverse mutation assay	OECD GL 471; *S. typhimurium* (strains: TA98, TA100, TA1535, and TA1537) and *E. coli* (WP2) Experiment 1 (plate incorporation method): 0, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate in DMSO with and without metabolic activation Experiment 2 (pre-incubation method): 0, 50, 150, 500, 1500 and 5000 µg/plate in DMSO with and without metabolic activation Positive control substances: 4-nitroquinoline-N-oxide, 2-nitrofluorene, sodium azide without metabolic activation Positive control substance: benzo(a)pyrene; 2-Aminoanthracene with metabolic activation.	Negative for genotoxicity with and without metabolic activation. Positive for cytotoxicity in Experiment 2 at 5000 µg/plate in the absence of S9 mix.	[10]
Eucalyptus Globulus Leaf Oil	Human chromosome aberration test	OECD GL 473 using human lymphocytes with and without metabolic activation. - Without S9 mix (3 h treatment and 18 h recovery): 10, 20, 40, 60, 80 and 1000 µg/ml in acetone - With S9 mix (3 h treatment and 18 h recovery): 100, 150, 200, 250, 275, 300, 325 and 350 µg/ml in acetone - Without S9 mix (21 h continuous treatment): 50, 60, 70, 80, 90, 100, 110 and 120 µg/ml in acetone. Positive control: mitomycin C 0.2 µg/ml (3-h treatment) and 0.1 µg/ml (21-h continuous treatment) without metabolic activation. Cyclophosphamide 5 µg/ml (3-h treatment) with metabolic activation.	No statistically significant increases in the chromosomal aberrations, polyploid or endoreduplicated metaphase cells were observed under any treatment condition at any concentration, with or without metabolic activation, when compared to the vehicle control. Cytotoxicity was observed in various concentrations and doses were selected based on the mitotic index data. The controls had the expected result.	[10]
Eucalyptus Globulus Leaf Oil	Mammalian cell gene mutation test	OECD GL 476 using mouse lymphoma L5178Y cells. Without S9 mix (3-h exposure): 10, 100, 150, 200, 225, 250, 275 and 300 µg/ml in acetone; Without S9 mix (3-h exposure, additional test): 10, 100, 115, 130, 145, 160, 175, 190, 210, 225, 250 and 300 µg/ml in acetone; With S9 mix (3-h exposure): 10, 100, 115, 130, 145, 160, 175, 190, 210, 225, 250 and 300 µg/ml in acetone; Without S9 mix (24-h exposure): 10, 50, 100, 150, 175, 200, 225, 250, 275 and 300 µg/ml in acetone. Positive control substance: methylmethanesulfonate: 10 µg/ml (3-h exposure); 5 µg/ml (24-h exposure) without metabolic activation; benzo(a)pyrene: 1 µg/ml (3-h exposure) with metabolic activation.	Not mutagenic with or without metabolic activation	[10]
Eucalyptus Globulus Leaf Oil	Somatic segregation assay	Using diploid strain of fungus *A. nidulans*, heterozygous for nutritional and conidia color markers. 0.12 and 0.25 µl/ml Test substance: eucalyptol (49.0 %), α-pinene (8.9%), β-pinene (1.5%), globulol (6.9%), α-eudesmol (1.12%), spathulenol (1.42%), γ-cadinene (1.45%), *trans*-β-elemenone (1.23%) and aromandendrene (2.3%), totaling 74 % of oil.	Increased mitotic instability of original diploid strain and number of diploid mitotic recombinants of *A. nidulans*. Genotoxicity of the oil was associated with induction of mitotic crossing-over or with oil-broken chromosomes.	[12]

Table 16. In vitro genotoxicity studies

Ingredient/substance	Assay	Details	Results	References
Eucalyptol	Ames assay	Concentration not specified *S. typhimurium* (TA98, TA100, TA1535, and TA1537)	No mutagenic effects with or without metabolic activation	[53]
Eucalyptol	Ames assay	Concentration not specified *S. typhimurium* (TA97a, TA98, TA100, and TA102)	No mutagenic effects with or without metabolic activation	[53]
Eucalyptol	Chromosome aberration assay	Concentration not specified CHO cells	No induced chromosome aberrations with or without metabolic activation	[53]
Eucalyptol	Sister chromatid exchange assay	Concentration not specified CHO cells	Sister chromatid exchanges were induced in CHO cells only in the absence of metabolic activation at doses that induced cell cycle delay.	[53]
Eucalyptol	Rec assay	Concentration not specified *B. subtilis*	No evidence of DNA damage	[53]
Eucalyptol	Rec assay	Concentration not specified *B. subtilis*	No evidence of DNA damage	[53]

CHO = Chinese hamster ovary; MSO = Dimethyl sulfoxide; OECD GL = Organisation for Economic Co-operation and Development Guideline

Table 17. Dermal irritation and sensitization

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION					
ALTERNATIVE STUDIES					
Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)	Neat	Human epidermis model	EpiSkin	Relative mean viability of treated tissue was 88.9% after 15 min exposure. Eucalyptol was predicted to be a non-irritant.	66
ANIMAL					
Eucalyptus Globulus Leaf Oil	Neat	Hairless mice (n not specified)	Dermally administered to backs	Not irritating	67
Eucalyptus Globulus Leaf Oil	Neat; 5000 mg/kg	Rabbits (n = 10)	Single dermal dose. Observed for 14 days.	Slight erythema was observed in 5 of 10 rabbits, moderate erythema in 3 of 10 rabbits, and moderate edema in 10 of 10 rabbits. No further details were provided.	10
Eucalyptus Globulus Leaf Oil	Neat	Rabbits (n not specified)	Administered to abraded and intact skin under occlusion for 24 h	Moderately irritating	67
Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)	Range not specified	Albino mice (n = 10)	Open mouse ear assay	ID_{50} was 1.008 g/5 L acetone (0.0202%).	10
Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)	100%	Rabbits (n not specified)	Administered to abraded and intact skin under occlusion for 24 h	Not irritating	54
HUMAN					
Eucalyptus Globulus Leaf Oil	10% in petrolatum	48h, n = 25; 24 h, n = 20	Administered under occlusion for 24 or 48 h	Not irritating	67
Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)	16% in petrolatum	n = 25	Administered under occlusion for 48 h	Not irritating	54
SENSITIZATION					
ANIMAL					
Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)	25% and 50% v/v in acetone/olive oil 4:1, and 100% v/v	Female mice (n = 5)	Local lymph node assay	SIs were: 25%, 1.43; 50%, 2.03; 100%, 5.08. Concentration of eucalyptol expected to cause a 3-fold increase in 3HTdR incorporation (EC3 value) was calculated to be 65.90%. Eucalyptol was considered to be a sensitizer at 100%, but not at 25% and 50%, under the conditions of the test.	66
Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)	0.25%; 0.1 ml	Harley albino guinea pigs (n = 10)	Modified Draize test. Administered by intradermal injection to the clipped flanks at 4 sites which overlie the two auxiliary inguinal lymph nodes. After a 14-day non-treatment period, an intradermal injection of eucalyptol (0.25%; 0.1 ml) was administered in one flank and a topical challenge (50%; 0.1 ml) was administered to the other flank and not covered. Test sites were scored 24 h after challenge, and scored and challenged again 7 days after first challenge. If there were no signs of irritation or sensitization, the procedure was repeated.	Eucalyptol was found to be a non-sensitizer	68

Table 17. Dermal irritation and sensitization

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			HUMAN		
Skin cream that contained Eucalyptus Globulus Leaf Oil	0.1%	n = 52	HRIPT Open and occlusive patches were administered 3 days per week for 10 applications. For occlusive patches, test substance was applied to pad of a bandage strip and put onto skin of upper back. Open patches were applied to volar surface of left arm. Both series of patches were read 48 h after administration. After ~ 2 weeks after last inductions, patches were repeated and read 48 h after administration.	Occlusive patch sites - 6 subjects had a weak, non-vesicular reaction (+) at 1 to 6 of the induction readings. None of the subject had a reaction after the challenge patch.	[69]
Lipstick that contained Eucalyptus Globulus Leaf Oil	0.5%; 20 mg	n = 107	HRIPT A total of 9 induction patches (48 or 72 h), using Finn chambers, were administered to one side of the back in infrascapular area. Test sites were examined for erythema, edema and other signs of cutaneous irritation before the next application. After a 2-week rest, challenge application was administered on opposite side of the back, which remained in place for 24 h. Challenge site was examined at 30 min and 48 h after removal.	There were no adverse events reported. It was concluded that there was no evidence of irritation or sensitization for this test substance.	[70]
Eucalyptus Globulus Leaf Oil	10% in petrolatum	n = 25	Maximization assay	Not sensitizing. No further details were provided.	[67]
Skin cream that contained Eucalyptus Globulus Leaf Oil	0.1%	n = 101	Schwartz-Peck prophetic patch test Conducted using open and occlusive patches. For occlusive patch, test substance was applied to pad of a bandage strip and put onto cleaned skin of upper back. Open patch was applied to volar surface of left arm. Both patches were read 48 h after administration. After ~ 2 weeks, patches were repeated and read 48 h after administration.	In closed patches, a weak, non-vesicular reaction (+) was observed in 4 subjects at first challenge reading, but not second, and in 2 other subjects only at second reading. In the open patches, there were no reactions observed at either reading.	[69]
Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)	16% in petrolatum	n = 25	Maximization assay	No signs of sensitization	[54]

HRIPT = human repeated insult patch test; ID_{50} = irritation dose in 50% of test individuals; SI = stimulation index

Table 18. Retrospective and multicenter studies of Eucalyptus Globulus Leaf Oil.

Concentration	n	Details	Results	Reference
Not specified	22	Retrospective study of dermatologic patients during the years 2010 to 2015 was conducted at the Contact Allergy Unit of the University Hospitals of Leuven	1 tested positive	[2]
2%	679	In patch tests conducted in 2000 to 2007 of cosmetic ingredients in subjects with suspected contact dermatitis from cosmetic products by the Mayo Clinic Contact Dermatitis Group	4 (0.6%) had positive results; 2 of these subjects had reactions with macular erythema and 2 had weak reactions	[92]
2% in petrolatum	96	Patch tests of subjects in a practice that specializes in contact dermatitis and eczema. Location of facility not provided.	5 subjects had positive reactions; 2 of the scored with a +/- reaction, 2 with a + reaction, and 1 with a ++ reaction	[75]
2% in petrolatum	6680	Patch tests of subjects with dermatitis and/or eczema (2000 to 2008) by the Information Network of Departments of Dermatology (IVDK)	0.24% of those tested had positive reactions; 0.41% scored with a ?/ irritant reaction, 0.19% with a + reaction, and 0.06 with a ++/+++ reaction	[72]
Not specified (in finished cosmetic products containing unspecified concentrations of Eucalyptus Globulus Leaf Oil)	301 subjects who reacted to a fragrance mix	Study (2000 to 2009) of "presence confirmed" of fragrance allergens in cosmetic products to which patients reacted positively in the Department of Dermatology, Contact Allergy Unit, University Hospital St Rafael, Belgium	Reactions were only observed with 1 of 23 bath and shower products and 1 of 88 skin care products; reactions were not observed for products containing "eucalyptus oil" in the other 13 cosmetic product categories,	[73]
Not specified	200	Patch tests of subjects with dermatitis at the Warsaw Medical School, Poland	3 subjects had positive reactions	[76]
Not specified	450	Patch tests of subjects with dermatitis at the Warsaw Medical School, Poland	5 subjects had positive reactions	[77]
Not specified	5315	Patch tests of subjects with dermatitis at the St. John's Hospital for Diseases of the Skin in London	1 subject had a positive reaction	[74]

Table 19. Case reports of *Eucalyptus globulus* exposure.

Summary	Reference
Dermal	
An 8-year-old-girl presented with a 3-day history of erythematous lesions on her neck, which appeared one day after the use of an inhalant ointment. The ointment consisted of Eucalyptus Globulus Leaf Oil and spruce oil (ratio not provided) and had been applied nightly to the collar of the girl's clothing for an unspecified period of time. She presented with a dusky red color, nummular patch that was 6 cm in diameter on her neck and a similar patch that was 4 cm diameter on her right upper clavicular area. She had a sharply-bordered erythematous macular lesion on her neck and upper chest. Patch testing was performed with the European baseline series using Finn Chambers (8 mm) for 48 h. The concentration and vehicle of the Eucalyptus Globulus Leaf Oil was not specified; the spruce oil was tested at 5% in petrolatum. Readings were taken at 30 min and 4 days after removal. Eucalyptus Globulus Leaf Oil had a positive reaction (++) as did the spruce oil (+++). The test was conducted on healthy controls (n = 3) with negative results.	[80]

Table 19. Case reports of *Eucalyptus globulus* exposure.

Summary	Reference
Eucalyptus Globulus Leaf Oil was used to treat a male subject who had chronic postoperative osteomyelitis of the right femur with a draining sinus that failed to respond to ciprofloxacin and rifampicin during 2 years of antibiotic therapy. The infected site was treated with a cream containing Eucalyptus Globulus Leaf Oil (1.0 g/day) to the sinus for 5 days and no antibiotics were used. The wound was completely healed at 2 weeks and no adverse effects from the Eucalyptus Globulus Leaf Oil were reported.	82
Eucalyptus Globulus Leaf Oil was used to treat a 42-year-old man with an infection after a mid-foot fracture and dislocation. The infected tissue was surgically debrided and a cream containing Eucalyptus Globulus Leaf Oil (0.5 g/day) was applied for 3 weeks. No antibiotics were used. The subject was clear of infection at 12 weeks with no adverse effects from Eucalyptus Globulus Leaf Oil were reported.	82
A 12-year-old boy splashed Eucalyptus Globulus Leaf Oil (amount unknown) on his face. No symptoms developed.	83
A 4-year-old boy was placed in a bath containing Eucalyptus Globulus Leaf Oil (amount unknown). He developed redness, irritation, and burning sensation on his buttocks and penis soon after being placed in the water. He was removed from the bath and rinse with water. The irritation resolved within 1 h.	83
A 6-year-old girl presented with slurred speech, ataxia and muscle weakness progressing to unconsciousness following the widespread application of a home remedy for urticaria. This remedy consisted of: apple cider vinegar (200 ml), olive oil (200 ml), methylated spirits (200 ml); 95% ethanol (containing no methanol), and Eucalyptus Globulus Leaf Oil (50 ml; double distilled, containing 80% to 85% eucalyptol oil). The concoction (approximately 400 ml) had been applied to her limbs and trunk under plastic wrap and the dressing changed every 2 to 4 h for 2 days. When she was not improving, the amount of Eucalyptus Globulus Leaf Oil was doubled in the concoction. Within 10 to 15 min of applying the bandages, she appeared “intoxicated” with slurred speech and unsteady gait. She improved following removal of the topical preparation and bathing but was still drowsy, nauseated, and vomiting. After a night in the hospital, her symptoms resolved, with no long-term effects.	79
A 65-year-old, otherwise healthy woman, who worked as an aromatherapist presented with eczema on her arms and upper trunk, which later spread to her legs, face, and hands. She had no history of skin disease in herself or her family. Her hand eczema became chronic and associate with handling household cleansers, sealing wax, paints, and the essential oils, which she diluted herself. When patch tested with Finn Chambers, she had a ++ reaction to Eucalyptus Globulus Leaf Oil at 5% in petrolatum, but not at 1%.	81
A 27-year-old professional athlete had been using an analgesic and anti-inflammatory cream for 2 years before pruritus and erythema appeared on the toes of the left foot. The next application of the cream caused papules and vesicles, with increasing pruritus. A topical corticosteroid relieved his symptoms; he still had a vesicular scaly eczema on the dorsa of the toes of the left foot. Patch testing with TRUE Test™ standard allergens and the Chemotechnique cosmetics series was negative. Eucalyptus Globulus Leaf Oil (1% in petrolatum) gave a + + reaction at Days 2 and 4; the other ingredients of the cream were negative. The controls were all negative at Days 2 and 4.	84
Oral	
After an evening meal an adult male took a large teaspoonful of Eucalyptus Globulus Leaf Oil. He immediately experienced esophageal pain followed by gasping for breath, restlessness, and convulsive movements of his hands. He was semi-comatose passing to coma. Vomiting was induced prior to him becoming comatose and he gradually recovered consciousness being quite well by next morning.	11
An adult male who took 10 ml to 15 ml of Eucalyptus Globulus Leaf Oil became ataxic and faint within 10 min. He soon had distressing dyspnea, weak pulse, and violent vomiting. His skin was greenish-yellow. Half an hour after ingestion he was very drowsy, had painful and excessive micturition and was experiencing violent diarrhea. For 3 days he was drowsy, ataxic and his skin retained the chlorotic hue. For nearly 2 weeks his breathe, feces, and skin smelt of the oil and it was a full 2 weeks before he fully recovered.	11
An adult male took approximately 25 ml of Eucalyptus Globulus Leaf Oil. Within 2 h he was dazed and friends successfully induced vomiting. Four hours after ingestion he was cyanosed with labored breathing, foaming at the mouth, congestion, rhonchi, and moist rales throughout both lungs. He was administered oxygen with a stimulant and 5 to 6 h later was recovered enough to answer questions. However 13 h after ingestion he complained of difficulty and pain in drawing his breathe. Breathing became more rapid and labored and his pulse was quick and thready. He died 40 h after taking the oil. Death was presumed to be due to bronchopneumonia.	11
An adult who ingested 120 to 220 ml Eucalyptus Globulus Leaf Oil had severe poisoning and was successfully treated with mannitol, hemodialysis, and peritoneal dialysis.	11
A 7 month old boy was offered a teaspoonful of Eucalyptus Globulus Leaf Oil. He coughed, choked and some of the oil was spilled. His skin was pale. He collapsed with rapid shallow respirations and feeble pulse 25 min after ingestion later. Limbs were flaccid, pupils pin-point, rhonchi was heard at both bases. His stomach was washed out and 3 h later he was showing spontaneous movement. At 24 h his general state was good. The odor stayed on his breath for 72 h.	85
A 6-year-old boy took 4 to 5 ml of Eucalyptus Globulus Leaf Oil and exhibited severe vomiting within 2 h. He was semi-comatose 5 h later. There was no coughing and his breathing was shallow. After approximately 8 h, he recovered from the heavy comatose condition and he slept until the next day where he appeared to have recovered. His breathe smelt of Eucalyptus Globulus Leaf Oil for 3 days. In summary the poisoning manifested itself as gastrointestinal irritation and cerebral paresis.	86

Table 19. Case reports of *Eucalyptus globulus* exposure.

Summary	Reference
A 10-year-old boy ingested approximately 15 ml of Eucalyptus Globulus Leaf Oil. In a few minutes he was gasping for air and vomited heavily once. He was breathing well for about an hour. He then began struggling for air, which increased until his death 15 h after ingestion of the oil. He spoke rationally several times within an hour of his death.	11
A 3-year-old boy ingested 10 ml of Eucalyptus Globulus Leaf Oil. Within 30 min he was deeply comatose and his breath smelt strongly of Eucalyptus Globulus Leaf Oil. Pupils were constricted, muscle tone markedly reduced, and tendon reflexes could not be elicited. Respirations were shallow and irregular. Respiratory rate, blood pressure, and pulse returned to normal after 2.5 h. After 5 h, consciousness was gradually regained and by 24 h, physical examination was normal apart from a faint smell of eucalyptus on the breathe.	88
A 6-year-old child was administered approximately 15 ml of Eucalyptus Globulus Leaf Oil and experienced only slight drowsiness.	11
A 2.5-year-old child was found after ingesting Eucalyptus Globulus Leaf Oil (estimated 5 ml). She had no symptoms at first, but after 45 min she was listless and unresponsive. She was taken to the emergency room and administered activated charcoal and a cathartic via a nasogastric tube. She vomited the charcoal. Heartrate after 3 h in the hospital was 117 beats/min. Her CNS symptoms gradually improved and resolved over the next 7 h. She had several apneic episodes during this time.	83
A 29-year-old male accidentally ingested Eucalyptus Globulus Leaf Oil (originally thought to be 3 to 4 ounces, but determined to be approximately 1 ounce (approximately 30 ml). He immediately started gagging and vigorous vomiting. At the emergency room, he was lavaged and administered activated charcoal and cathartic. Within 40 min, he was drowsy, but not comatose. Pulse ranged from 68 to 80 beats per min and BP ranged from 90/60 to 110/70 mmHg. After approximately 3.5 h, he experienced PVCs-trigeminal runs, described as 1 to every 6 beats to 1 to every 3 beats. The subject has no history of cardiac abnormalities. The cardiac symptoms continued for 8 to 10 h while his BP was around 90/60. Symptoms resolved within 24 h.	83
A 6-year-old boy presented with status epilepticus within 10 min of accidental ingestion of Eucalyptus Globulus Leaf Oil (10 ml). He had eight episodes of tonic-clonic convulsions which were controlled with intravenous phenytoin and valproate. There was no previous history of seizures. His kidney function tests, liver function tests, blood sugar, and serum calcium were normal. His EEG showed spikes. Child improved substantially within 20 h and was discharged.	87
A 3-year-old boy presented with status epilepticus within 10 min of accidental ingestion of Eucalyptus oil (5 ml). He had four episodes of tonic-clonic convulsions which were controlled with i.v. phenytoin. There was no previous history of seizures. His kidney function tests, blood sugar, and serum calcium were normal. He improved and was discharged.	87
Inhalation	
A 46-year-old woman with a past medical history of hypothyroidism, migraine headaches, peptic ulcer disease, depression, and allergic rhinitis became ill when she developed a sore throat and complained of episodic dyspnea that appeared primarily at work. She reported that chest tightness and wheezing seemed to be associated with exposure to a *Eucalyptus* sp. plant. In one instance her respiratory symptoms was severe enough to require hospitalization. Spiral chest computed tomography excluded pulmonary emboli, and high-resolution chest computed tomography showed a few areas of ground-glass densities. She had a normal IgE level (63 IU/ml). She was treated with corticosteroids and bronchodilators but had no improvement in her symptoms. Re-exposure to *Eucalyptus* sp. plant caused recurrent bouts of chest tightness, dyspnea, cough, hoarseness, and wheezing. She had negative skin test results for immediate hypersensitivity to a variety of inhalant allergens. The patient underwent 2 challenges to *Eucalyptus* sp. performed 1 month apart. All stimuli were applied to gauze held approximately 5" from the nares. Dry *Eucalyptus* sp. leaves were used to impregnate the test gauze. The initial challenge was with *Eucalyptus* and was not masked. There was obvious adduction of the vocal cords within 30 seconds of the inhalation. The second test was water first, followed by ammonia, pine oil, and an ammonia-*Eucalyptus* mixture. She began to experience the paradoxical vocal cord motion after a few minutes of exposure. The VCD persisted for several minutes after the testing and was exacerbated with talking.	89
The accidental administration of Eucalyptus Globulus Leaf Oil to 9 children (ranging from 1 month to 3 years of age) in the form of nose drops. The children were reported cry out after instillation. All children smelled of eucalyptol. Four had irritated nasal mucous membranes and one had tachycardia. All of their noses were rinsed with NaCl (0.9%). Some of the children were treated with gastric lavage. The symptoms of Eucalyptus Globulus Leaf Oil poisoning were nasal and epigastric burning, nausea, vomiting, dizziness, muscular weakness, miosis, tachycardia, and a feeling of suffocation. Cyanosis, delirium, and convulsions may be exhibited, especially in infants.	90

BP – blood pressure; CNS – central nervous system; EEG = electroencephalogram; PVC - premature ventricular contractions; VCD - vocal cord dysfunction

REFERENCES

1. Nikitakis, J and Lange B (eds). Web-Based Ingredient Dictionary (wINCI). http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC. Last Updated 2017. Date Accessed 5-2-2017.

2. Goossens, A. Cosmetic Contact Allergens. *Multidisciplinary Digital Publishing Institute: Cosmetics*. 2016;3(5):1-11.

3. Hagvall, L, Karlberg, A, and Christensson, J. Contact allergy to air-exposed geraniol: clinical observations and report of 14 cases. *Contact Dermatitis*. 2012;67(1):20-27.

4. Hagvall, L, Karlberg, A, and Christensson, J. Finding the optimal patch test material and test concentration to detect contact allergy to geraniol. *Contact Dermatitis*. 2013;68(4):224-234.

5. Nijkamp, MM, Bokkers, B, Bakker, M, Exendam, J, and Delmaar, J. Quantitiative risk assessment of the aggregate dermal exposure to the sensitizing fragrance geraniol in personal care products and household cleaning products. *Regulatory Toxicology and Pharmacology*. 2015;73(1):9-18.

6. Tisserand, R and Young, R. Essential Oil Safety. 2 *ed*. Edinburgh, UK: Churchill Livingstone, Elsevier, 2014.

7. World Health Organization (WHO). WHO monographs on selected medicinal plants, Vol. 2. http://apps.who.int/medicinedocs/pdf/s4927e/s4927e.pdf. Geneva. Last Updated 1999.

8. Shah, G, Kaur, M, Singh, P, Rahar, S, Dhabliya, F, Arya, Y, and Shri, R. Pharmacognostic parameters of *Eucalyptus globulus* leaves. *Pharmacognosy Journal*. 2012;4(24):38-43.

9. Bergfeld, WF, Belsito, DV, Klaassen, CD, Liebler, DC, Hill, RA, Marks Jr, JG, Shank, RC, Slaga, TJ, Snyder, PW, Gill, LJ, and Becker, LC. Safety assessment of phytosterols as used in cosmetics. Washington, DC, Cosmetic Ingredient Review. 2013. pp. 1-23.

10. European Chemicals Agency (ECHA). Eucalyptus globulus, ext. http://echa.europa.eu/registration-dossier/-/registered-dossier/14864. European Chemicals Agency (ECHA). Last Updated 5-28-2017. Date Accessed 7-10-0017.

11. International Program of Chemical Safety (INCHEM). Eucalyptus oil. http://www.inchem.org/documents/pims/pharm/pim031.htm#PartTitle:1.%20NAME. Last Updated 1998. Date Accessed 9-5-2017.

12. European Medicines Agency (EMA). Assessment report on *Eucalytus* [sic] *globulus* labil., *Eucalyptus polybractea* R.T. Baker and/or *Eucalyptus smithii* R.T. Baker, aetheroleum. London, United Kingdom, European Medicines Agency. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2013/07/WC500147006.pdf. Date Accessed 7-13-2017. Report No. EMA/HMPC/307782/2012. pp. 1-38.

13. Vuong, QV, Chalmers, A, Bhyan, D, Bowyer, M, and Scarlett, C. Botanical, phytochemical, and anticancer properties of the *Eucalyptus* species. *Chemistry & Biodiversity*. 2015;12(6):907-924.

14. U.S. National Plant Germplasm System. Taxon: *Eucalyptus globulus* Labill. http://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?id=15919. Last Updated 3-13-2017. Date Accessed 7-10-2017.

15. British Pharmacopoeia 2008. 5 *ed*. London: British Parmacopoeia Commission, 2008.

16. Saveyn, A, Steppe, K, Ubierna, N, and Dawson, T. Woody tissue photoshynthesis and its contribution to trunk growth and bud development in young plants. *Plant, Cell & Environment*. 2010;33(11):1949-1958.

17. Santos, RL. The Eucalyptus of California; Seeds of Good or Seeds of Evil? [pamphlet]. Denair, CA: Alley-Cass Publications; 1997.

18. Eyles, A, Pinkard, E, O'Grady, A, Worledge, D, and Warren, C. Role of corticular photosynthesis following defoliation in *Eucalyptus globulus*. *Plant, Cell & Environment*. 2009;32(8):1004-1014.

19. Kaur, G, Mohiuddin, I, and Aulakh, J. An approach on phytochemistry and pharmacological studies of Eucalyptus globulus plant parts. *Research Journal of Material Sciences*. 2017;5(4):1-9.

20. Boutkhatem, MN, Amine, F, Kameli, A, Saidi, F, Walid, K, and Mohamed, S. Quality assessment of the essential oil from *Eucalyptus globulus* Labill of Blida (Algeria) origin. *International Letters of Chemistry, Physics and Astronomy*. 2014;36(3):303-315.

21. Boelens, MH. Essential oils and aroma chemicals from Euclayptus Globlulus Labill. *Perfumer and Flavorist*. 1984;9(December/January):2-14.

22. Personal Care Products Council. 12-14-2017. Eucalyptus Globulus Leaf Extract. Unpublished data submitted by Personal Care Products Council.

23. Song, A, Wang, Y, and Liu, Y. Study on the chemical constituents of the essential oil of the leaves of *Eucalyptus globulus* Labill from China. *Asian Journal of Traditional Medicines*. 2009;4(4):134-140.

24. Subramanian, PA, Gebrekidan, A, and Nigussie, K. Yeild, contents and chemical composition variations in the essential oils of different *Eucalyptus globulus* trees from Tigray, Northern Ethiopia. *Journal of Pharmaceutical and Biomedical Sciences.* 2012;17(11):1-6.

25. Matura, M, Skõld, M, Börje, A, Andersen, K, Bruze, M, Frosch, P, Goossens, A, Johansen, J, Svedman, C, White, I, and Karlberg, A. Not only oxidized R-(+)- but also S-(-)-limonene is a common cause of contact allergy in dermatitits patients in Europe. *Contact Dermatitis.* 2006;55(5):274-279.

26. Bickers D, Calow P, Greim H, Hanifin JM, Rogers AE, Saurat JH, Sipes IG Smith RL, and Tagami H. A toxicologic and dermatologic assessment of linalool and realated esters when used as fragrance ingredients. *Food and Chemical Toxicology*. 2003;41(7):919-942.

27. Duke JA. Handbook of phytochmical constituents of GRAS herbs and other economic plants. Boca Raton, FL: CRC Press, 1992.

28. National Toxicology Program (NTP). NTP technical report on the toxicology and carcinogenesis studies of β-myrcene (CAS No. 123-35-3) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC, National Institutes of Health. 2010. http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr557.pdf. Report No. 11-5898. 169.

29. Roe, FJC and Field, W. Chronic toxicity of essential oils and certain other products of natural origin. *Food and Cosmetics Toxicology*. 1965;3(2):311-324.

30. Homberger, F and Boger, E. The carcinogenicity of essential oils, flavors, and spices: A review. *Cancer Research.* 1968;28(11):2372-2374.

31. National Toxicology Program (NTP). NTP Techinacal Report on the toxicity studies of α-pinene (CAS No. 80-56-8) administered by inhalation to F344/N rats and B6C3F1/N mice. Research Triangle Park, NC, National Toxicology Program (NTP. 2016. http://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox081_508.pdf. Report No. 81. pp. 1-119.

32. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, and Lines TC. A critical review of the data related to the safety of quercetin and lack of evidene of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. *Food and Chemical Toxicology*. 2007;45(11):2179-2205.

33. Poginsky B, Westendorf N, Prosenc N, Kuppe M, and Marquardt H. St. John's wort (*Hypericum perforatum* L.). Genotoxicity induced by quercetin content. *Deutsche Apotheker Zeitung*. 1988;128(26):1364-1366.

34. International Fragrance Association (IFRA). IFRA Standards. 2017. http://www.ifraorg.org/en-us/standards-library. Date Accessed 1-30-2017.

35. Native Extracts. 2017. Specification technical data sheet NE Tasmanian Blue Gum Extract Cosmetic. Unpublished data submitted by Personal Care Products Council.

36. Native Extracts. 2017. Safety data sheet: NE Tasmanian Blue Gum Extract. Unpublished data submitted by Personal Care Products Council.

37. Anonymous. 2-2-2018. Eucalyptus Globulus Leaf Extract: Summary specification information. Unpublished data submitted by Personal Care Products Council.

38. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD, 2018. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3 2018; received February 5 2018).

39. Personal Care Products Council. 2-20-2018. Updated Concentration of Use by FDA Product Category: Eucalyptus globulus-Derived Ingredients. Unpublished data submitted by Personal Care Products Council.

40. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;14(11):24-27.

41. Rothe H. Special aspects of cosmetic spray safety evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C.

42. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

43. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett.* 8-28-2011;205(2):97-104. PM:21669261.

44. United States Pharmacopeial Convention. The United States Pharmacopeia, The National Formulary. 27 *ed*. Rockville, MD, USA: United States Pharmacopeial Convention, 2009.

45. Food and Drug Administration (FDA). Cosmetics Program; Import and domestic. Chapter: 29. In: *Food and Drug Administration Compliance Program Guidance Manual*. 2016:1-43.

46. European Commission. CosIng database: following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/growth/tools-databases/cosing/. Last Updated 2015. Date Accessed 7-12-2017.

47. European Commission Scientific Committee on Food. Opinion of the Scientific Committee on Food on euclalyptol. Brussel, Belgium, European Commission Health & Consumer Protection Directorate-General. 2002. http://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out126_en.pdf. Date Accessed 9-19-2017. Report No. SCF/CS/FLAV/FLAVOUR/20 ADD2 Final. pp. 1-10.

48. Health Canada. Natural Health Products; Aromatherapy - essential oils. 2015. http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=aromatherap&lang=eng. Date Accessed 1-19-2017.pp. 1-14.

49. Karpanen, TJ, Conway, B, Worthington, T, Hilton, A, and Elliott, T. Enhanced chlorhexidine skin penetration with eucalyptus oil. *BMC Infectious Diseases*. 2010;10(278):1-6.

50. Shen, T, Xu, H, Weng, W, and Zhang, J. Development of a reservoir-type transdermal delivery system containing eucalyptus oil for tettramethylpyrazine. *Drug Delivery*. 2013;20(1):19-24.

51. Amrish, C and Kumar, S. Transermal delivery of ketorolac. *Yakugaku Zasshi*. 2009;129(3):373-379.

52. Abdulla, D, Ping, Q, and Liu, G. Enhancing effect of essential oils on the penetration of 5-fluorouracil through rat skin. *Acta Parmaceutica Sinica*. 1996;31(3):214-221.

53. Scientific Committee on Food. Opinion of the Scientific Committee on Food on eucalyptol. http://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out126_en.pdf. Bruxelles/Brussel, Belgium. Last Updated 2002. Date Accessed 9-19-2017.

54. Opdyke, DLJ. Fragrance raw materials monographs: Eucalyptol. *Food and Chemical Toxicology*. 1975;13(1):105-106.

55. Bhowal, M and Gopal, M. Eucalyptol: Safety and phamacological profile. *RGUHS Journal of Phamaceutical Sciences*. 2015;5(4)-125.

56. Kovar, KA, Gropper, B, Friess, D, and Ammon, H. Blood levels of 1,8-cineole and locomotor activity of mice after inhalation and oral administration of rosemary oil. *Planta Medica*. 1987;53(4):315-318.

57. Gebremickael, A. Acute and sub-chronic oral toxicity evaluation of Eucalyptus globulus essential oil-water emulsion in mice. *Journal of Cytology & Histology*. 2017;8(3):1-7.

58. Hu, Z, Feng, R, Xiang, F, Song, X, Yin, Z, Zhang, C, Zhao, X, Jia, R, Chen, Z, Li, L, Yin, L, Liang, X, He, C, Shu, G, Lv, C, Zhao, L, Ye, G, and Shi, F. Acute and subchronic toxicity as well as evaluation of safety pharmacology of eucalytus oil-water emulsions. *International Journal of Clinical and Experimental Medicine*. 2014;7(12):4835-4845.

59. Shalaby, SEM, El-Din, M, Abo-Donia, S, Mettwally, M, and Attia, Z. Toxicological affects of essential oils from eucalyptus *Eucalyptus globules* and clove *Eugenia caryophyllus* on albino rats. *Polish Journal of Environmental Studies*. 2011;20(2):429-434.

60. Boyd, EM and Sheppard, E. The effect of steam inhalation of volatile oils on the output and composition of respriatory tract fluid. *The Journal of Pharmacology and Experimental Therapeutics*. 1968;163(1):250-256.

61. Bastos, VPD, Gomes, A, Lima, F, Brito, T, Soares, P, Pinho, J, Silva, C, Santos, A, Sourza, M, and Magalhães, P. Inhaled 1,8-cineole reduces inflammatory parameters of ovalbumin-challenged guinea pigs. *Basic & Clinical Pharmacology & Toxicology*. 2010;108(1):34-39.

62. Alzergy, AA, Mohamed, N, and Itia, A. Toxicity of aqueous extract of *Eucalyptus* in Swice [sic] albino mice. *Suez Canal Veterinary Mdicine Journal (SCVMJ)*. 2010;15(1):199-214.

63. Arise, RO, Malomo, S, Adebayo, J, and Igunnu, A. Effects of aqeous extract of *Eucalyptus globulus* on lipid peroxication and selected enzymes of rat liver. *Journal of Medicinal Plants Research*. 2009;3(2):077-081.

64. Dhibi, S, Mbarki, S, Elfeki, A, and Hfaiedh, N. *Eucalyptus globulus* extract protects upon acetaminophen-induced kidney damages in male rat. *Bosnian Journal of Basic Medical Sciences*. 2014;14(2):99-104.

65. Roe, FJC, Palmer, A, and Worden, A. Safety evaluation of toothpaste containing chloroform I. Long-term studies in mice. *Journal of Environmental Pathology and Toxicology*. 1979;2(3):799-819.

66. European Chemicals Agency (ECHA). Cineole. http://echa.europa.eu/registration-dossier/-/registered-dossier/13231/1. European Chemicals Agency (ECHA). Last Updated 9-26-2017. Date Accessed 10-19-2017.

67. Opdyke, DLJ. Fragrance raw materials monographs: Eucalyptus oil. *Food and Chemical Toxicology*. 1975;13(1):107-108.

68. Sharp, DW. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. *Toxicology*. 1978;9(3):261-271.

69. Research Testing Laboratories Incorporated. 1980. Human subject patch test study: Schwartz-Peck Prophetic Patch and Draize-Shelanski Repeat Insult test of a skin cream containing 0.1% Eucalyptus Oil. Unpublished data submitted by Personal Care Products Council.

70. TKL Research Inc. 2010. Human repeated insult patch test with challenge (lipstick containing 0.5% Eucalyptus Globulus Leaf Oil). Unpublished data submitted by Personal Care Products Council.

71. Placzek, M, Frömel, W, Eberlein, B, Gilbertz, K-P, and Przybilla, B. Evaluation of phototoxic properties of fragrances. *Acta Dermato Venereologica*. 2007;87(4):312-316.

72. Uter, W, Schmidt, E, Geier, J, Lessmann, H, Schnuch, A, and Frosch, P. Contact allergy to essential oils: Current patch test results (2000-2008) from the Information Network of Departments of Dermatology (IVDK). *Contact Dermatitis*. 2010;63(5):277-283.

73. Nardelli, A, Drieghe, J, Claes, L, Boey, L, and Goossens, A. Fragrance allergens in "specific" cosmetic products. *Contact Dermatitis.* 2011;64(4):212-219.

74. Rudzki, E and Grzywa, Z. Allergy to perfume mixture. *Contact Dermatitis*. 1986;15(2):115-116.

75. Guin, JD. Use of consumer product ingredients for patch testing. *Dermatitis.* 2005;16(2):71-77.

76. Rudzki, E, Grzywa, Z, and Bruo, W. Sensitivity to 35 essential oils. *Contact Dermatitis*. 1976;2(4):196-200.

77. Rudzki, E and Grzywa, Z. Balsam of Peru as screening agent for essential oils sensitivity. *Dermatolagica*. 1977;155(2):115-121.

78. Tibballs, J. Clinical effects and management of eucalyptus oil ingestion in infants and young children. *Medical Journal of Austrailia.* 1995;163(4):177-180.

79. Darben, T, Cominos, B, and Lee, C. Topical eucalyptus oil poisoning. *Australiasian Journal of Dermatology*. 1998;39(4):265-267.

80. Kartal, D, Kartal, L, Çinar, S, and Borlu, M. Allergic contact dermatitis caused by both eucalyptus oil and spruce oil. *International Journal of Medical and Parmaceutical Case Reports.* 2016;7(2):1-3.

81. Selvaag, E, Holm, J-Ø, and Thune, P. Allergic contact dermatitis in an aroma therapist with multiple sensitizations to essential oils. *Contact Dermatitis*. 1995;33(5):354-355.

82. Sherry, E, Boeck, H, and Warnke, P. Topical application of a new formulation of eucalyptus oil phytochemical clears methicillin-resistant *Staphylococcus aureus* infection. *American Journal of Infection Control*. 2001;29(5):346

83. Spoerke, DG, Vandenberg, S, Smolinske, S, Kulig, K, and Rumack, B. Eucalyptus oil: 14 cases of exposure. *Veterinary and Human Toxicology*. 1989;31(2):166-168.

84. Vilaplana, J and Romaguere, C. Allergic contact dermatitis due to eucalyptol in an anti-inflammatory cream. *Contact Dermatitis*. 2000;43(2):118

85. Craig, JO. Poisoning by the volatile oils in childhood. *Archives of Disease in Childhood.* 1953;28(142):475-483.

86. Foggie, WE. Eucalyptus oil poisoning. *The British Medical Journal*. 1911;1(February 18, 2616):359-360.

87. Kumar, KJ, Sonnathi, S, Anitha, C, and Santhoshkumar, M. Eucalyptus oil poisoning. *Toxicology International*. 2015;22(1):170-171.

88. Patel, S and Wiggins, J. Eucalyptus oil poisoning. *Archives of Disease in Childhood*. 1980;55(5):405-406.

89. Huggins, JT, Kaplan, A, Martin-Harris, B, and Sahn, S. Eucalyptus as a specific irritant causing vocal cord dysfunction. *Annals of Allergy, Asthma & Immunology*. 2004;93(3):299-303.

90. Melis, K, Bochner, A, and Janssens, G. Accidental nasal eucalyptol and menthol instillation. *European Journal of Pediatrics.* 1989;148(8):786-787.

91. Anonymous. 2011. Certificate of analysis Australian Eucalyptus Oil. Unpublished data submitted by Personal Care Products Council.

92. Wetter, DA, Yiannias, J, Prakash, A, Davis, M, Farmer, S, and el-Azhary, R. Results of patch testing to personal care product allergens in a standard series and a supplemental cosmetic series: An analysis of 945 patients from the Mayo Clinic Contact Dermatitis Group, 2000-2007. *Journal of the American Academy of Dermatology*. 2010;63(5):789-798.

2018 VCRP Data for Eucalyptus-Derived Ingredients

02A - Bath Oils, Tablets, and Salts	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	2
02D - Other Bath Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
03D - Eye Lotion	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	2
04C - Powders (dusting and talcum, excluding aftershave talc)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
05A - Hair Conditioner	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	3
05F - Shampoos (non-coloring)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	7
05I - Other Hair Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	7
07C - Foundations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
07E - Lipstick	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
08E - Nail Polish and Enamel	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
08G - Other Manicuring Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
10A - Bath Soaps and Detergents	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	3
10B - Deodorants (underarm)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	4
10E - Other Personal Cleanliness Products	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
12A - Cleansing	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	6
12B - Depilatories	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
12C - Face and Neck (exc shave)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	6
12D - Body and Hand (exc shave)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	4
12F - Moisturizing	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	16
12H - Paste Masks (mud packs)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	1
12J - Other Skin Care Preps	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF EXTRACT	8
		77

01A - Baby Shampoos	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
01B - Baby Lotions, Oils, Powders, and Creams	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	4
01C - Other Baby Products	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	2
02A - Bath Oils, Tablets, and Salts	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	47
02B - Bubble Baths	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	7
02D - Other Bath Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	5
03D - Eye Lotion	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
03G - Other Eye Makeup Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
04A - Cologne and Toilet waters	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1

04B - Perfumes	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
04E - Other Fragrance Preparation	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	15
05A - Hair Conditioner	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	13
05B - Hair Spray (aerosol fixatives)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
05E - Rinses (non-coloring)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
05F - Shampoos (non-coloring)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	29
05G - Tonics, Dressings, and Other Hair Grooming Aids	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	5
05H - Wave Sets	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
05I - Other Hair Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	4
06D - Hair Shampoos (coloring)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
07C - Foundations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
07I - Other Makeup Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
08E - Nail Polish and Enamel	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
08G - Other Manicuring Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
09A - Dentifrices	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	4
09C - Other Oral Hygiene Products	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3
10A - Bath Soaps and Detergents	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	53
10B - Deodorants (underarm)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3
10E - Other Personal Cleanliness Products	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	12
11B - Beard Softeners	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	4
11D - Preshave Lotions (all types)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	2
11E - Shaving Cream	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3
11G - Other Shaving Preparation Products	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	9
12A - Cleansing	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	17
12C - Face and Neck (exc shave)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	18
12D - Body and Hand (exc shave)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	23
12E - Foot Powders and Sprays	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	7
12F - Moisturizing	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	64
12H - Paste Masks (mud packs)	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	11
12I - Skin Fresheners	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3
12J - Other Skin Care Preps	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	52
13B - Indoor Tanning Preparations	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	1
		433

12A - Cleansing	EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF POWDER	2

02A - Bath Oils, Tablets, and Salts	EUCALYPTUS	7
04B - Perfumes	EUCALYPTUS	5
04E - Other Fragrance Preparation	EUCALYPTUS	5
05F - Shampoos (non-coloring)	EUCALYPTUS	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	EUCALYPTUS	1
08G - Other Manicuring Preparations	EUCALYPTUS	2
10A - Bath Soaps and Detergents	EUCALYPTUS	1
10E - Other Personal Cleanliness Products	EUCALYPTUS	1
12C - Face and Neck (exc shave)	EUCALYPTUS	2
12D - Body and Hand (exc shave)	EUCALYPTUS	6
12F - Moisturizing	EUCALYPTUS	1
12J - Other Skin Care Preps	EUCALYPTUS	10
		42

02A - Bath Oils, Tablets, and Salts	EUCALYPTUS EXTRACT	1
05F - Shampoos (non-coloring)	EUCALYPTUS EXTRACT	1
10A - Bath Soaps and Detergents	EUCALYPTUS EXTRACT	2
10E - Other Personal Cleanliness Products	EUCALYPTUS EXTRACT	1
12A - Cleansing	EUCALYPTUS EXTRACT	1
12E - Foot Powders and Sprays	EUCALYPTUS EXTRACT	1
12F - Moisturizing	EUCALYPTUS EXTRACT	4
		11

There were no reported uses in the 2018 VCRP for:

Eucalyptus Globulus Leaf
Eucalyptus Globulus Leaf/Twig Oil
Eucalyptus Globulus Leaf Water

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: February 23, 2018

SUBJECT: Draft Tentative Report: Safety Assessment of *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients as Used in Cosmetics (draft prepared for the March 5-6, 2018 CIR Expert Panel Meeting)

The Council respectfully submits the following comments on the draft tentative report, Safety Assessment of *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients as Used in Cosmetics.

Key Issues

In addition to the 1975 RIFM monograph on eucalyptol, there is a 1975 RIFM monograph on Eucalyptus Oil (previously provided by the Council as Opdyke 1975 (*Food and Cosmetics Toxicology* 13(1): 107-108)). Although the species is not included in the name of the ingredient, the description of the oil clearly states that the main constituent is eucalyptol and that it is prepared by the steam-distillation of leaves of *E. globulus* and other species of Eucalyptus. The 1975 RIFM monograph includes a maximization test of 10% Eucalyptus oil in petrolatum in 25 volunteers. It was negative. This information, and other information from the RIFM monograph, such as irritation studies, still need to be added to the CIR report.

Non-Cosmetic Use - For comparison, the concentration of Eucalyptus globulus oil permitted in nasal decongestant products (1.2-1.3%) listed in 21 CFR 341.40 should be added to the report.

ADME - The review by Bhowal and Gopal (2015) (reference 51) cites a study on the metabolism of 1,8-cineole (eucalyptol) from rosemary oil. They reported that in mice orally dosed with up to 200 mg/kg 1,8-cineole there was rapid absorption and metabolism. Metabolism slowed at higher doses suggesting saturation. The primary reference should be obtained and added to this CIR report.

Discussion - It is misleading to state that there are no data at the maximum concentration of use. There is a negative human maximization study of 10% eucalyptus oil included in the RIFM monograph on eucalyptus oil. The negative maximization study of 16% eucalyptol

included in the RIFM monograph of eucalyptol should also be mentioned in the Discussion.

Additional Considerations

Introduction - It does not make sense to state that CIR is not reviewing information on individual constituents, then to state that relevant data on eucalyptol is being reviewed.

Constituents of Concern - It is not clear why phellandrene is being considered a constituent of concern. It is not listed in Table 9. The summary of data on phellandrene in the *Essential Oils Safety Handbook* indicates that it was not genotoxic to CHO cells and not carcinogenic by itself. On what basis is it being considered genotoxic or a potential carcinogen?

Cosmetic Use - This section mentions that there are NF specifications for Eucalyptus globulus oil. They should be added to the CIR report.

Non-Cosmetic Use - It is not correct to state that Eucalyptus globulus oil is used in OTC smoking deterrents. This is from 21 CFR 310 - the section listing materials for which there is a lack of data to support use.

ADME - The first sentence does not make sense. It states: "Eucalyptus Globulus Leaf Oil is readily absorbed when orally administered and is expected to increase the presence of lipids in substances such as milk." It is probably trying to say (as written in the third paragraph of the ADME section): "Eucalyptol is quickly absorbed from the gastrointestinal tract. It is lipid soluble and absorption is enhanced in the presence of milk." It is not clear why this needs to be said for both the oil and eucalyptol.

Acute, Inhalation - As Eucalyptus oil was added to boiling water for exposure, please indicate if the stated doses are mg/kg body weight.

Acute, Human, Oral - It is not clear why mention of nephritis is not included in the same sentence in which urinary tract symptoms are discussed.

Clinical Studies, Oral - The number of subjects included in the study of children from Australia (reference 74) should be added to the report.

Summary - Please indicate the material for which "The probable oral lethal dose for adult humans is 0.05 mL to 0.5 mL/kg."

Please state the doses of Eucalyptus Globulus Oil that had no effect on the volume of respiratory tract fluid.

The maximization studies included in the RIFM monographs for eucalyptol and eucalyptus oil still need to be added to the summary.

Table 17 - The location of the study is mentioned in the Details column for all but reference 68. Please add the location of the study for reference 68.

Reference 62 - The date for this reference should be 1975 not 2017. The page numbers should be 105-106 for eucalyptol and 107-108 for eucalyptus oil.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: April 2, 2018

SUBJECT: Tentative Report: Safety Assessment of *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients as Used in Cosmetics (release date March 16, 2018)

The Council respectfully submits the following comments on the tentative report, Safety Assessment of *Eucalyptus globulus* (Eucalyptus)-Derived Ingredients as Used in Cosmetics.

Introduction - As the dossier on the ECHA website was prepared by organizations submitting the information, it is not correct to say "including reports by the European Chemicals Agency (ECHA)...".

Composition/Constituents - "reported by ECHA" should be changed to "reported to ECHA"

Impurities, Table 11 - It should be made clear that the allergens that were measured were the 26 fragrance allergens defined by the 7th amendment of the EU cosmetics directive.

ADME - The two sentences "Eucalyptol undergoes oxidation in vivo with the formation of hydroxycineole which is excreted as [a] glucuronide." and "Eucalyptol is reported to undergo oxidation in vivo forming hydroxycineole, which is excreted as hydroxycineole-glucuronic acid." are saying the same thing (hydroxycineole-glucuronic acid is the glucuronide inferred in the first sentence). One of these sentences should be deleted.

Short-Term, Oral, Eucalyptus Globulus Leaf Extract, Summary, Table 15 - The meaning of "130 mg/dry leaves/kg" is not clear. It does not appear to represent a dose as Table 15 indicates that the rats were given 1 g/L in the drinking water. Perhaps the extract was prepared with 130 mg of dry leaves/kg of 80% aqueous ethanol?

Short-Term, Oral, Eucalyptus Globulus Leaf Oil - Please state the frequency of dosing, e.g., /day, for references 57 and 10 (first study). The third study described (with 3 rats/group) was a dose range-finding study for the gavage combined repeated dose and reproductive/developmental toxicity study. Please delete: "(route not stated)".

Short-term, Oral, Eucalyptol - It should be made clear that encapsulated eucalyptol was added to the diet (not given as a bolus dose).

Chronic, Oral, Summary - It is not clear if the stated doses are mg Eucalyptol/kg/day or mg

toothpaste/kg/day.

Irritation, Eucalyptol - It is not clear what the "/5 μL" represents? If this is the volume of vehicle, the vehicle should be stated.

Discussion, third paragraph - As the word data is plural "data is" needs to be corrected to "data are" in two places in this paragraph.

With the exception of the leaf and leaf powder, these ingredients are liquids. In this case, the particles of concern are those produced by aerosol products: "of these ingredients, as manufactured" should be changed to "of aerosol and other spray products".

Table 13, first row - In the description of the Results of the first study, the results of the 24 hour study should be a separate sentence, and it should be made clear that CHG was studied, e.g., "With and without 50% Eucalyptus Globulus Leaf Oil, [CHG] was detected at negligible levels in receptor compartment over 24 h, suggesting that CHG did not permeate through full skin thickness, and was retained within tissue."

Table 13, last three rows - If the plant part was not identified, perhaps the ingredient should be called "Eucalyptus Globulus Oil" (which is generally derived from the leaves). If it was stated that the oil was derived from the leaves, "(plant parts not specified)" should be deleted.

Table 13, third row - Did reference 51, titled "Transdermal delivery of ketorolac", really look at penetration enhancement or did they look at release from a transdermal patch? The results state: "When a gel incorporated with crushed apricot see was rubbed onto the skin prior to administration of patch, the ER for the addition of [Eucalypts] Globulus Leaf Oil (10%) was 5.16." From what species did the skin come from? Was this an *in vitro* or *in vivo* study?

Table 13, third and fourth row - Please use *E. globulus* oil (or leaf oil as appropriate) rather than "Globulus Leaf Oil" as a short form of Eucalyptus Globulus Leaf Oil.

Table 13, fourth row - What was the receptor fluid?

Table 15 - The column headed "Ingredient (concentration)" actually contains "Ingredient (dose)"

Table 15, reference 58, Results - The following is not a complete sentence: "In livers of experimental groups, central venous extended with hyperemia and varying degrees of vacuolar degeneration of hepatocytes."

Table 17, reference 76 - It is not clear what was tested in this study. If finished products containing Eucalyptus Globulus Leaf Oil were tested, in the Concentration column, rather than "Not specified" it would be much clearer if it stated: "Finished cosmetic products containing unspecified concentrations of Eucalyptus oil"

Table 18, reference 84 - Please correct: "gave a +++ reactions to at Days 2 and 4"

Reference 4 - Please correct: "germaniol"