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

Status: Draft Tentative 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.



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MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.

Scientific Analyst and Writer

Date: February 9, 2018

Subject: Safety Assessment of Eucalyptus globulus (Eucalyptus)-Derived Ingredients As Used

In Cosmetics

Attached is the draft tentative report of *Eucalyptus globulus* (Eucalyptus)-derived ingredients as used in cosmetics. [*Eucaly032018Rep*] The source for all of these ingredients is the leaf of the plant; one ingredient is obtained from the twigs as well.

In December 2017, the Panel issued an Insufficient Data Announcement for this safety assessment. The data needs were:

- Sensitization at maximum concentration of use (i.e., Eucalyptus Globulus Leaf Oil at 5.5%)
- 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 Council has provided a specification technical data sheet and a MSDS on a trade name mixture containing 10% Eucalyptus Globulus Leaf Extract [*Eucaly032018Data_2*] and an HRIPT on a lipstick containing Eucalyptus Globulus Leaf Oil (0.5%). [*Eucaly032018Data_1*] Wave 2 data from December 2017 (irritation, sensitization, and photosensitization) have been added to the report. These data have been marked with lines in the margins. No other data have been submitted.

The data on eucalyptol that the Panel examined in December (for potential inference to Eucalyptus Globulus Leaf Oil), as well as a few additional studies (acute inhalation, oral toxicity, sensitization, oral carcinogenicity), have been incorporated into the report and those data are also marked with lines in the margins.

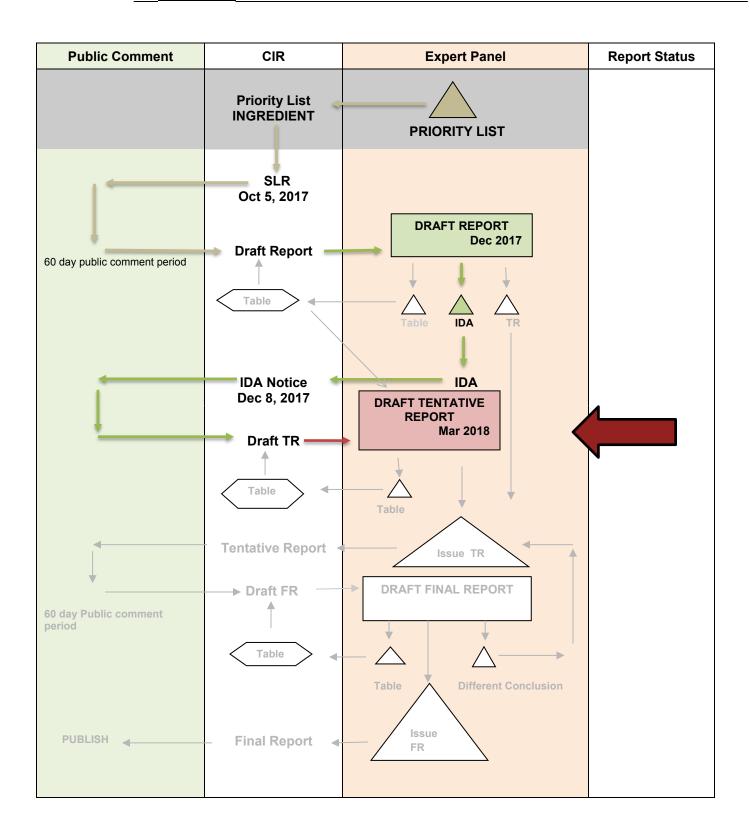
In October 2017, the Scientific Literature Review was posted for public comment with a request for a clarification of the definition of Eucalyptus Globulus Leaf Oil, which states that the oil may be sourced from leaves of other *Eucalyptus* species (in addition to *Eucalyptus globulus*). Industry has provided some information on the essential oil, in general, but has not provided information specific to cosmetic ingredients (e.g., which other species are sources for Eucalyptus Globulus Leaf Oil).

The Panel should come to a Conclusion on safety for these ingredients, further develop the Discussion and Abstract, and issue a Tentative Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Eucalyptus globulus (Eucalyptus) -derived ingredients

MEETING March 2018



HISTORY - Eucalyptus globulus-Derived Ingredients

2016 – Eucalyptus globulus added to the priority list.

September, 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;
- 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?

The Panel should review the report and come to a conclusion of safety, further develop the Discussion and Introduction, and issue a Tentative Report.

Eucalyptus globulus-Derived Ingredients Data Profile for March 2018. Writer – Lillian Becker																					
					Acute oxicity		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	Χ			Х	Χ	Χ	Х			Χ		Χ	Χ			Χ		Χ	Χ		Χ
Eucalyptus Globulus Leaf	Χ																				
Eucalyptus Globulus Leaf Extract	Χ						Χ												Х		
Eucalyptus Globulus Leaf Powder	Χ																				
Eucalyptus Globulus Leaf/Twig Oil						Χ															
Eucalyptus Globulus Leaf Water	Х																				
Euralypean Globalds Boar Water	•																				
Eucalyptol	Х			х		Х	Х				Х	Х		Х	Х				Х	Х	
			•											_							

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 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. Okav.
- 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 0.05

- 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 [vou'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: Okav.
- 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 0.05 mils to 0.5 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: Jav. do vou 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.

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 skinconditioning 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. With *Eucalyptus globulus*-derived ingredients, the Panel was concerned about the presence of geraniol and the oxidation products of linalool in cosmetics. Industry should use good manufacturing practices to limit impurities. The Panel concluded that *Eucalyptus globulus* (eucalyptus)-derived ingredients are [*To be determined*]

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).

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 generally excludes 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 reported to function only as fragrance ingredients. However, personal 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 current 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*.

The CIR 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. The Panel reviewed the safety of phytosterols, which are plant-derived sterols, in 2013 and concluded that the phytosterols are safe as used. 8

Eucalyptol, the chief component of Eucalyptus Globulus Leaf Oil, is a cosmetic ingredient that has not been reviewed by CIR. Eucalyptus Globulus Leaf Oil consists of not less than 70% (w/w) eucalyptol (also known as cineol, cineole, or 1,8-cineole). Therefore, 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 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/cir-report-format-outline). Unpublished data are provided by the cosmetics and chemicals industries, as well as by other interested parties.

Pertinent data were discovered in reports prepared by other organizations, including reports by the European Chemicals Agency (ECHA), ¹⁰ the International Program of Chemical Safety (INCHEM), ¹¹ the World Health Organization

(WHO), and the European Medicines Agency (EMA) Products Committee on Herbal Medicinal Products (HMPC). Reports by these organizations are cited in this assessment to identify the source of the summary data obtained.

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. ⁹ 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. 9,12

Eucalyptus globulus is a large tree with smooth, very pale or ash-grey bark, which grows up to 3 to 20 m high.

9,12,16,17,17-20 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).

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 by 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. 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. 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. Table 5 shows the major constituent groups found by using different extract media.

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. ^{20,22,23}

Eucalyptus Globulus Leaf/Twig Oil

In general, the major constituent of Eucalyptus Globulus Leaf/Twig Oil is eucalyptol (54% to 95%). In addition, there are 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. Leaf/Twig Oil also contains monoterpenes such as β -pinene, limonene, geraniol and camphene.

Constituents of Concern

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

Potential sensitizers include geraniol²⁻⁶ (found in the essential oil) and the hydroperoxides of limonene^{2,6,24} (leaf essential oil) and linalool^{2,25} (leaf and leaf essential oil).²⁶

Other constituents of concern found in the Eucalyptus globulus plant are myrcene (leaf essential oil), phellandrene (essential oil, leaf, and leaf essential oil), pinene (essential oil, leaf, and leaf essential oil) and quercetin (leaf and stem bark). These constituents are potential carcinogens or are genotoxic. 27-29,29-32

The International Fragrance Association (IFRA) publishes restrictions for fragrance ingredients.³³ Constituents of *Eucalyptus globulus* leaves and oil that have restrictions established by the International Fragrance Association Standards are listed in Table 10. IFRA Standards form the basis for the globally accepted and recognized risk management system for the safe use of fragrance ingredients.

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.³⁴ This supplier also reported specifications for this same trade name mixture that certain constituents that may be allergens, including eugenol, geraniol, and linalool, are not detected (limit of detection 0.001%), (Table 11).³⁵

<u>USE</u>

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 2017, Eucalyptus Globulus Leaf Oil is reported to be used in 414 formulations (208 leave-on formulations, 151 rinse-off formulations, and 55 formulations that are diluted for the bath). Eucalyptus Globulus Leaf Extract is reported to be used in 73 formulations and Eucalyptus Globulus Leaf Powder is reported to be used in 2 formulations. The VCRP included an ingredient with the non-INCI name "Eucalyptus" with 41 reported uses (Table 12).

The results of the concentration of use survey conducted by the Council in 2017 indicate Eucalyptus Globulus Leaf Oil has the highest reported maximum concentration of use; it is used at up to 5.5% in body and hand products.³⁷ The rest of these ingredients with reported concentrations of use are used at 1.4% or less.

In some cases, no uses were reported in the VCRP, but concentration of use data were received from industry. For instance, Eucalyptus Globulus Leaf had no reported uses in the VCRP, but a use concentration in a skin cleansing formulation was provided in the industry survey. Therefore, it should be presumed there is at least one use in every category for which a concentration is reported.

There were no uses reported to the VCRP or industry survey for Eucalyptus Globulus Leaf/Twig Oil.

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 $> 10~\mu m$, with propellant sprays yielding a greater fraction of droplets/particles $< 10~\mu m$ compared with pump sprays. 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. 40,41

The cosmetic ingredient SD Alcohol 38-B may be denatured with any of several essential oils, including *Eucalyptus globulus* oil. Essential oils used as a denaturant must meet National Formulary (NF) specifications. [27 CFR 21.92]

The FDA lists "Eucalyptus globulus" as a non-traditional preservative for cosmetics in its Compliance Program Guidance Manual. 42

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.⁴³

Non-Cosmetic

Food

Eucalyptus globulus leaves are food additives for direct addition to food for human consumption and as a flavoring agent. [21 CFR 172.510]

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 with honey when used at 2g or less *Eucalyptus globulus* oil per hive, where the eucalyptus oil contains 80% or more eucalyptol. [40 CFR 180.1271]

In the U.S. *Eucalyptus globulus* is not generally used for human food, but as an additive.¹⁷ 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.

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).⁴⁴ 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) smoking deterrents. [21 CFR 310.544] Eucalyptus globulus oil may be used in OTC products that treat nasal decongestant (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 may be used in the

manufacture of denatured alcohol, rum, and other denatured spirits. [27 CFR 21.65; 27 CFR 21.151]

Eucalyptus globulus oil is permitted in combinations containing a nasal decongestant and an analgesic-antipyretic. [21 CFR 341.40]

For permitted combinations containing camphor, menthol, and *Eucalyptus globulus* oil, the labeling for antitussive ingredients should be used. [21 CFR 341.85]

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. 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. For example: 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; or mouthwash as 20 mL of a 0.91 mg/mL solution, gargled twice daily. Dosing by inhalation include 12 drops /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

Essential Oil Safety⁶ recommended that the maximum adult daily oral dose is 600 mg and the maximum dermal use level is 20%. 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. ⁴⁵ 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.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

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 ingredients for the specified uses. [21 CFR 310.545]

TOXICOKINETIC STUDIES

Obtaining data on the toxicokinetics of unknown, complex mixtures would be impractical in practice, as is the case with many botanical ingredients. However, if the compositions are well understood, including the concentrations of constituents, such studies may be useful.

Dermal Penetration

Data on dermal penetration were neither found in the public literature, nor were such data submitted.

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) increased in a concentration-dependent manner with Eucalyptus Globulus Leaf Oil through human skin samples over 24 h. 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. ⁴⁷ The TMP flux across the human chest skin with 5% Eucalyptus Globulus Leaf Oil was 17-fold greater (346.0 mg/cm²/h) than the flux (20.1 mg/cm²/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. Eucalyptus Globulus Leaf Oil increased the dermal penetration of 5-fluorouracil (5-FU) through rat skin when using 2-cell diffusion cells; the enhancement ratios ranged from 58.49 to 82.55, depending on temperature (100°C through 140°C).

Absorption, Distribution, Metabolism, and Excretion (ADME)

Human

Eucalyptus Globulus Leaf Oil is readily absorbed when orally administered and is expected to increase the presence of lipids in substances such as milk.¹¹ It is excreted via the lungs, urine, skin, and feces.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol undergoes oxidation in vivo with the formation of hydroxycineole which is excreted as glucuronide.⁵⁰ 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.

Eucalyptol is quickly absorbed from the gastrointestinal tract. It is lipid soluble and absorption is enhanced in the presence of milk.⁵¹

TOXICOLOGICAL STUDIES

Acute Dose Toxicity

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

ANIMAL

Dermal

Eucalyptus Globulus Leaf Oil

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

Oral

Eucalyptus Globulus Leaf Oil

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.⁵² 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, 53 2334.3 mg/kg, 54 and 4400 mg/kg 10 in three different studies in rats.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Mice orally administered a single dose of eucalyptol (500 mg/kg) had an increase in liver enzyme activity. ⁵⁰ Reported oral LD₅₀s of eucalyptol in rats were 2480 mg/kg and 1560 mg/kg. ⁵⁰

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.⁵⁵ A second collecting tube was also installed. Steam 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, 0.5, 1.0, 1.5, 3.0, 4.0, 6.0, 7.5, 9.0, 27, 81, 243, 729, 2187, 6561, and 19,683 mg/kg in ethyl alcohol; not known if leaf or leaf/twig oil) was added to the boiling water bath; respiratory tract fluid was collected 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). ⁵⁶ 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, TNF α , 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 with little or no information on source plant parts, method of manufacture, or concentration/purity.

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.

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) can be affected by oral ingestion. 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. 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. Nephritis is rare but has been recorded. 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. The following is a summary of this information. The substances are referred to 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. 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.⁵⁷ 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. Eucalyptus Globulus Leaf Extract (130 mg/dry leaves/kg) administered to rats in drinking water for 42 days caused no changes in creatinine, urea, protein, or uric acid in the blood. 9

Eucalyptus Globulus Leaf Oil

Eucalyptus Globulus Leaf Oil (0, 1.5, or 2.0 mL/kg), 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.⁵²

In a combined repeated dose and reproduction/developmental study, Eucalyptus Globulus Leaf Oil (0, 100, 300, or 1000 mg/kg) 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 The no-observed-adverse-effect level (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 man. The NOAEL for females was 300 mg/kg based on effects on body weight and feed consumption.

Eucalyptus Globulus Leaf Oil (100, 300, or 1000 mg/kg/day) orally administered (route not specified) 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 bw/day.

Eucalyptus Globulus Leaf Oil (0 or 233 mg/kg 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.⁵⁴

Eucalyptus Globulus Leaf Oil (0, 396, 792, and 1188 mg/kg) 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. ⁵³ In the livers of the experimental groups, the central venous extended with hyperemia and varying degrees of vacuolar degeneration of hepatocytes.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol (150, 300, 600 and 1200 mg/kg) administered by stomach tube or in encapsulated form (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.⁵⁰

Eucalyptol (150, 300, 600 and 1200 mg/kg) administered by stomach tube or in encapsulated form (381 to 3342 mg/kg/day for males and 353 to 3516 mg/kg/day for females) to mice for 28 days caused a dose-related 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.⁵⁰

Eucalyptol (0, 500, or 1000 mg/kg/day) orally administered by gavage to 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.⁵⁰

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/kg/day; 1 mL) was administered by gavage to pathogen-free CFLP mice (n = 52) 6 days/week for 80 weeks followed by 16 and 24 weeks rest.⁵⁰ 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; in corn oil) was administered by gavage to Crl:CD(SD) rats (n = 10/sex). The study was conducted in accordance with OECD GL 422. [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 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. At microscopic examination, there were no findings attributed to treatment for offspring examined before or at the end of the experiment. A slightly high incidence of cold to touch was observed in litters in the 1000 mg/kg/day group. 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/d 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 $5000 \,\mu\text{g/plate}$ 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 $5000~\mu g/plate$, 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 $0.25 \mu L/mL$ was found to increase the mitotic instability of the original diploid strain and the number of diploid mitotic recombinants of *Aspergillus nidulans*. The genotoxicity of the oil was associated with the induction of mitotic crossing-over or with oil-broken chromosomes.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol was not mutagenic in two Ames assays, to Chinese hamster ovary (CHO) cells in a chromosome aberration assay and a sister chromatid exchange assay, and in two rec assays using *Bacillus subtilis*. ⁵⁰

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. ⁶⁰ 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. ²⁸ 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 μ g; 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

In Vitro

In an EpiskinTM assay of eucalyptol (100%) using a human epidermis model, the relative mean viability of the treated tissue was 88.9% after 15 min exposure. Eucalyptol was predicted to be a non-irritant. 61

Animal

Eucalyptus Globulus Leaf Oil

Eucalyptus Globulus Leaf Oil (neat; 5000 mg/kg) was dermally administered to rabbits (n = 10) in a single dose. The rabbits were 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.

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

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 μ g/5 μ L (0.0202%). The observation period was 24 and 48 h.

Eucalyptol (100%) administered to intact and abraded skin of rabbits for 24 h under occlusion was not irritating. 62

Human

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol (16% in petrolatum) administered to human subjects (n = 25) under occlusion for 24 h did not produce any irritation effects. 62

Sensitization

Animal

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol (25% and 50% v/v in acetone/olive oil 4:1, and 100 % v/v) was tested in a local lymph not assay (LLNA) using female mice (n = 5). The stimulation indexes (SI) were: 25%, 1.43; 50%, 2.03; 100%, 5.08. The 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 under the conditions of the test.

In a modified Draize test using Harley albino guinea pigs (n = 10), eucalyptol (0.25%; 0.1 mL) was administered by intradermal injection to the clipped flanks at 4 sites which overlie the two auxiliary inguinal lymph nodes. After a 14-day rest, 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. The test sites were scored 24 h after the challenge, and scored and challenged again 7 days after the first challenge. If there were no signs of irritation or sensitization, the procedure was repeated. Eucalyptol was found to be a non-sensitizer.

Human

Eucalyptus Globulus Leaf Oil

A Draize-Shelanski human repeated insult patch test (HRIPT; n = 52) was conducted with a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%). Open and occlusive patches were administered 3 days per week for 10 applications. For the occlusive patches, the test substance was applied to the pad of a bandage strip and put onto the skin of the upper back. The open patches were applied to the volar surface of the left arm. Both series of patches were read 48 h after administration. After approximately 2 weeks after the last inductions, the patches were repeated and read 48 h after administration. Six subjects had a weak, non-vesicular reaction (+), ranging from 1 to 6 of the induction readings in the occlusive patch sites; none of the subject had a reaction after the challenge patch.

A HRIPT (n = 107) was conducted on a lipstick (20 mg) that contained Eucalyptus Globulus Leaf Oil (0.5%) using Finn chambers. Induction patches were administered to one side of the back in the infrascapular area, for 48 or 72 h, for a total of nine applications. The test sites were examined for erythema, edema and other signs of cutaneous irritation before the next application. After a two-week rest, the challenge application was administered on the opposite side of the back, which remained in place for 24 h. The 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.

In a combined sensitization and photosensitization test, a Schwartz-Peck prophetic patch test (n=101) of a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%) was conducted using open and occlusive patches. ⁶⁴ For the occlusive patch, the test substance was applied to the pad of a bandage strip and put onto the cleaned skin of the upper back. The open patch was applied to the volar surface of the left arm. Both patches were read 48 h after administration. After approximately 2 weeks, the patches were repeated and read 48 h after administration. In the closed patches, a weak, non-vesicular reaction (+) was observed in four subjects at the first challenge reading, but not the second, and in two other subjects only at the second reading. In the open patches, there were no reactions observed at either reading. [See Photosensitization/Phototoxicity section for photosensitization data.]

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

In a maximization test, Eucalyptol (16% in petrolatum) administered to human subjects (n = 25) produced no signs of sensitization. ⁶²

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. The ultraviolet A (UVA)-rich light source was a UVASUN 5000 lamp (320 to 460 nm; 42 mW/cm²) 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/cm² [UVB] and 0.4 mW/cm² [UVA]). There was no hemolysis observed under the test conditions. Therefore, the authors concluded that the test substance is not expected to be photosensitizing.

Human

In a combined sensitization and photosensitization patch test, a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%) was applied to the pad of a bandage strip and put onto the skin on the backs of subjects (n = 101). The application was repeated approximately 2 weeks later. 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 administration of 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.]

In a combined Draize-Shelanski sensitization and photosensitization patch test (n = 52), occlusive patches of a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%) were administered 3 days per week for 10 applications; the test substance was applied to the pad of bandage strips and put onto the skin of the upper back. The test sites were read 48 h after each application. The backs of subjects were exposed to an UV light (wavelength included 3600°) at a distance of 12" (30.48 cm) for 1 min after the first, fourth, seventh, and tenth induction patches and the challenge patch were read. Induction applications were rotated between three sites; irradiation was administered to the same test site. The challenge was administered to a naïve site. There were no signs of photo-sensitization in any subject at any reading. [See Sensitization section for sensitization data.]

OCULAR IRRITATION STUDIES

In Vitro

Eucalyptol (for inference to Eucalyptus Globulus Leaf Oil)

Eucalyptol (100%) was not considered to be an ocular corrosive or severe irritant when tested in a bovine corneal opacity and permeability assay. 61

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. 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 animals 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 17. In a retrospective study of dermatologic patients during the years 2010 to 2015, 1 of 22 subjects was sensitized with Eucalyptus Globulus Leaf Oil. 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%). In patch tests of subjects (n = 96) with dermatitis and/or eczema, 5 subjects had positive reactions to Eucalyptus Globulus Leaf Oil (2% in petrolatum). 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. 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 (method not clear) of patients (n = 200) in Poland with dermatitis, 3 subjects had positive reactions to Eucalyptus Globulus Leaf Oil (concentration not specified). 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). In sensitization tests (method not clear) of patients (n = 5315) in London with dermatitis, 1 subject had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified).

Oral

In a respective study of accidental ingestion of Eucalyptus Globulus Leaf Oil by children in Australia, 41% had no

effects, 30% resulted in minor poisoning, 25% resulted in moderate poisoning, and 3% resulted in severe and life threatening poisoning. 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 18.

Dermal effects ranged from none to eczema, erythematous macular lesions, papules and vesicles, and/or pruritus. 75-80 Oral effects included esophageal pain, gasping for breath, restlessness, dyspnea, weak pulse, vomiting, drowsiness, and convulsions. 11,79,81-84 Inhalation effects included strong characteristic smell on the breath, coughing, chest tightness, dyspnea, hoarseness, and wheezing. 79,85

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.⁸⁶

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.

Eucalyptus Globulus Leaf Oil consists of not less than 70% (w/w) eucalyptol. Therefore, it is appropriate to include relevant toxicity data on eucalyptol as supporting information for the *Eucalyptus globulus* (eucalyptus)-derived ingredients. Representative data are included in this safety assessment.

The 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 2017, Eucalyptus Globulus Oil is reported to be used in 414 formulations (208 leave-on formulations, 151 rinse-off formulations, and 55 formulations that are diluted for the bath). Eucalyptus Globulus Leaf Extract is reported to be used in 73 formulations and Eucalyptus Globulus Leaf Powder is reported to be used in 2 formulations. The VCRP included an ingredient with the non-INCI name "Eucalyptus" with 41 reported uses. The results of the concentration of use survey conducted by the Council in 2017 indicate Eucalyptus Globulus Leaf Oil has the highest reported maximum concentration of use; it is used at up to 5.5% in body and hand products. The rest of these ingredients with reported concentrations of use are used at 1.4% 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.

Eucalyptol undergoes oxidation in vivo with the formation of hydroxycineole which is excreted as glucuronide. In rats, 2-hydroxycineole, 3-hydroxycineole and 1,8-dihydroxycineol-9-oic acid were identified as main urinary metabolites. Eucalyptol is quickly absorbed from the gastrointestinal tract. It's lipid soluble and absorption is enhanced in the presence of milk.

The dermal LD₅₀ was > 5000 mg/kg Eucalyptus Globulus Leaf Oil (the highest dose tested) in rabbits.

The oral LD_{50} for Eucalyptus Globulus Leaf Oil was 3320 mg/kg in male mice. There were no signs of toxicity or mortality in the mice in groups administered up to 2.0 mL/kg Eucalyptus Globulus Leaf Oil. At doses at and above 2.5 mL/kg, toxic effects were observed; the clinical signs disappeared in surviving mice, mostly after a day. 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. Necropsy revealed no noticeable changes in the appearance of the observed internal organs (stomach, liver, and kidney) in all treatment groups.

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.

Mice orally administered eucalyptol (500 mg/kg) had an increase in liver enzyme activity. The oral $LD_{50}s$ of eucalyptol in rats were reported to be 2480 mg/kg and 1560 mg/kg.

The probable oral lethal dose 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. 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.

Rabbits inhaling steam (cooled to body temperature) containing Eucalyptus Globulus Leaf Oil died; the output of respiratory tract fluid was significantly augmented at 19,683 mg/kg; lower doses had no effect on the volume of respiratory tract fluid.

OVA-sensitized guinea pigs exposed to aerosolized eucalyptol for 15 min had no differences in the numbers of eosinophils, neutrophils, lymphocytes and macrophages in the treatment group compared to the control group. Cytokine

levels were also similar.

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

An aqueous Eucalyptus Globulus Leaf Extract (2000 mg/kg/d) orally administered to mice for 10 days caused no mortalities but necropsy showed pale livers; histological examination of the treated mice showed damage to hepatic cells manifested by swollen hepatocytes with vacuolated cytoplasm.

In short-term oral toxicity studies, Eucalyptus Globulus Leaf Extract administered to rats showed hepatic effects in some studies and none in others. In a 2-week study, activity of SOD was increased in the liver starting at 100 mg/kg with an increase in the level of MDA in the liver of all treatment groups and in the serum at 120 mg/kg. In another study, the NOAEL for males was 1000 mg/kg based on hyaline droplet nephropathy at all dose levels (only observed in male rats); however this response is considered to be rat specific and to have no counterpart in man. In contrast, Eucalyptus Globulus Leaf Extract (130 mg/dry leaves/kg) administered in drinking water for 42 days to rats resulted in no mortalities or toxic effects to the kidneys or livers.

In short-term oral toxicity studies, Eucalyptus Globulus Leaf Oil caused hepatic effects in both mice and rats. Oral administration of Eucalyptus Globulus Leaf Oil for 84 days caused hepatic effects at 2.0 mL/kg in mice, but no effects were observed in the kidneys. In another study where Eucalyptus Globulus Leaf Oil was administered to rats for 2 weeks, the 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. The LOAEL in male rats could be considered as 100 mg/kg bw/day. There were relatively moderate pathological changes in the liver as congestion of the blood vessels in the portal area associated with inflammatory infiltration in rats administered Eucalyptus Globulus Leaf Oil (233 mg/kg) by gavage every 3 days for 30 days. In contrast, rats administered Eucalyptus Globulus Leaf Oil for 30 days showed no clinical signs and the serum biochemical parameters were similar between groups except that there were significant differences between the control group and the mid- and high-dose groups (792 and 1188 mg/kg) for: aspartate transaminase (higher), creatinine (higher), and glucose (lower).

Eucalyptol (150 to 1200 mg/kg) administered by stomach tube or in encapsulated form (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. There was a dose-related decrease of body weight gain starting at 600 mg/kg and an absence of a normal degree of hepatic centrilobular cytoplasmic vacuolization observed in male rats.

Eucalyptol (500 or 1000 mg/kg/day) orally administered for 28 days to rats, there were 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 $\alpha 2u$ -globulin in the cytoplasm of proximal tubular epithelial cells was observed in kidneys.

There were 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 observed when mice were orally administered a toothpaste containing eucalyptol up to 32 mg/kg/day for 80 weeks.

In a combined repeated dose and reproduction/developmental study of Eucalyptus Globulus Leaf Extract administered to rats, 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 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 g/kg/day group. This effect may be associated with test material entering the milk. However, a NOAEL at 300 mg/kg/d was determined for systemic effect 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.

Eucalyptus Globulus Leaf Extract was not mutagenic, with and without metabolic activation, at up to $5000~\mu g/p$ late in an in vitro mammalian cell gene mutation test using mouse lymphoma cells.

Eucalyptus Globulus Leaf Oil at 0.12 and 0.25 μ L/mL was found to increase the mitotic instability of the original diploid strain and the number of diploid mitotic recombinants of *A. nidulans*. The genotoxicity of the oil was associated with the induction of mitotic crossing-over or with oil-broken chromosomes. Eucalyptus Globulus Leaf Oil was not genotoxic in a bacterial reverse mutation assay at up to 5000 μ g/plate, with and without metabolic activation. Eucalyptus Globulus Leaf Oil was not genotoxic in an in vitro mammalian chromosome aberration test using human lymphocytes (up to 1000 μ g/mL) and an in vitro mammalian cell gene mutation test using mouse lymphoma L5178Y cells (up to 300 μ g/mL).

Eucalyptol was not mutagenic in two Ames assays, to CHO cells in a chromosome aberration assay and a sister chromatid exchange assay, and in two rec assays using *B. subtilis*.

In mice treated with a single dose of DMBA, papillomas were observed on 4 of 14 mice dermally administered 0.25 mL Eucalyptus Globulus Leaf Oil (neat) weekly for 33 weeks; none of the 13 control mice had papillomas.

Slight erythema was observed in 5 of 10 rabbits, moderate erythema in 3 of 10 rabbits, and moderate edema in 10 of 10 rabbits dermally administered 5000 mg/kg Eucalyptus Globulus Leaf Oil (neat). In an open mouse ear assay of eucalyptol

using albino mice, the ID_{50} was 1.008 μ g/5 μ L (0.0202%).

In an LLNA of eucalyptol, the EC3 was calculated to be 65.91%.

In a Draize-Shelanski HRIPT conducted on a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%), open and occlusive patches were used. Six subjects had a weak, non-vesicular reaction (+) at a few of the induction readings; however, none of the subject had a reaction after the challenge patch. In a Schwartz-Peck prophetic patch test of a skin cream that contained Eucalyptus Globulus Leaf Oil (0.1%) using open and occlusive patches, a weak, non-vesicular reaction (+) was observed in four subjects at the first reading, but not the second, and in two other subjects only at the second reading in the occlusive patch sites. In the open patches, there were no reactions observed at either reading. In a HRIPT conducted on a lipstick that contained Eucalyptus Globulus Leaf Oil (0.5%), there were no adverse events reported and it was concluded that there was no evidence of sensitization for this test substance. Eucalyptol was found to be a non-sensitizer in a modified Draize test with an intradermal induction concentration of 0.25% and a topical challenge concentration of 50%.

In an in vitro photohemolysis test, Eucalyptus Globulus Leaf Oil 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%).

Eucalyptus Globulus Leaf Oil (1 mL) caused moderate conjunctival irritation in all treated eyes 1 h after treatment. Conjunctival irritation was minimal at the 24- and 48-h observations in rabbits 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 patch tests of subjects (n = 96) with dermatitis and/or eczema, 5 subjects had positive reactions to Eucalyptus Globulus Leaf Oil (2% in petrolatum). 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. 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 = 200) in Poland with dermatitis, 3 subjects had positive reactions to Eucalyptus Globulus Leaf Oil (concentration not specified). When this study was continued on patients (n = 450) with dermatitis, 5 subjects had a positive reaction to Eucalyptus Globulus Leaf Oil (concentration not specified). In sensitization tests (method not clear) 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, restlessness, dyspnea, weak pulse, vomiting, drowsiness, and convulsions. Inhalation effects included strong characteristic smell on the breath, 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

[Draft Discussion. To be further developed.]

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 at relevant concentrations of these ingredients. The genotoxicity studies and the carcinogenicity study on eucalyptol gave no cause for concern.

Case studies describe 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 is 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 is not as robust, and enable consideration of the entire group.

The Panel requested sensitization data at maximum concentration of use (i.e., Eucalyptus Globulus Leaf Oil at 5.5%). This data has not been submitted. However, additional data on eucalyptol have been incorporated into this report, including a modified Draize test (induced at 0.25% and challenged at 50%).

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 a trade name mixture containing Eucalyptus Globulus Leaf Extract, lack of dermal irritation in the human patch test, the lack of sensitization in HRIPTs, and the small number of positive results in retrospective studies, supported by data on eucalyptol, assured the Panel that dermal irritation and sensitization from these constituents is not a concern in the cosmetic use of *Eucalyptus globulus*-derived ingredients.

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 to avoid adverse effects have been published for several such constituents found in 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 these ingredients 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 greater than would be used in cosmetics. The Expert Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. The Panel noted that 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, no irritation or sensitization in tests of dermal exposure, 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 [To be developed]:

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

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

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 <i>Eucalyptus globulus</i> and other species of <i>Eucalyptus</i> .	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 <i>Eucalyptus globulus</i> .	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 <i>Eucalyptus globulus</i> .	Abrasive		
Eucalyptus Globulus Leaf/Twig Oil	Eucalyptus Globulus Leaf/Twig Oil is the volatile oil obtained from the leaves and twigs of <i>Eucalyptus globulus</i> .	Fragrance ingredient		
Eucalyptus Globulus Leaf Water	Eucalyptus Globulus Leaf Water is an aqueous solution of the steam distillate obtained from the leaves of <i>Eucalyptus globulus</i> .	Fragrance ingredient		

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

Property	operty Value						
Fucalyntus Clabulus Loof							
Eucalyptus Globulus Leaf							
Odor	Aromatic, camphoric						
	Eucalyptus Globulus Leaf Oil						
Physical Form	Mobile liquid	87					
,	Liquid/oil	11					
	Liquid	10					
Color	Pale yellow	87					
	Colorless to pale yellow	11					
	Clear, yellow to pale yellow	10					
Odor	Fresh, eucalyptol-like	87					
	Changes over time: terpene-like, harsh, conifer	21					
	to fresh, characteristic of eucalyptol, minty,						
	camphoraceous to hay- and cumic-like,						
	rosemary to wood, dusty, powdery						
Density @ 20°C	0.913 to 0.92	10					
@ 20°C	0.909	10					
Specific Gravity @ 20°C	0.907	87					
	0.9005 to 0.930 ^a	21					
@ 20°C	0.919^{b}	9					
Melting Point °C	< -20	10					
Boiling Point °C	153 to 184	10					
Water Solubility	Insoluble	11					
Other Solubility							
Alcohol (70%)	Soluble	11					
Alcohol (90%)	Miscible	11					
	Eucalyptus Globulus Leaf/Twig Oil						
Physical Form	Liquid	9					
Color	Colorless or pale yellow	9					
Odor	Aromatic, camporic	9					
Taste	Aromatic, pungent, bitter	9					
Specific Gravity	0.9005 to 0.930	21					
Other Solubility							
Ethanol	Soluble	9					

^a Specific gravity increases as eucalyptol content increases ^b Collect by steam distillation

Table 3. Methods of manufacture reported in the literature.

Ingredient	Method	Reference
Eucalyptus Globulus Leaf Oil	Freshly collected <i>Eucalyptus</i> 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.	52
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.	54
Eucalyptus Globulus Leaf Oil	Eucalyptus Globulus Leaf Oil used for medicinal purposes is manufactured from fresh leaves or fresh terminal branchlets of <i>Eucalyptus globulus</i> plants. Oil is extracted by steam distillation and retification.	12
Eucalyptus Globulus Leaf Extract	Freshly collected <i>Eucalyptus globulus</i> 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.	57
Eucalyptus Globulus Leaf Extract	Freshly collected <i>Eucalyptus globulus</i> 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.	58
Eucalyptus Globulus Leaf Extract	The extract was prepared by powdering <i>Eucalyptus globulus</i> 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%.	59

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	-	-	-	-	+	-
<i>p</i> -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.⁷

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.⁸⁷

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. ^{20,22,23}

	Algeria	China	Northern
Compounds	(%)	(%)	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	2,6,24
Linalool	Hydroperoxides are potential dermal sensitizers. Safe at up to	2,25
	4.3% (20% in a consumer fragrance)	
Quercetin	Positive genotoxic effect in an Ames assay	31,32
	Consistently genotoxic in in vitro tests and in some in vivo	
	studies of i.p. exposures, but was consistently nongenotoxic in	
	oral exposure studies	
β-Myrcene	Oral dosing for 2 years caused kidney cancers in male rats (0.25	27
	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.	
α-Pinene	Potential carcinogen. Increased incidence of transitional	29,30
	epithelium hyperplasia of urinary bladder in male and female	
	mice at 100 ppm or more, the severity of which increased with	
	increasing exposure concentration.	

Table 10. Constituents of *Eucalyptus globulus* leaves and oil that have IFRA standards.³³

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

Table 11. Allergens that are specified to not be detected in a trade name mixture containing Eucalyptus Globulus Leaf Extract at 10% (detection limit 0.001%). 35

Amyl cinnamal	Amyl cinnamal alcohol	Anise alcohol
Benzyl alcohol	Benzyl benzoate	Benzyl cinnamate
Benzyl salicylate	Cinnamal	Cinnamyl alcohol
Citral	Citronellol	Coumarin
Eugenol	Farnesol	Geraniol
Hexyl cinnamal	Hydroxycitronellal	Isoeugenol
Butylphenyl metahylpropional	D-Limonene	Linalool
Hydroxyisohexyl 3-cyclohexene	Methyl 2-octynoate	α-Isomethyl ionone
carboxaldehyde		

^{*} Use categories are based on types of skin contact (e.g., skin, lips), length of contact (e.g., leave-on, rinse-off), or type of use (e.g., mouthwash)

Table 12. Frequency of use according to duration and exposure of *Eucalyptus globulus*-derived ingredients.³⁶

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	
, , , , , , , , , , , , , , , , , , ,	Eucalyptus Globulus Leaf Oil		Eucaly	ptus Globulus Leaf		Eucalyptus Globulus Leaf Extract		Eucalyptus Globulus Leaf Powder	
Total/range	414	5.5	NR	1.2	73	0.000006-0.41	2	1	
Duration of use									
Leave-on	208	5.5	NR	NR	52	0.000006- 0.005	NR	NR	
Rinse-off	151	0.74	NR	1.2	20	0.000008-0.41	2	1	
Diluted for (bath) use	55	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	4	0.008-0.74	NR	NR	1	0.058-0.41	NR	NR	
Incidental Inhalation-sprays	17; 81 ^a ; 33 ^b	0.00056-0.4; 0.00001-0.74 ^a	NR	NR	15 ^a ; 9 ^b	0.000006- 0.005; 0.00005-0.058 ^a	NR	NR	
Incidental inhalation-powders	4°; 33 ^b	0.001-5.5°	NR	NR	1; 9 ^b	0.005°	NR	NR	
Dermal contact	356	0.000002-5.5	NR	1.2	55	0.00005-0.025	2	1	
Deodorant (underarm)	3ª	NR	NR	NR	4 ^a	NR	NR	NR	
Hair-noncoloring	51	0.00001-0.12	NR	NR	15	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	116	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	

		otus Globulus af Water	"Euca	alyptus"d	
Total/range	NR	0.02-1.4	41	NS	NR = Not Reported; NS = Not Surveyed; Totals = Rinse-
Duration of use					off + Leave-on + Diluted for Bath Product Uses.
Leave-on	NR	1.4	32	NS	Note: Because each ingredient may be used in cosmetics
Rinse-off	NR	0.02-0.1	2	NS	with multiple exposure types, the sum of all exposure typ
Diluted for (bath) use	NR	NR	7	NS	uses may not equal the sum total uses. a It is possible these products <u>may</u> be sprays, but it is not
Exposure type					specified whether the reported uses are sprays.
Eye area	NR	NR	NR	NS	b Not specified whether a powder or a spray, so this information is captured for both categories of incidental
Incidental ingestion	NR	NR	NR	NS	inhalation. c It is possible these products may be powders, but it is no
Incidental Inhalation-sprays	NR	NR	10; 2 ^a ; 8 ^b	NS	specified whether the reported uses are powders. d "Eucalyptus" is not an INCI name but was reported in
Incidental inhalation-powders	NR	1.4°	8 ^b	NS	the VCRP. It is not known if this is a cosmetic ingredien in this report.
Dermal contact	NR	0.02-1.4	38	NS	in this report.
Deodorant (underarm)	NR	NR	NR	NS	
Hair-noncoloring	NR	0.02-0.1	1	NS	
Hair-coloring	NR	NR	NR	NS	
Nail	NR	NR	2	NS	
Mucous Membrane	NR	NR	9	NS	
Baby	NR	NR	NR	NS	

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 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 cm²). Receptor cells filled with PBS. CHG (2% w/v) was also mixed with Eucalyptus Globulus Leaf Oil (10% 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.	Generally, dermal penetration of CHG increased in a concentration-dependent manner of the Eucalyptus Globulus Leaf Oil through skin samples over 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. Eucalyptus Globulus Leaf Oil. 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. 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. CHG, with and without 50% Eucalyptus Globulus Leaf Oil, 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.	46
Eucalyptus Globulus Leaf Oil (plant parts not specified) 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 cm²) 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/cm²/h) than the flux (20.1 mg/cm²/h) of a saturated solution of TMP without the oil.	47
Eucalyptus Globulus Leaf Oil (plant parts not specified; 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.	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: 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.	48
Eucalyptus Globulus Leaf Oil (plant parts not specified) 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 cm²)	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 > Globulus Leaf Oil > peppermint oil > turpentine oil	49

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
			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.	52
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).	53
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.	54
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.	50
Eucalyptol	Rats	Not specified	Administered by gavage.	LD50 = 2480 mg/kg	50
Eucalyptol	Rats	Not specified	Administered by gavage.	LD50 =1560 mg/kg Lethal dose caused rapid cyanosis and stupor accompanied by irregular breathing, extreme sensitivity to noise, convulsions, and death from respiratory failure.	50

Table 15. Short-term oral studies

Ingredient (concentration)	Animal (n)	Procedure	Results	Reference
Eucalyptus Globulus Leaf Extract (2000 mg/kg/d 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	57
Eucalyptus Globulus Leaf Extract (0, 80, 100, or 120 mg/kg 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 live and control of the control of the level of the	dense fragmented nuclei were observed. 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 a 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.	58
Eucalyptus Globulus Leaf Extract (130 mg/dry leaves/kg; method of manufacture is presented in Table 3)	Male Wistar rats (8)	in liver and serum. Administered in drinking water (1 g/L) for 42 days. 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.	59
Eucalyptus Globulus Leaf Oil (0, 1.5, or 2.0 mL/kg)	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 1.5mL/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.	52
Eucalyptus Globulus Leaf Oil (0, 100, 300, or 1000 mg/kg; 4 mL/kg in corn oil)	Crl:CD(SD) rats (10/sex)	OECD GL 422 A combined repeated dose and reproduction/developme ntal 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.	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.	10

Table 15. Short-term oral studies

Ingredient (concentration)	Animal (n)	Procedure	Results	Reference
		Rats were killed and necropsied.	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	
Eucalyptus Globulus Leaf Oil (100, 300, or 1000 mg/kg/day in corn oil)	Crl:CD (SD) rats (3/sex)	Administered for 2 weeks.	weight and feed consumption 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 1000 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 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.	54
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 midand 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. In spleens, red pulp extended with hyperemia and a large number of macrophages and	53

Table 15. Short-term oral studies

Ingredient (concentration)	Animal (n)	Procedure	Results	Reference
(11000000	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.	
Eucalyptol (Stomach tube: 150, 300, 600 and 1200 mg/kg Encapsulated form in diet: 3750, 7500, 15000 and 30000 mg/kg, 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.	50
Eucalyptol (Stomach tube: 150, 300, 600 and 1200 mg/kg Encapsulated form in diet: 3750, 7500, 15,000 and 30,000 mg/kg; 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 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.	50
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 α2u-globulin in the cytoplasm of proximal tubular epithelial cells was observed.	50

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. Genotoxicity studies

Ingredient/substance	Assay	Details	Results	References
Eucalyptus Globulus Leaf Extract	In vitro 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-Noxide, 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	In vitro mammalian 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	In vitro 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 Aspergillus nidulans, heterozygous for nutritional and conidia color markers. 0.12 and 0.25 µL/mL	Using diploid strain of fungus <i>A. nidulans</i> , 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%), <i>trans</i> -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 <i>A. nidulans</i> . Genotoxicity of the oil was associated with induction of mitotic crossing-over or with oilbroken chromosomes.	12
Eucalyptol	Ames assay S. typhimurium (TA98, TA100, TA1535, and	Concentration not specified	No mutagenic effects with or without metabolic activation	50

Table 16. Genotoxicity studies

Ingredient/substance	Assay	Details	Results	References
	TA1537)			
Eucalyptol	Ames assay	Concentration not specified	No mutagenic effects with or	50
	S. typhimurium		without metabolic activation	
	(TA97a, TA98,			
	TA100, and			
	TA102)			
Eucalyptol	Chromosome	Concentration not specified	No induced chromosome	50
	aberration assay	_	aberrations with or without	
	CHO cells		metabolic activation	
Eucalyptol	Sister chromatid	Concentration not specified	Sister chromatid exchanges were	50
	exchange assay	_	induced in CHO cells only in the	
	CHO cells		absence of metabolic activation at	
			doses that induced cell cycle delay.	
Eucalyptol	Rec assay	Concentration not specified	No evidence of DNA damage	50
71	B. subtilis	•	•	
Eucalyptol	Rec assay	Concentration not specified	No evidence of DNA damage	50
71	B. subtilis	•	•	

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

Table 17. 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	67
2% in petrolatum	96	Patch tests of subjects in a practice that specializes in contact dermatitis and eczema	5 subjects had positive reactions; 2 of the scored with a +/- reaction, 2 with a + reaction, and 1 with a ++ reaction	68
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	69
Not specified	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 in 1 of 23 bath and shower products and 1 of 88 skin care products, and not the other 13 cosmetic product categories, containing "eucalyptus oil"	70
Not specified	200	Patch tests of subjects with dermatitis at the Warsaw Medical School, Poland	3 subjects had positive reactions	
Not specified	450	Patch tests of subjects with dermatitis at the Warsaw Medical School, Poland	5 subjects had positive reactions	72
Not specified	5315	Patch tests of subjects with dermatitis at the St. John's Hospitalf or Diseaseosf the Skin in London	1 subject had a positive reaction	73

Table 18. Case reports of Eucalyptus Globulus Leaf Oil.

	Referen
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	76
ointment. The ointment consisted of Eucalyptus Globulus Leaf Oil and spruce oil (ratio not provided) and had been applied nightly to the	
ollar of the girl's clothing for an unspecified period of time. She presented with dusky red color, nummular patch that was 6 cm in	
iameter on her neck and a similar patch that was 4 cm diameter on her right upper clavicular area. She had a sharply-bordered	
rythematous macular lesion on her neck and upper chest. Patch testing was performed with the European baseline series using Finn	
hambers (8 mm) for 48 h. The concentration and vehicle of the Eucalyptus Globulus Leaf Oil was not specified; the spruce oil was tested	
5% in petrolatum. Readings were taken at 30 min and 4 days after removal. Eucalyptus Globulus Leaf Oil had a positive reaction (++)	
is did the spruce oil $(+++)$. The test was conducted on healthy controls $(n = 3)$ with negative results.	
ucalyptus Globulus Leaf Oil was used to treat a male subject who had chronic postoperative osteomyelitis of the right femur with a	78
raining sinus that failed to respond to ciprofloxacin and rifampicin during 2 years of antibiotic therapy. The infected site was treated with	
cream containing Eucalyptus Globulus Leaf Oil (1.0 g/day) to the sinus for 5 days and no antibiotics were used. The wound was	
ompletely healed at 2 weeks and no adverse effects from the Eucalyptus Globulus Leaf Oil were reported.	
ucalyptus Globulus Leaf Oil was used to treat a 42-year-old man an infection after a mid-foot fracture and dislocation. The infected	78
ssue was surgically debrided and a cream containing Eucalyptus Globulus Leaf Oil (0.5 g/day) was applied for 3 weeks. No antibiotics	
rere used. The subject was clear of infection at 12 weeks with no adverse effects from Eucalyptus Globulus Leaf Oil were reported.	
12-year-old boy splashed Eucalyptus Globulus Leaf Oil (amount unknown) on his face. No symptoms developed.	79
4-year-old boy was placed in a bath containing Eucalyptus Globulus Leaf Oil (amount unknown). He developed redness, irritation, and	79
urning sensation on his buttocks and penis soon after being placed in the water. He was removed from the bath and rinse with water. The	
ritation resolved within 1 h.	
	75
6-year-old girl presented with slurred speech, ataxia and muscle weakness progressing to unconsciousness following the widespread	
oplication of a home remedy for urticaria. This remedy consisted of: apple cider vinegar (200 mL), olive oil (200 mL), methylated spirits	
00 mL); 95% ethanol (containing no methanol), and Eucalyptus Globulus Leaf Oil (50 mL; double distilled, containing 80% to 85%	
calyptol oil). The concoction (approximately 400 mL) had been applied to her limbs and trunk under plastic wrap and the dressing	
anged every 2 to 4 h for 2 days. When she was not improving, the amount of Eucalyptus Globulus Leaf Oil was doubled in the	
ncoction. Within 10 to 15 min of applying the bandages, she appeared "intoxicated" with slurred speech and unsteady gait. She	
approved following removal of the topical preparation and bathing but was still drowsy, nauseated, and vomiting. After a night in the	
spital, her symptoms resolved, with no long-term effects.	77
65-year-old, otherwise healthy woman, who worked as an aromatherapist presented with eczema on her arms and upper trunk, which	,,
er 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	
sociate with handling household cleansers, sealing wax, paints, and the essential oils, which she diluted herself. When patch tested with	
nn Chambers, she had a ++ reaction to Eucalyptus Globulus Leaf Oil at 5% in petrolatum, but not at 1%.	80
27-year-old professional athlete had been using an analgesic and anti-inflammatory cream for 2 years before pruritus and erythema	80
ppeared on the toes of the left foot. The next application of the cream caused papules and vesicles, with increasing pruritus. A topical	
orticosteroid relieved his symptoms; he still had a vesicular scaly eczema on the dorsa of the toes of the left foot. Patch testing with	
RUE Test™ standard allergens and the Chemotechnique cosmetics series was negative. Eucalyptus Globulus Leaf Oil (1% in	
etrolatum) gave a + + reaction to at Days 2 and 4; the other ingredients of the cream were negative. The controls were all negative at	
ays 2 and 4.	
Oral	
	11
fter an evening meal an adult male took a large teaspoonful of Eucalyptus Globulus Leaf Oil. He immediately experienced esophageal	11
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Table 18. Case reports of Eucalyptus Globulus Leaf Oil.

Summary	Reference
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.	
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.	79
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.	83
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.	83
Inhalation	
Three subjects (age and sex not provided) inhaled Eucalyptus Globulus Leaf Oil (amounts not provided). Symptoms were primarily the strong smell of the oil on the breath and, in 1 case, coughing (this subject did have a cold).	79
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 <i>Eucalyptus</i> 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 <i>Eucalyptus</i> 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 <i>Eucalyptus</i> sp. performed 1 month apart. All stimuli were applied to gauze held approximately 5" from the nares. Dry <i>Eucalyptus</i> sp. leaves were used to impregnate the test gauze. The initial challenge was with <i>Eucalyptus</i> 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- <i>Eucalyptus</i> 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	85
exacerbated with talking. 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.	86

 $BP-blood\ pressure;\ CNS-central\ nervous\ system;\ EEG=electroence phalogram;\ PVC-premature\ ventricular\ contractions;\ VCD-vocal\ cord\ dysfunction$

REFERENCES

- 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.
- 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 germaniol. *Contact Dermatitis*. 2013;68(4):224-234.
- 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.
- 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.
- 8. 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.
- 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.
- 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.
- 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.
- European Medicines Agency (EMA). Assessment report on Eucalytus [sic] globulus labil., Eucalytus polybractea R.T. Baker and/or Eucalytus 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.
- 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.
- 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.
- 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.
- 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. 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.
- 23. 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.

- Matura, M, Sköld, 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.
- 25. 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.
- 26. Duke JA. Handbook of phytochmical constituents of GRAS herbs and other economic plants. Boca Raton, FL: CRC Press, 1992.
- 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.
- 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.
- 29. Homberger, F and Boger, E. The carcinogenicity of essential oils, flavors, and spices: A review. Cancer Research. 1968;28(11):2372-2374.
- 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.
- 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.
- 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.
- 33. International Fragrance Association (IFRA). IFRA Standards. 2017. http://www.ifraorg.org/en-us/standards-library. Date Accessed 1-30-2017.
- Native Extracts. 2017. Specification technical data sheet NE Tasmanian Blue Gum Extract Cosmetic. Unpublished data submitted by Personal Care Products Council.
- 35. Native Extracts. 2017. Safety data sheet: NE Tasmanian Blue Gum Extract. Unpublished data submitted by Personal Care Products Council.
- 36. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients; FDA Database. Washington, DC, FDA. 2017.
- Personal Care Products Council. 9-29-2017. Concentration of Use by FDA Product Category: Eucalyptus globulus-Derived Ingredients.
 Unpublished data submitted by Personal Care Products Council.
- 38. Johnsen MA. The Influence of Particle Size. Spray Technology and Marketing. 2004;14(11):24-27.
- 39. Rothe H. Special aspects of cosmetic spray safety evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C.
- 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.
- 41. 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.
- 42. Food and Drug Administration (FDA). Cosmetics Program; Import and domestic. Chapter: 29. In: Food and Drug Administration Compliance Program Guidance Manual. 2016:1-43.
- 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.
- 44. 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.
- 45. 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.
- 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.

- 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.
- 48. Amrish, C and Kumar, S. Transermal delivery of ketorolac. Yakugaku Zasshi. 2009;129(3):373-379.
- 49. 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.
- 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.
- 51. Bhowal, M and Gopal, M. Eucalyptol: Safety and phamacological profile. RGUHS Journal of Phamaceutical Sciences. 2015;5(4)-125.
- 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.
- 53. 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.
- 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.
- 55. 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.
- 56. 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.
- 57. 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.
- 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.
- 59. 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.
- 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.
- 61. 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.
- 62. Opdyke DL. Monographs on fragrance raw materials. Food Cosmet. Toxicol. 2017;13(1):91-112.
- 63. Sharp, DW. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology. 1978;9(3):261-271.
- 64. 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.
- 65. 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.
- 66. 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.
- 67. 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.
- 68. Guin, JD. Use of consumer product ingredients for patch testing. Dermatitis. 2005;16(2):71-77.
- 69. 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.
- Nardelli, A, Drieghe, J, Claes, L, Boey, L, and Goossens, A. Fragrance allergens in "specific" cosmetic products. Contact Dermatitis. 2011;64(4):212-219.

- 71. Rudzki, E, Grzywa, Z, and Bruo, W. Sensitivity to 35 essential oils. Contact Dermatitis. 1976;2(4):196-200.
- 72. Rudzki, E and Grzywa, Z. Balsam of Peru as screening agent for essential oils sensitivity. Dermatolagica. 1977;155(2):115-121.
- 73. Rudzki, E and Grzywa, Z. Allergy to perfume mixture. Contact Dermatitis. 1986;15(2):115-116.
- Tibballs, J. Clinical effects and management of eucalyptus oil ingestion in infants and young children. Medical Journal of Austrailia. 1995;163(4):177-180.
- 75. Darben, T, Cominos, B, and Lee, C. Topical eucalyptus oil poisoning. Australiasian Journal of Dermatology. 1998;39(4):265-267.
- 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.
- 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.
- 78. 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
- 79. 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.
- 80. Vilaplana, J and Romaguere, C. Allergic contact dermatitis due to eucalyptol in an anti-inflammatory cream. Contact Dermatitis. 2000;43(2):118
- 81. Craig, JO. Poisoning by the volatile oils in childhood. Archives of Disease in Childhood. 1953;28(142):475-483.
- 82. Foggie, WE. Eucalyptus oil poisoning. The British Medical Journal. 1911;1(February 18, 2616):359-360.
- 83. Kumar, KJ, Sonnathi, S, Anitha, C, and Santhoshkumar, M. Eucalyptus oil poisoning. Toxicology International. 2015;22(1):170-171.
- 84. Patel, S and Wiggins, J. Eucalyptus oil poisoning. Archives of Disease in Childhood. 1980;55(5):405-406.
- 85. 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.
- 86. Melis, K, Bochner, A, and Janssens, G. Accidental nasal eucalyptol and menthol instillation. *European Journal of Pediatrics*. 1989;148(8):786-787
- 87. Anonymous. 2011. Certificate of analysis Australian Eucalyptus Oil. Unpublished data submitted by Personal Care Products Council.

2017 VCRP Data for Eucalyptus globulus (Eucalyptus)-Derived Ingredients

02A - Bath Oils, Tablets, and Salts	EUCALYPTUS GLOBULUS	2
	(EUCALYPTUS) LEAF EXTRACT	
02D - Other Bath Preparations	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF EXTRACT	
03D - Eye Lotion	EUCALYPTUS GLOBULUS	2
•	(EUCALYPTUS) LEAF EXTRACT	
04C - Powders (dusting and talcum,	EUCALYPTUS GLOBULUS	1
excluding aftershave talc)	(EUCALYPTUS) LEAF EXTRACT	
05A - Hair Conditioner	EUCALYPTUS GLOBULUS	2
	(EUCALYPTUS) LEAF EXTRACT	
05F - Shampoos (non-coloring)	EUCALYPTUS GLOBULUS	6
1 (3/	(EUCALYPTUS) LEAF EXTRACT	
05I - Other Hair Preparations	EUCALYPTUS GLOBULUS	7
· · · · · · · · · · · · · · · · · · ·	(EUCALYPTUS) LEAF EXTRACT	
07C - Foundations	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF EXTRACT	
07E - Lipstick	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF EXTRACT	•
08E - Nail Polish and Enamel	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF EXTRACT	•
08G - Other Manicuring Preparations	EUCALYPTUS GLOBULUS	1
occ carlor marilearing resparations	(EUCALYPTUS) LEAF EXTRACT	
10A - Bath Soaps and Detergents	EUCALYPTUS GLOBULUS	3
rorr zam obapo ana zotorgomo	(EUCALYPTUS) LEAF EXTRACT	•
10B - Deodorants (underarm)	EUCALYPTUS GLOBULUS	4
,	(EUCALYPTUS) LEAF EXTRACT	
10E - Other Personal Cleanliness	EUCALYPTUS GLOBULUS	1
Products	(EUCALYPTUS) LEAF EXTRACT	
12A - Cleansing	EUCALYPTUS GLOBULUS	6
3	(EUCALYPTUS) LEAF EXTRACT	
12B - Depilatories	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF EXTRACT	
12C - Face and Neck (exc shave)	EUCALYPTUS GLOBULUS	6
120 Tabbana Mosk (oxe shave)	(EUCALYPTUS) LEAF EXTRACT	·
12D - Body and Hand (exc shave)	EUCALYPTUS GLOBULUS	3
in the second se	(EUCALYPTUS) LEAF EXTRACT	•
12F - Moisturizing	EUCALYPTUS GLOBULUS	15
121 Molotaniang	(EUCALYPTUS) LEAF EXTRACT	
12H - Paste Masks (mud packs)	EUCALYPTUS GLOBULUS	1
tata maana (maa paana)	(EUCALYPTUS) LEAF EXTRACT	
12J - Other Skin Care Preps	EUCALYPTUS GLOBULUS	8
c onto our our ropo	(EUCALYPTUS) LEAF EXTRACT	3
	(200.1211 100) 2211 27111101	73
		13

01A - Baby Shampoos	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF OIL	
01B - Baby Lotions, Oils, Powders, and	EUCALYPTUS GLOBULUS	4
Creams	(EUCALYPTUS) LEAF OIL	
01C - Other Baby Products	EUCALYPTUS GLOBULUS	2
	(EUCALYPTUS) LEAF OIL	
02A - Bath Oils, Tablets, and Salts	EUCALYPTUS GLOBULUS	43
	(EUCALYPTUS) LEAF OIL	
02B - Bubble Baths	EUCALYPTUS GLOBULUS	6
	(EUCALYPTUS) LEAF OIL	
02D - Other Bath Preparations	EUCALYPTUS GLOBULUS	6
•	(EUCALYPTUS) LEAF OIL	
03D - Eye Lotion	EUCALYPTUS GLOBULUS	1
•	(EUCALYPTUS) LEAF OIL	
03G - Other Eye Makeup Preparations	EUCALYPTUS GLOBULUS	1
, , ,	(EUCALYPTUS) LEAF OIL	
04A - Cologne and Toilet waters	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF OIL	
04B - Perfumes	EUCALYPTUS GLOBULUS	1
O ID I GITAINIGG	(EUCALYPTUS) LEAF OIL	•
04E - Other Fragrance Preparation	EUCALYPTUS GLOBULUS	14
0+L - Other Fragrance Freparation	(EUCALYPTUS) LEAF OIL	17
05A - Hair Conditioner	EUCALYPTUS GLOBULUS	15
OSA - Hall Collulionel	(EUCALYPTUS) LEAF OIL	13
05B - Hair Spray (aerosol fixatives)		1
USB - Hall Spray (aerosol lixatives)	EUCALYPTUS GLOBULUS	1
OFF Diness (non-seleving)	(EUCALYPTUS) LEAF OIL	1
05E - Rinses (non-coloring)	EUCALYPTUS GLOBULUS	ı
055 Observed (1997)	(EUCALYPTUS) LEAF OIL	
05F - Shampoos (non-coloring)	EUCALYPTUS GLOBULUS	25
	(EUCALYPTUS) LEAF OIL	
05G - Tonics, Dressings, and Other Hair	EUCALYPTUS GLOBULUS	5
Grooming Aids	(EUCALYPTUS) LEAF OIL	
05H - Wave Sets	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF OIL	
05I - Other Hair Preparations	EUCALYPTUS GLOBULUS	2
	(EUCALYPTUS) LEAF OIL	
06D - Hair Shampoos (coloring)	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF OIL	
07C - Foundations	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF OIL	
07I - Other Makeup Preparations	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF OIL	
08E - Nail Polish and Enamel	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF OIL	
08G - Other Manicuring Preparations	EUCALYPTUS GLOBULUS	1
-	(EUCALYPTUS) LEAF OIL	
09A - Dentifrices	EUCALYPTUS GLOBULUS	3
	(EUCALYPTUS) LEAF OIL	
09C - Other Oral Hygiene Products	EUCALYPTUS GLOBULUS	1
70	(EUCALYPTUS) LEAF OIL	
		4.4
10A - Bath Soaps and Detergents	EUCALTPTUS GLUBULUS	44
10A - Bath Soaps and Detergents	EUCALYPTUS GLOBULUS (FUCALYPTUS) LEAF OIL	44
	(EUCALYPTUS) LEAF OIL	
10A - Bath Soaps and Detergents 10B - Deodorants (underarm)	(EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS	3
10B - Deodorants (underarm)	(EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3
	(EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS	
10B - Deodorants (underarm) 10E - Other Personal Cleanliness Products	(EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3
10B - Deodorants (underarm)	(EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS	3
10B - Deodorants (underarm) 10E - Other Personal Cleanliness Products 11B - Beard Softeners	(EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3 13 3
10B - Deodorants (underarm) 10E - Other Personal Cleanliness Products	(EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS	3
10B - Deodorants (underarm) 10E - Other Personal Cleanliness Products 11B - Beard Softeners	(EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL EUCALYPTUS GLOBULUS (EUCALYPTUS) LEAF OIL	3 13 3

	(EUCALYPTUS) LEAF OIL	
11G - Other Shaving Preparation Products	EUCALYPTUS GLOBULUS	9
• .	(EUCALYPTUS) LEAF OIL	
12A - Cleansing	EUCALYPTUS GLOBULUS	21
	(EUCALYPTUS) LEAF OIL	
12C - Face and Neck (exc shave)	EUCALYPTUS GLOBULUS	18
	(EUCALYPTUS) LEAF OIL	
12D - Body and Hand (exc shave)	EUCALYPTUS GLOBULUS	26
	(EUCALYPTUS) LEAF OIL	
12E - Foot Powders and Sprays	EUCALYPTUS GLOBULUS	7
	(EUCALYPTUS) LEAF OIL	
12F - Moisturizing	EUCALYPTUS GLOBULUS	53
	(EUCALYPTUS) LEAF OIL	
12H - Paste Masks (mud packs)	EUCALYPTUS GLOBULUS	11
	(EUCALYPTUS) LEAF OIL	
12I - Skin Fresheners	EUCALYPTUS GLOBULUS	4
	(EUCALYPTUS) LEAF OIL	
12J - Other Skin Care Preps	EUCALYPTUS GLOBULUS	57
	(EUCALYPTUS) LEAF OIL	
13B - Indoor Tanning Preparations	EUCALYPTUS GLOBULUS	1
	(EUCALYPTUS) LEAF OIL	
		414

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

02A - Bath Oils, Tablets, and Salts	EUCALYPTUS	7
04B - Perfumes	EUCALYPTUS	5
04E - Other Fragrance Preparation	EUCALYPTUS	5
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
		41

No uses were reported in the 2017 VCRP for: Eucalyptus Globulus Leaf Eucalyptus Globulus Leaf/Twig Oil Eucalyptus Globulus Leaf Water



Memorandum

TO:

Bart Heldreth, Ph.D.

Executive Director - Cosmetic Ingredient Review (CIR)

FROM:

Beth A. Jonas, Ph.D.

Industry Liaison to the CIR Expert Panel

DATE:

December 5, 2017

SUBJECT:

Eucalyptus Globulus Leaf Oil

TKL Research. 2010. Human repeated insult patch test with challenge (lipstick containing 0.5% Eucalyptus Globulus Leaf Oil).



TKL Study No. DS110709

TKL Study Report No. DS110709-5

Human Repeated Insuit Patch Test with Challenge

(FINN CHAMBERS 48 H)

contains 0,5% Lip Stick Eucalyplus Globulus Leaf of

Sponsor:

Document type:

Clinical Study Report

Investigational Product:

Batch No.:

Product Type:

Study Monitor:

Investigator:

Investigating Site:

TKL Research Inc.

1 Palmer Terrace

Carlstadt, NJ 07072

Investigating Laboratory:

TKL Research Inc.

365 W. Passaic Street Rochelle Park, NJ 07662

Number of Pages:

39

Document Version:

Final

Date: February 4, 2010

Prepared by TKL Research, Inc. 365 W. Passaic Street Rochelle Park, NJ 07662 USA



Page 2 TKL Study Report No. DS110709-5

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6 [1]. The report accurately reflects the raw data for this study.

Jonathan S. Dosik, MD Principal Investigator

Dermatologist

Date

Kathleen Georgeian

Director, Dermatologic Safety Testing



Date

¹ ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.



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STATEMENT OF TKL RESEARCH, INC. QUALITY CONTROL

All data and supporting documentation for this study have been reviewed by the TKL Quality Control Department and found to be accurate, complete and in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and this report has been reviewed and accurately reflects the raw data for this study.

The Quality Control Department has conducted the following inspections for this study. Written status reports of inspections and findings are submitted to Management according to TKL Research, Inc. Standard Operating Procedures.

Date of Inspection	Type of Inspections	Date Reported to Management
11/20/2009	Initial Binder Review Prior to Study Start	11/20/2009
12/03/2009	Screeners/Consents 100% Review	12/03/2009
01/13/2010	After Study Binder Review	01/13/2010
01/14/2010	Tables and Data Listings	01/14/2010
02/04/2010	Final Study Report	02/04/2010

Ouality Control

2/4/10 Date



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Study Title:

Human Repeat Insult Patch Test with Challenge

Sponsor:



Protocol #:

Contract Research Organization:

TKL Research, Inc. 365 W. Passaic Street Rochelle Park, NJ 07662 USA

TKL Study Report #: DS110709-5

Investigating Site:

TKL Research, Inc. 1 Palmer Terrace Carlstadt, NJ 07072

Dates of Study:

November 30, 2009 – January 8, 2010

STUDY PERSONNEL

Principal Investigator

Director, Dermatological Safety Testing

Kathleen Georgeian

Clinical Research Coordinator

Michelle Medina

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SUMMARY

One investigational product,	was evaluated as supplied to determine if the
application of the investigational product,	did not cause a delayed contact
allergic response in volunteer subjects with normal sk	cin using an occlusive human repeat insult patch
test. One hundred seven (107) subjects completed the	e study.
Under the conditions employed in this study,	was found to be non-irritating
and there was no evidence of sensitization.	



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1 INTRODUCTION

The test consists in the repeated dermal application of the investigational product to human volunteer subjects under conditions which exaggerate the normal conditions of product use.

2 STUDY OBJECTIVE

The main objective of this study was to confirm that the application of a cosmetic product to volunteer subjects under maximized conditions according to the "modified Marzulli and Maibach" method did not cause a delayed contact allergic response.

Secondarily, skin compatibility of certain products may have been evaluated during the induction phase.

3 STUDY DESIGN

3.1 OVERALL STUDY DESIGN

This was a single center, within-subject comparison study of the investigational product. All subjects had sites designated for the investigational product on the infrascapular area of the back for the purpose of determining sensitization potential.

During the induction phase of the study, the study products were applied to 1 side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites was assessed clinically using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation. A total of 9 applications were made during the induction phase.

Following induction, subjects had a 2-week rest phase, after which they entered the challenge phase that consisted of one 48-hour patch application to the original site and a naive site on the opposite side of the back. Observations at the naive site during challenge and the patterns of reactivity during the induction period provided a basis for an interpretation of contact allergic response.

If a cutaneous response observed in the challenge phase indicated possible sensitization, or at the discretion of the dermatologist investigator, a rechallenge was performed. In such cases, a narrative description of reactions in the challenge and rechallenge phases were reported together with the opinion of the dermatologist investigator as to whether such reactions were felt to be indicative of contact allergic response.

A total of 10 patch applications were made over a period of 6 weeks.

3.2 DISCUSSION OF DESIGN

This study design is based on the Modified Draize procedure (Marzulli & Maibach 1974), and is accepted standard methodology used for assessment of skin sensitization [2, 3].

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular investigational product can be applied safely to human skin without significant risk of adverse reactions [4].



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Repeated insult patch test (RIPT) evaluation is a predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure.

3.3 STUDY PROCEDURES

3.3.1 Screening / Day 1

At screening, the subjects were informed of the study procedures and the informed consent of each volunteer was obtained. Background information, including the date of birth, gender, and race, and a medical history for each subject was reviewed and recorded at screening. Eligibility was determined by review of the inclusion/non-inclusion criteria. If the subject fulfilled all the inclusion and none of the non-inclusion criteria, he/she was allowed to participate in the study, and received a unique enrollment number in order to preserve the subject's confidentiality. Qualified subjects were given oral and written instructions as follows:

- When bathing, avoid getting the patches and the application areas wet by taking a low tub bath or shower the front of your body only.
- No swimming is permitted during the study.
- You must notify staff if patches come off.
- Do not engage in activities (especially sports) that cause excessive sweating.
- Throughout the entire study, and for 2 weeks after study completion, avoid exposure to the sun or tanning beds.
- Avoid excessive scrubbing around patch area, which may cause irritation and may remove patch site markings.
- Do not apply any products in or around the patch area (including sunscreens). You must notify the staff if you do.
- Inform the staff of any vaccinations and/or use of medications during the study.
- Notify the staff if anything unusual occurs at any time during the study or within 2 weeks of completing the study. Please bear in mind that if TKL discontinues your participation in this study due to an adverse event or severe reaction, you will be paid for your participation.
- Please inform us if you experience any discomfort beyond mild itching. Contact us as soon as possible at (201)587-0505.
- During the entire study, including rest week, we ask that you do not participate in any other patch or photopatch study with any research company.
- Do not participate in a similar study within 3 months of completing this study.

3.3.2 Induction

The induction phase consisted of a series of 9 applications of the investigational product and subsequent evaluations of the application sites. Patches were applied on Mondays, Wednesdays, and Fridays for 3 consecutive weeks. The subjects returned to the facility at 48-hour intervals to have the patches removed. Using a tissue, the dermatologist investigator-trained evaluator removed any remaining excess investigational product to avoid transference of products between sites. The sites were evaluated 15 to 30 minutes after patch removal by a dermatologist investigator-trained evaluator using the scoring system detailed in Table 3.1 in Appendix 1. Scores were entered into the



data sheets by the evaluator. Identical patches were then applied to the same sites. Patches applied on a Friday remained in place for 72 hours until Monday.

3.3.3 Rest Period

During the 2-week rest period, subjects did not receive any application of the investigational product.

3.3.4 Challenge

At challenge, subjects who completed the induction phase and the rest period had identical patches applied to the original sites and to naive sites. Patches remained in place for 24 hours. The sites were graded at least 30 minutes as well as 48 hours following patch removal (ie, 48 and 96 hours after patch application) using the procedures described above for the induction phase.

3.3.5 Rechallenge

At the discretion of the dermatologist investigator and after discussion with the sponsor, a subject may have been rechallenged to the investigational product in the event of a doubtful reaction during the challenge phase. Rechallenge patches would be applied as soon as challenge reactions had resolved. The investigational product would be applied to naive sites on the back for 48 hours and graded at 48, 72, and 96 hours after application and if necessary, every day until resolution.

A similar or more severe response observed at rechallenge would have been considered indicative of a sensitization reaction. At the dermatologist investigator's discretion, further follow-up or retesting may have been necessary to confirm an interpretation of the finding.

3.3.6 Study Flow Chart

Week 1

- Obtained informed consent, reviewed completed medical screening form, applied patches
- 3 Staff removed patches, graded, applied patches
- 5 Staff removed patches, graded, applied patches

Week 2

- 1 Staff removed patches, graded, applied patches
- 3 Staff removed patches, graded, applied patches
- 5 Staff removed patches, graded, applied patches

Week 3

1-7 Same as Week 2

Week 4

- 1 Staff removed patches, graded
- 2-7 Began rest period

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Week 5

1-7 Rest period

Week 6

- 1 Staff applied patches
- 3 Staff removed patches, graded
- 5 Staff graded

3.4 SELECTION OF SUBJECTS

A sufficient number of subjects were enrolled in order to provide 100 completed subjects evaluable for analysis; an individual subject was allowed to participate in the study 1 time only.

To be considered a **completed case**, a subject must have had 9 applications of the investigational product and 9 subsequent readings during induction and 1 application followed by 2 subsequent readings during challenge. Only completed cases were used to assess sensitization.

3.4.1 Inclusion Criteria

Subjects included in the study were those who:

- 1. were healthy males or females, 18 to 65 years of age (no more than 10% ages 60-65), with a permanent address,
- 2. were able to give written consent,
- 3. were informed of the test procedures, were capable of reading the documents presented to them, and were capable of understanding them in the language used,
- 4. were subjects who benefited from social security or medical insurance (according to the legislation in force in the country where the test takes place),
- 5. were subjects selected according to the procedures established by the Investigating Laboratory. These criteria were evaluated using the questionnaires recorded in the Investigator's CRF.

3.4.2 Non-inclusion Criteria

Subjects excluded from the study were those who:

- 1. refused to undertake to refrain from participating simultaneously in other bio-medical studies.
- 2. did not comply with the non-inclusion period stipulated at the time of their participation in the previous test,



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- 3. had been deprived of their freedom by a legal or administrative decision, or people undergoing an emergency medical treatment (article L 209-5 French Law),
- 4. were minors or subjects protected by law, as well as those admitted into a health, social, or mental institution (article L 209-6 French law),
- 5. refused to give their agreement by not signing the informed consent declaration,
- 6. had an organ removed (kidney, lung, spleen, hepatic lobe, etc), a transplant, or suffered from a cranial trauma with after-effects,
- 7. were pregnant or nursing women, or those who have not taken contraceptive precautions,
- 8. presented a condition which is considered unacceptable for the study: such as skin marks at the test site that may interfere with the evaluation of the skin reactions (pigmentation problems, scarring, excessive hair growth, excessive numbers of freckles and moles, sunburn, etc), an immune deficiency, a previous history of contact allergies, immediate allergic reactions currently under treatment (asthma, periodic spasmodic rhinitis, conjunctivitis, etc), a fever lasting for more than 24 hours, in the 8 days preceding the product application,
- 9. had undergone long-term treatment or who were currently undergoing long-term treatment involving insulin, antihistamines, corticoids, beta-blockers (including eye drops), antibiotics, immunosuppressive drugs (cyclosporine), and/or in a period of de-sensitization,
- 10. had treatment with vitamin A or its derivatives less than 3 months before the beginning of the study,
- 11. had been vaccinated in the 3 weeks prior to the study or intend to be vaccinated during the study,
- 12. had been presenting cutaneous hyperactivity or skin disorder,
- 13. had strong reactions to sticking plaster of patches,
- 14. had been exposed to natural sunshine or UV lamp on the test area, during the month preceding the study,
- 15. showed a disorder due to excessive alcohol or drug use.

3.4.3 Informed Consent

A properly executed informed consent document in compliance with FDA regulations (21 CFR Part 50) and the Helsinki Declaration (1964) and subsequent amendments [5] was obtained from each subject prior to entering the study. Each subject dated and signed an informed consent document, which was witnessed and dated and signed by the dermatologist investigator's designee. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix III).



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3.4.4 Interruption or Discontinuation of Treatment

In accordance with legal requirements and ICH-GCP guidelines, every subject or his/her legal representative had the right to refuse further participation in the study at any time and without providing reasons. A subject's participation was terminated immediately upon his/her request. The dermatologist investigator or designee was to seek to obtain and record the reason.

The termination of an individual's participation was to be considered in the case of a serious adverse event (SAE). If the subject, during the course of the study, developed a condition(s) which would have prevented his/her entry into the study according to the safety-related medical non-inclusion criteria, he/she was to be withdrawn immediately.

The subject may have been withdrawn from the study at any time at the discretion of the dermatologist investigator for medical reasons and/or due to non-adherence to the treatment scheme and other duties stipulated in the study protocol. The reasons were to be fully documented on the CRF.

An erythema score of 2 or more to a study product (see Table 3.1 in Appendix 1 for interpretation of scores) observed at the first or second reading of the induction phase would have indicated the subject was most likely presensitized and the sponsor was to be immediately notified. Application of the product in question would have been discontinued at the original site and the treatment moved to an adjacent site. The grading will continue on the 1st site until the effects are reversed and on the 2nd site until the end of the induction phase. The site may only be changed once. In the case of a suspected allergic reaction, the product would not be applied again and the decision to reapply would be discussed with the sponsor.

Withdrawals

The following medical and other reasons justified a premature termination (by subject or dermatologist investigator) of any of the study products:

- withdrawal of informed consent,
- serious adverse events,
- allergic reactions to the investigational products,
- subject's request,
- occurrence of one of the safety criteria for non-inclusion after treatment had been instituted,
- the patches became dislodged or were misplaced such that continuous contact with the skin had been interrupted,
- subject was lost to follow-up, and/or
- dermatologist investigator's judgment.

If a subject withdrew from the study, all efforts were made to complete a final evaluation, if possible. Subjects discontinued for having experienced an adverse event (AE) were followed until the AE was resolved, a reasonable explanation was provided for the event, or the subject was referred to his/her own primary medical doctor (PMD). The specific AE in question was recorded on the appropriate CRF.



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3.5 INVESTIGATIONAL PRODUCT (IP)

3.5.1 Investigational Product Specifications

IP Category : <u>Lipstick</u>

Formula No. :

Batch No. :

Description : Colorless Paste

Amount Applied : 20 mg
Patch Type : Occlusive
Evaporation : None
Dilution : None

Storage Conditions : Room Temperature

Special Instructions: Switched to semi-occlusive conditions if a reaction of 2 or greater

occurred.

3.5.2 Description of Patch Conditions

Products-evaluated under occlusive patch conditions are applied under a Finn Chamber. This chamber, formed of an 8 mm aluminum cup affixed to Scanpor tape, provides an isolation chamber in which the investigational product is placed. An amount of investigational product sufficient to fill the chamber (20 μ L) is placed within the Finn Chamber such that it does not extend onto the adhesive tape surfaces. Liquid investigational product is soaked into a small filter disk placed within the Finn Chamber. For gels and ointments, an amount sufficient to fill the chamber is applied. The chamber is maintained in place by a hypoallergenic adhesive strip (Micropore) and serves to limit the investigational product to the designated skin contact site. Liquids are applied to the patch using an Eppendorf single channel adjustable pipette set at the appropriate amount to be applied to the patch, usually 20 μ L. Creams, semi-solids, and solids are weighed by applying product to a patch that has been pre-weighed on a pre-calibrated weight balance. The product and patch are then weighed on the pre-calibrated weight balance to determine the appropriate amount of product, usually 20 mg. The weighed patch is used as a visual guide to prepare patches.

3.5.3 Storage, Handling, and Documentation of the Investigational Product

Receipt of the investigational product used in this study was documented in a general log book which serves as a permanent record of the receipt, storage, and disposition of all investigational products received by TKL Research, Inc. On the basis of information provided by the sponsor, the investigational product was considered reasonably safe for evaluation on human subjects. The investigational product was kept locked in product storage rooms at the TKL clinical site at 4 Forest Avenue, Paramus, NJ 07652 prior to the start of the study and at the completion of the study. During the study the product was kept at the TKL clinical test site at 1 Palmer Terrace, Carlstadt, NJ 07072. The product was only accessible to TKL clinical staff members. The investigational product was destroyed upon acceptance of the final report and a sample was retained for a period of 6 months.

3.5.4 Treatment Compliance

All patches were applied and removed by clinical study staff. Whereas bathing was allowed (low tub bath/frontal showers), the patched area was not to be soaked and was to be kept as dry as possible, per the instructions given to each subject (see Section 3.3.1). A dermatologist investigator-trained,



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experienced evaluator assessed study compliance. Records of patch applications and visit schedule compliance were recorded on the subjects' CRFs.

3.6 SAFETY EVALUATIONS

3.6.1 Local Tolerability Assessments

Assessment of the patch sites was performed 9 times during the induction phase, 2 times following challenge and, if applicable, 3 times following rechallenge. The examination of the treated sites was carried out under an artificial 60 watt blue light. The scores outlined in Table 3.1, Appendix 1 were used to express the response observed at the time of examination. Allergy was evaluated according to the International Contact Dermatitis Research Group [6].

3.6.2 Adverse Events

An adverse event is defined as an occurrence of a new symptom(s) of a medical nature during use of the investigational product whether or not considered related to the investigational product, eg, headache, influenza, broken bones, fever, nausea. A serious adverse event is defined as death, a life threatening adverse experience, inpatient hospitalization, a persistent or significant disability/incapability, or a congenital anomaly/birth defect. Serious adverse events were to be reported to the sponsor within 24 hours of the investigative personnel's knowledge of the event. All AEs, whether observed by the clinical staff or by the subject, and whether or not thought to be study-related, were to be recorded on an Adverse Event form. Assessment of severity and causality will be based on definitions found on the AE form. Pregnancy, although not itself an adverse event, was also to be reported on an adverse event form.

Expected Adverse Events

Any observed response that was denoted using the irritation criteria summarized in Table 3.1 was not considered an AE. Likewise, any tape-related irritation was not noted as an AE.

3.7 QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, the medical screening forms and informed consent documents were reviewed in-process of the study, and the regulatory binder was reviewed post-study.

4 DATA MANAGEMENT

4.1 DOCUMENTATION

Case report forms were designed by TKL Research, Inc. to identify each subject by subject entry number and, where appropriate, the subject's initials. Originals or copies of all CRFs, source documents, correspondence, and study reports, etc. will be kept on hard-copy file by TKL Research, Inc. for a minimum of 10 years from completion of the study. The hard-copy file will be maintained at the study site, TKL Research, Inc. at 4 Forest Avenue, Paramus, NJ, 07652, in a secured room accessible only to TKL employees for a period of 1 year, after which it will be sent to the off-site archive location, Allstate Business Archives, 80 Beckwith Avenue, Paterson, NJ, 07503,



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that provides a secure environment with burglar/fire alarm systems, camera detection, and controlled temperature and humidity, for a period of 9 years. Archive destruction will be done only by a formalsigned written agreement from the sponsor. The dermatologist investigator/institution permit study-related monitoring, audits, fRB/IEC review, and regulatory inspection, and provide direct access to source data/documents on the premises of TKL Research, or at a secure location off-site.

4.2 DATABASE MANAGEMENT AND QUALITY CONTROL

Data were double-keyed and validated using ClinPlus (DZS Software Solutions), which directly generated SAS[®] data sets. After resolution of double-key discrepancies and a combination of manual and automated data review procedures, the final data sets were subject to a quality control (QC) audit. SAS[®] programs for data analysis and presentation were applied to secure validated data sets.

5 INTERPRETATION OF THE RESULTS

5.1 SAMPLE SIZE

With a sample size of 100, in the absence of any sensitization reactions, a 95% upper confidence bound on the population rate of sensitization would be 3.5% [7].

5.2 POPULATIONS

All subjects who were treated were evaluable for adverse events. The evaluation of sensitization was based on all subjects who completed the challenge phase of the study.

5.3 CRITERIA OF EVALUATION OF SKIN COMPATIBILITY

Skin compatibility was evaluated from the skin reactions observed (number, intensity, frequency) and compared with that established for the chosen investigational product as a reference with the untreated control site. The analysis of skin compatibility includes all subjects in the test, however many times they were evaluated during the induction phase.

5.4 DERMAL SENSITIZATION POTENTIAL

The determination of dermal sensitization potential was based on specific scoring criteria derived from observations in the challenge phase of the study, and confirmed in the rechallenge phase, if necessary.

The recurrence of a cutaneous response at rechallenge equivalent to or more severe than that observed at challenge was considered indicative of a sensitization reaction. The observation of such a response in even a single subject suggested that the study product may have the potential to cause hypersensitivity.

For all subjects who entered rechallenge, a narrative description of reactions in the challenge and rechallenge phases was to be provided together with the opinion of the dermatologist investigator as to whether such reactions were felt to be indicative of contact allergic response.

6 RESULTS

Summary data tables are provided in Appendix 1 of this report. Supportive listings are provided in Appendix 11.



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6.1 SUBJECTS EVALUATED

6.1.1 Subject Disposition

Subject disposition is shown in Table 1 and summarized in Text Table 6-1; these data are supported by Data Listing 1.

Text Table 6-1 Subject Disposition

Number of subjects enrolled	116
Number of subjects treated	116
Number of subjects discontinued	9
Lost to follow-up	8
Voluntary withdrawal	1
Number of subjects completed	107

Source: Table 1, Appendix I

6.1.2 Protocol Deviations

TKL Research, Inc. used an artificial 60 watt blue light during subject evaluations. This light is not consistent with the D65 North daylight Illuminator specified in the protocol. This deviation did not affect the validity of the study.

The in-phase inspection was conducted bi-yearly in accordance with TKL Research, Inc.'s Standard Operating Procedures. An audit was not conducted for this study as specified in the protocol. This deviation did not affect the validity of the study.

This report does not include the summary in French as specified in the protocol. This is in agreement with the sponsor and the deviation does not affect the validity of the study.

Thirteen (13) subjects, 11% were in the age range of 60-65. No more than 10% within that age range were to participate in the study, as specified in the protocol. This deviation did not affect the validity of the study.

6.1.3 Protocol Amendments

No amendments to the protocol were issued for this study.

6.1.4 Baseline Demographic and Background Characteristics

All subjects met the inclusion and the non-inclusion criteria. Demographic information is summarized in Table 2, Appendix 1; these data are supported by Data Listing 2, Appendix II. The study population comprised 24 (21%) males and 92 (79%) females, of whom 67 (58%) were Caucasian, 47 (41%) were Hispanic, 1 (1%) was American Indian and 1 (1%) was Asian. Subject ages ranged from 18 to 65 years; the mean was 46 years.



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6.2 SAFETY RESULTS

6.2.1 Induction and Challenge Responses

One hundred seven (107) subjects completed the induction phase and were included in determining the presence of significant irritation. One hundred seven (107) subjects completed the challenge phase of the study and were included in the sensitization analysis. There was no requirement for a re-challenge phase to be conducted.

A summary of the repeated insult patch test responses during the induction and challenge phases of the study is provided in Table 3, Appendix 1, a by-subject listing of the sensitization response data is provided in Data Listings 3, Appendix 11.

6.2.2 Overall Experience of Adverse Events

There were no adverse events reported.

7 CONCLUSIONS

Under the conditions employed in this study, was found to be non-irritating and there was no evidence of sensitization.

8 REFERENCES

- 1. ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" ICH Harmonised tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.
- 2. Jordan, WP. 24-, 48-, and 48/48-hour Patch Tests. Contact Dermatitis 1980. 6: 151-152.
- 3. Marzulli F. N.; Maibach H. l. Contact Allergy: Predictive Test in Man. *Contact Dermatitis* 1976, 2:1-17
- 4. Lanman, BM, EB Elvers, and CJ Howard. "The Role of Human Patch Testing in a Product Development Program." Joint Conference on Cosmetic Goods Association, Washington DC, April 21-23, 1968.
- 5. Declaration of Helsinki adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; 35th World Medical Assembly, Venice, Italy, October 1983; 41st World Medical Assembly, I-long Kong, September 1989; 48th World Medical Assembly, Somerset West, Republic of South Africa, October 1996; 52nd World Medical Assembly, Edinburgh, Scotland, October 2000; 53rd World Medical Assembly, Washington, USA, 2002; 55th World Medical Assembly, Tokyo, Japan, 2004; 59th General Assembly, Seoul, Korea, October 2008.
- 6. CDRG = The International Contact Dermatitis Research Group, Fregert S. Manual of Contact Dermatitis, 2nd Edition
- 7. Mood AM, Graybill FA, Boes DC. Introduction to the Theory of Statistics. 3rd ed. New York: McGraw-Hill Higher Ed; 1974:Chapter 7.



Memorandum

TO:

Bart Heldreth, Ph.D.

Executive Director - Cosmetic Ingredient Review (CIR)

FROM:

Carol Eisenmann, Ph.D.

Personal Care Products Council

DATE:

December 14, 2017

SUBJECT:

Eucalyptus Globulus Leaf Extract

Native Extracts reports that their Eucalyptus Globulus Leaf Extract is a water extract of the leaves that contains no eucalyptol.

Native Extracts. 2017. Specification technical data sheet NE Tasmanian Blue Gum Extract Cosmetic.

Native Extracts. 2017. Safety data sheet: NE Tasmanian Blue Gum Extract.

SPECIFICATION TECHNICAL DATA SHEET



1. PRODUCT IDENTIFICATION AND SUBSTANCE

NE Tasmanian Blue Gum Extract Cosmetic Trade Name:

Product Name: Tasmanian Blue Gum Extract 1.2

1.3 Botanical Name: Eucalyptus globulus Product Code: ANE0342SB-10 1.4

INCI Name US/EU: Glycerin (and) Water/Aqua (and) Eucalyptus globulus (Tasmanian Blue Gum) Leaf

Extract (and) Sodium Benzoate

2. COMPANY DETAILS

NATIVE EXTRACTS Pty Ltd 2.1 Name: Address: 3/4 Endeavour Close BALLINA NSW 2478

AUSTRALIA

+61 2 6686 5725 2.3 Telephone:

2.4 Email: enquiries@nativeextracts.com 2.5 Website: www.nativeextracts.com

3. QUANTITATIVE PARAMETERS

3.1 Not available

4. PHYSICAL PARAMETERS

	ANALYSIS	TEST METHOD	RANGE
4.1	Appearance:	Visual	Yellow to brown
4.2	Refractive Index @20°C	Internal method	1.370 - 1.550
4.3	Specific Gravity @ 20°C:	Internal method	1.130 - 1.280

5. COMPOSITION INFORMATION ON INGREDIENTS

	SUBSTANCES CHEMICAL NAME	PERCENTAGE	NUMBER
5.1	Glycerin	<70%	CAS: 56-81-5
5.2	Water/Aqua	<35%	CAS: 7732-18-5
5.3	Eucalyptus globulus (Tasmanian Blue Gum) Leaf Extract*	10%	CAS: 84625-32-1
5.4	Preservative: Sodium Benzoate	<1%	CAS: 532-32-1
5.5	* Concentrate Extract		

6. QUALITIVE PARAMETERS LCMS

6.1 Available on request

7. MICROBIOLOGY

Total Bacterial Count

8. USAGE

B.1 Use in Cosmetic products at <5.0%

9. EXPOSURE, 5 O AGE AND SHELF LIFE

9.1 Product must be kept in the original packaging, protected from moisture and properly closed under pressure.

<100cfu/g

Product not tested on animals

9.2 Storage temperature between 10 - maximum 20°C.

- Shelf life of 12 months unopened from date of manufacture.
- Certain material will degrade more rapidly than others and ultimate shelf life is dependant upon good storage conditions and handling procedures.

10. TOXICOLOGY INFORMATION

10.1 ANIMAL TESTING

10.2 GENETICALLY MODIFIED ORGANISMS (GMO)

GMO free 10.3 ALLERGENS None detected

Crested Date: 2018-07-20	Revision: 2017-03-14	Review Date: 2018-07-20	Prest Date: 14/00	i/2017 9.43 am
NATIVE EXTRACTS 1 NE:2 TOS:3 SB:1	WORD DOCUMENTS: NE Taumanian Blu	e Gum Extract ANEO43258-10 TDS.docx		Page 1 of 2

SPECIFICATION TECHNICAL DATA SHEET



10.4 CARCINOGENS, MUTAGENS OR

REPRODUCTIVE TOXINS [CMR]

None identified

10.5 NANOPARTICLE

Not applicable

10.6 BOVINE SPONGIFORM ENCEPHALOPATHY (BSE) Not applicable

11. DISCLAIMER

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Created Date: 2016-07-20	Revision: 2017-03-14	Review Data; 2019-07-20	Print Date: 14/0	13/2017 9:43 am
NATIVE EXTRACTS:1, NE.2, TDS:3, SB:1.	WORD DOCUMENTS NE Tesmenian Blue Gun	Extract ANEO43258-10 TDS docx		Page 2 of 2



SECTION 1 IDENTIFICATION OF THE SUBSTANCE AND SUPPLIER

PRODUCT IDENTIFIER

TRADE NAME: 1.1 PRODUCT DESCRIPTION: 1.2

NE Tasmanian Blue Gum Extract Cosmetic Dilution 1:10 Tasmanian Blue Gum Extract

BOTANICAL NAME: 1.3

Eucalyptus globulus

PRODUCT CODE: 1.4

ANE03425B-10

1.5 INCI NAME (EU - USA): Glycerin (and) Water/Aqua (and) Eucalyptus globulus (Tasmanian Blue Gum) Leaf

Extract (and) Sodium Benzoate

EU (Cosing) INCI NUMBER: 1.6

283-406-2 84625-32-1

CAS NUMBER: 1.7 1.8 UN NUMBER:

Not required

REACH REGISTRATION: 1.9

Exempt from registration ex Annex V

1,10 HS CODE:

1302.19.90

RECOMMENDED USE OF THE CHEMICAL AND RESTRICTIONS ON USE

1.11 RELEVANT IDENTIFIED USES: Cosmetic ingredient, topical application, not to be ingested

1.12 USAGE:

<5.0%

SUPPLIER DETAILS

NATIVE EXTRACTS Pty Ltd 3/4 Endeavour Close **BALLINA NSW 2478 AUSTRALIA**

Tel: 612 6686 5725

Email: enquiries@nativeextracts.com

EMERGENCY TELEPHONE NUMBERS (24H/24H) - INSTITUTIONAL CENTRES WITHIN YOUR COUNTRY

1.13 AUSTRALIA:

Poisons Information Centre 13 11 26

1.14 USA:

Poison Control Centre 1-800-222-1222 Federal Institute for Risk Assessment

1.15 GERMANY: 1.16 ITALY:

National Institute of Health

UNITED KINGDOM: 1.17

National Poison Information Services

1.18 OTHER COUNTRIES:

Please contact relevant government services

SECTION 2 HAZARDS IDENTIFICATION

CLASSIFICATION OF THE SUBSTANCE OR MIXTURE

POISONS SCHEDULE:

Not applicable

HAZARDOUS CHEMICAL - NON-DANGEROUS GOODS: According to the WHS Regulations and the ADG Code

2.2 **CLASSIFICATION:** Skin Corrosion/Irritation

Category 3

Serious Eye Damage/Eye Irritation

Category 2B

Specific Target Organ Toxicity Single Exposure

Category 3

LABEL ELEMENTS

GHS LABEL ELEMENTS: 2.3



2.4 SIGNAL WORD: WARNING

HAZARD STATEMENT(S):

H316

Causes mild skin irritation. Causes eye irritation.

H320 H335

May cause respiratory irritation.

PRECAUTIONARY STATEMENT(S)

2.5 PREVENTION:

Print Data: 3 May 2017 NATIVE EXTRACTS: 1. NE:3: SDS:3: SB:1. WORD DOCUMENTS:NE Teamenten Blue Gum Extract ANEO432SB-10 SDS docx Page 1 of 10



P101

P103

If medical advice is needed, have product container or label at hand.

Read label before use.

P262 P261 Wash hands thoroughly after handling. Avoid breathing mist/vapour/spray.

PRECAUTIONARY STATEMENT(S)

2.6 RESPONSE:

P332+P313

If skin irritation occurs: Get medical advice/attention.

P305+P351+P388 IF IN EYES. Rinse cautiously with water for several minutes. Remove contact

lenses, if present and easy to do. Continue rinsing. If eye irritation persists: Get medical advice/attention.

P337+P313 P304+P340

IF INHALED: Remove victim to fresh air and keep at rest in a position

comfortable for breathing.

PRECAUTIONARY STATEMENT(S)

2.7 STORAGE:

P403+P233

Store in a well-ventilated place. Keep container tightly closed

PRECAUTIONARY STATEMENT(S)

DISPOSAL:

P501

Dispose of contents/container in accordance with local/national/international

regulations.

SECTION 3: COMPOSITION INFORMATION ON INGREDIENTS

SUBSTANCES CHEMICAL NAME	CAS No	EINECS-No	[%w/w]
Glycerin	56-81-5	200-289-5	<70%
Water/Aqua	7732-18-5	231-791-2	<35%
Eucalyptus globulus (Tasmanian Blue Gum) Leaf Extract*	84625-32-1	283-406-2	10%
Sodium Benzoate	532-32-1	208-534-8	<1%

BOTANICAL ORIGIN:

STATUS:

Cellular Extraction of Eucalyptus globulus leaf
Natural extract preserved with Sodium Benzoate

* Concentrate Extract

SECTION 4 FIRST AID MEASURES

DESCRIPTION OF FIRST AID MEASURES

4.1 EYE CONTACT:

If this product comes into contact with the eye:

> Wash out immediately with fresh running water.

Ensure complete irrigation of the eye by keeping eyelids apart and away from eye and moving the eyelids by occasionally lifting the upper and lower lids.

 Seek medical attention without delay; if pain persists or recurs seek medical attention.

• Removal of contact lenses after an eye injury should only be undertaken by skilled personnel.

42 SKIN CONTACT:

If skin contact occurs

Immediately remove all contaminated clothing, including footwear.

Flush skin and heir with running water (and soap if available)

Seek medical attention in event of irritation.

4.3 INHALATION:

If fumes or combustion products are inhaled remove from contaminated area.

Lay patient down. Keep warm and rested.

Prostheses such as false teeth, which may block airway, should be removed, where possible, prior to initiating first aid procedures.

 Apply artificial respiration if not breathing, preferably with a demand value resuscitator, bag-valve mask device, or pocket mask as trained. Perform CPR if necessary.

Transport to hospital, or doctor, without delay.

4.4 SWALLOWED:

Immediately give a glass of water.

First aid is not generally required. If in doubt, contact a Poisons Information

Centre or doctor.

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INDICATION OF ANY IMMEDIATE MEDICAL ATTENTION AND SPECIAL TREATMENT NEEDED Treat symptomatically.

SECTION 5: FIRE FIGHTING MEASURES

EXTINGUISHING MEDIA

Water spray or fog; Foam; Dry chemical powder; BCF (where regulations permit).

SPECIAL HAZARDS ARISING FROM THE SUBSTANCE

5.1 FIRE INCOMPATIBILITY:

Avoid contamination with oxidising agents i.e. nitrates, oxidising acids, chlorine

bleaches, pool chlorine etc. as ignition may result.

ADVICE FOR FIRE-FIGHTERS

5.2 FIRE FIGHTING:

Alert Fire Brigade and tell them location and nature of hazard.

Wear full body protective clothing with breathing apparatus.

▶ Prevent, by any means available, spillage from entering drains or watercourse.

Use water delivered as a fine spray to control fore and cool adjacent area.

5.3 FIRE/EXPLOSION HAZARD:

▶ Combustible.

> Slight fire hazard when exposed to heat or flame.

> Heating may cause expansion or decomposition leading to violent rupture of

containers.

> On combustion, may emit toxic fumes or carbon monoxide (CO).

 Combustion products include, carbon dioxide (CO2) acrolein, other pyrolysis products typical of burning organic material. May emit poisonous fumes. May

emit corrosive fumes

5.4 HAZCHEM:

Not applicable

SECTION 6. ACCIDENTAL RELEASE M. ASURES

PERSONAL PRECAUTIONS, PROTECTIVE EQUIPMENT AND EMERGENCY PROCEDURES

See Section 8.

ENVIRONMENTAL PRECAUTIONS

See Section 12.

METHODS OF MATERIAL FOR CONTAMINATION AND CLEANING UP

6.1 MINOR SPILLS:

Remove all ignition sources.

Clean up all spills immediately.

Avoid breathing vapours and contact with skin and eyes.

> Control personal contact with the substance, by using protective equipment.

6.2 MAJOR SPILLS:

▶ MODERATE HAZARD: Clear area of personnel and move upwind.

Alert Fire Brigade and tell them location and nature of hazard.

Wear breathing apparatus plus protective gloves.

SECTION-7=HAMBLING AND STURAGE

PRECAUTIONS FOR SAFE HANDLING

7.1 SAFE HANDLING:

Avoid all personal contact, including inhalation,

Wear protective clothing when risk of exposure occurs.

Use in a well-ventilated area.

Prevent concentration in hollows and sumps.

Do not allow clothing wet with substance to stay in contact with the skin.

7.2 OTHER INFORMATION:

> Store in original containers.

> Keep containers securely sealed.

No smoking, naked lights or ignition sources.

> Store in a cool, dry, well-ventilated area.

CONDITIONS FOR SAFE STORAGE, INCLUDING AND INCOMPATIBILITIES

7.3 SUITABLE CONTAINER:

Packaging as recommended by manufacturer.

> Check all containers are clearly labelled and free from leaks.

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7.4 STORE INCOMPATIBILITY:

Avoid reaction with oxidising agents.















0

Warning

Corrosive

Х Must not be stored together

May be stored together with specific preventions 0

May be stored together

SECTION 8: EXPOSURE CONTROLS / PERSONAL PROTECTION

CONTROL PARAMETERS

The product is not classified. No control parameters are to be mentioned.

EXPOSURE CONTROLS

APPROPRIATE ENGINEERING CONTROLS:

- > Engineering controls are used to remove a hazard or place a barrier between the worker and the hazard. Well-designed engineering controls can be highly effective in protecting workers and will typically be independent of worker interactions to provide third high level of protection.
- > The basic types of engineering controls are; Process controls which involve changing the way a job activity or process is done to reduce the risk.
- Enclosure and/or isolation of emission source which keeps a selected hazard 'physically' away from the worker and ventilation that strategically adds and 'removes' air in the work environment

8.2 PERSONAL PROTECTION:













EYE AND FACE PROTECTION: 83

- Safety glasses with side shield.
- ▶ Chemical goggles.
- Contact lenses may pose a special hazard; soft contact lenses may absorb and concentrate irritants. A written policy document, describing the wearing of lenses or restrictions on use, should be created for each workplace or task.

SKIN PROTECTION: 8.4

See Hand Protection below.

HAND/FEET PROTECTION:

- Wear chemical protective gloves, e.g. PVC.
- Wear safety footwear or safety gumboots, e.g. Rubber.
- The selection of suitable gloves does not only depend on the material, but also on further marks of quality, which vary from manufacturer to manufacturer.
- Where the chemical is a preparation of several substances, the resistance of the glove material cannot be calculated in advance and has therefore to be checked prior to the application.
- The exact break through time for substances has to be obtained from the manufacturer of the protective gloves and has to be observed when making a final choice.
- Personal hygiene is a key element of effective hand care.

BODY PROTECTION: 8.6

▶ See Other Protection below.

6.7 OTHER:

- > Overalls
- ▶ PVC Apron
- ▶ Barrier Cream

The following Australian Standards will provide general advice regarding safety clothing and equipment:

AS/NZS 1715:

Respiratory Equipment Protective Gloves

AS 1161: AS2919:

Industrial Clothing

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AS1336/AS/NZS 1337:

Industrial Eye Protection

AS/NZS2210:

Occupational Protective Footwear

THERMAL HAZARDS:

Not available

SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES

9.1	APPEARANCE:	Slightly Viscous Liquid
92	ODOUR:	Characteristic
9.3	COLOUR:	Yellow to brown
9.4	TASTE:	Not determined
9.5	REFRACTIVE INDEX @20°C:	1.370 - 1.550
9.6	SPECIFIC GRAVITY@20°C:	1.130 - 1,280
9.7	WATER SOLUBILITY:	Soluble
9.8	FLASH POINT:	160°C
9.9	EVAPORATION RATE:	Non-volatile
9.10	pH:	No data available
9.11	FLAMMABILITY LIMITS:	Not available
9.12	AUTO-IGNITION TEMPERATURE:	Not available
9.13	MELTING POINT/	40
	FREEZING POINT:	Not available
9 14	BOILING POINT RANGE:	Not available

9.14 BOILING POINT RANGE: 9.15 VAPOUR PRESSURE:

No deta available

9 16 DENSITY: 9.17 VISCOSITY, KINEMATIC: Not available No data available

9 18 OXIDISING PROPERTIES:

Not oxidising Not explosive

9.19 EXPLOSIVE PROPERTIES: 9 20 BULK DENSITY: 9.21 RELATIVE VAPOUR DENSITY: 9.22 EVAPORATION RATE:

Not applicable No data available No data available

9.23 ADDITIONAL PARAMAETRES:

None available

SECTION 10: STABILITY AND REACTIVITY

- 10.1 REACTIVITY: ▶See Section 7
- 10.2 CHEMICAL STABILITY:

POSSIBILITY OF HAZARDOUS

REACTIONS:

See Section 7

▶ This product is chemically stable

10.4 CONDITIONS TO AVOID:

▶ See Section 7

10.5 INCOMPATIBLE MATERIALS:

▶ See Section 7

10.6 HAZARDOUS DECOMPOSITION

PRODUCTS:

See Section 5

SECTION 11: TOXICOLOGICAL INFORMATION

INFORMATION ON TOXICOLOGICAL EFFECTS

- 11.1 INHALED:
- > The material can cause respiratory irritation in some persons. The body's response to such irritation can cause further lung damage.
- Not normally a hazard due to non-volatile nature of product.
- 11.2 INGESTION:
- Although ingestion is not thought to produce harmful effects (as classified under EC Directives), the material may still be damaging to the health of the individual, following ingestion, especially where pre-existing organ (e.g. liver, kidney (damage is evident.
- Ingestion of large quantities may cause nausea, diarrhoea and vomiting.
- 11.3 SKIN CONTACT:
- The material may accentuate any pre-existing dermatitis condition.
- > Skin contact is not thought to have harmful health effects (as classified under EC Directives); the material may still produce health damage following entry though wounds, lesions or abrasions.
- Den cuts, abraded or irritated skin should not be exposed to this material.
- Entry into the blood stream, through, for example, cuts abrasions or lesions, may produce systemic injury with harmful effects. Examine the skin prior to the use of the material and ensure that any external damage is suitably protected.

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The material may cause mild but significant inflammation of the skin either following direct contact or after a delay of some time. Repeated exposure can cause contact dermatitis, which is characterised by redness, swelling and blistering.

11.4 EYE:

 Evidence exits, or practical experience predicts, that the material may cause eye irritation in a substantial number of individuals. Prolonged eye contact may cause inflammation characterised by a temporary redness of the conjunctiva (similar to windburn).

11.5 CHRONIC:

- ▶ Long term exposure to respiratory irritants may result in disease of the airways involving difficult breathing and related systemic problems
- Substance accumulation, in the human body, may occur and may cause some concern following or long term occupational exposure.

SCCNFP ALLERGENS ANNEX III - COSMETIC DIRECTIVE 2003/15/EC

7th Amendment Detection Limit 0.0015 CONSTITUENT	% JFRA	EFFA	CAS	EINECS	RANGE
Amyl Cinnamal:	Yes	No	122-40-7	204-541-5	Not detected
Amyl Cinnamyl Alcohol:	Yes	No	101-85-9	202-982-8	Not detected
Anise Alcohol:	No	Yes	105-13-5	203-273-6	Not detected
Benzyl Alcohol:	No	Yes	100-51-6	202-859-9	Not detected
Benzyl Benzoate:	No	Yes	120-51-4	204-402-9	Not detected
Benzyl Cinnamate:	No	Yes	103-41-3	203-109-3	Not detected
Benzyl Salicylate:	No	Yes	118-58-1	204-262-9	Not detected
Cinnamal:	Yes	Yes	104-55-2	203-213-9	Not detected
Cinnamyl Alcohol:	Yes	Yes	104-54-1	203-212-3	Not detected
Citral:	Yes	Yes	5392-40-5	226-394-6	Not detected
Citronellol:	No	Yes	106-22-9	203-375-0	Not detected
Coumarin:	No	Yes	91-64-5	202-086-7	Not detected
Eugenol:	Yes	Yes	97-53-0	202-589-1	Not detected
Farnesol:	Yes	Yes	4602-84-0	225-004-1	Not detected
Geraniol:	No	Yes	106-24-1	203-377-1	Not detected
Hexyl Cinnamal:	Yes	No	101-86-0	202-983-3	Not detected
Hydroxycitronellal	Yes	No	107-75-5	203-518-7	Not detected
Isoeugenol:	Yes	Yes	97-54-1	202-590-7	Not detected
Butylphenyl Methylpropional	Yes	No	80-54-6	201-289-8	Not detected
d-Limonene	Yes	Yes	5989-27-5	227-813-5	Not detected
Linalool:	Yes	Yes	78-70-6	201-134-4	Not detected
Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde:	No	No	31906-04-4	250-863-4	Not detected
Methyl 2-Octynoate:	Yes	No 🕖	111-12-6	203-836-6	Not detected
Alpha-Isomethyl Ionone:	Yes	No	127-51-5 90028-68-5	204-846-3 289-861-3	Not detected
Evernia Prunastri Extract (Oakmoss):	Yes	No	9000-50-4 6817-10-2		Not detected
All		-	90028-67-4	289-860-8	
Evernia Furfuracea Extract [Treemoss]:	Yes	No	68648-41-9		Not detected

ADDITIONAL EFFA LISTED SENSITISERS & IFRA NOTIFIABLE SUBSTANCES.

Detection Limit 0.001% CONSTITUENT	IFRA	EFFA	CAS	EINECS	RANGE
No Additional Sensitisers:	No	No	Not allocated	Not allocated	Not detected
No Additional Notifiable Substances:	No	No	Not allocated	Not allocated	Not detected

SECTION 12: ECOLOGICAL INFORMATION

12:1	ECO-TOXICITY:	None established; Use according to good working practice; Avoid pollution to
		soil, rivers and the ocean.

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12.2 PERSISTENCE AND DEGRADABILITY:

- ▶ Low persistence level and readily biodegradable; During natural decomposition.
- No dangerous products are developed; Use according to good working practice; pollution to soil, rivers and the ocean.
- 12.3 BIO-ACCUMULATIVE POTENTIAL: None established.
- 12.4 MOBILITY IN SOIL;

None established.

12.5 OTHER ADVERSE EFFECTS:

None established.

SECTION 13: DISPOSAL CONSIDERATIONS

WASTE TREATMENT METHODS

13.1 PRODUCT/PACKAGING DISPOSAL:

- Legislation addressing waste disposal requirements may differ by country, state and/or territory. Each user must refer to laws operating in their area. In some areas, certain wastes must be tracked.
- ▶ Do not allow wash water from cleaning or process equipment to enter drains.
- It may be necessary to collect all wash water for treatment before disposal.
- In all cases disposal to sewer may be subject to local laws and regulations and these should be considered first.
- Where in doubt contact the responsible authority
- ▶ Recycle wherever possible or consult manufacturer for recycling options
- ▶ Consult State Land Waste Authority for disposal.
- Bury or incinerate residue at an approved site.
- > Recycle containers if possible, or dispose of in an authorised landfill.

SECTION 14: TRANSPORT INFORMATION

LABELS REQUIRED

14:1 MARINE POLLUTANT:

No

14.2 HAZCHEM:

Not applicable

LAND TRANSPORT (ADG):

AIR TRANSPORT (ICAO-IATA/DGR): SEA TRANSPORT (IMDG-Code/GGVSee): Not regulated for transport of Dangerous Goods Not regulated for transport of Dangerous Goods Not regulated for transport of Dangerous Goods

14.3 UN NUMBER:

Not required Not required

14.4 PROPER SHIPPING NAME:

Not applicable

14.5 TECHNICAL SHIPPING NAME: 14.6 DG CLASS/SUBSIDIARY RISK:

Not allocated

14.7 PACKAGING GROUP:

Not allocated

14 B SPECIAL PRECAUTIONS:

Not established

14.9 HAZCHEM CODE:

Not allocated

SECTION 15: REGULATORY INFORMATION

SAFETY, HEALTH AND ENVIRONMENTAL REGULATIONS/LEGISLATION SPECIFIC FOR THE SUBSTANCE OR MIXTURE

The substance is not listed as a hazardous chemical under the following international agreements

- 15 1 Montreal Protocol on Substances that Deplete the Ozone Layer
- 15.2 Stockholm Convention on Persistent Organic Pollutents.
- 15.3 Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade.
- 15.4 Vasel convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal.
- 15.5 International Convention for the Prevention of Pollution from Ships (MARPOL).
- 15.6 Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).
- 15.7 Agriculture and Veterinary Chemicals Code Act 1994.
- 15 8 Australian Inventory of chemical Substances (AICS).

Eucalyptus globulus (Tasmanian Blue Gum) Leaf Extract

NATIONAL INVENTORY	COUNTRY	STATUS ✓×
Australian Inventory of Chemical Substances (AICS)	AUSTRALIA	✓
Domestic Substances List (DSL)	CANADA	✓

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Non-Damestic Substances List (NDSL)	CANADA	×
Inventory of Existing Chemical Substances Produced for Imported to China (IECSC)	CHINA	✓
European Chemicals Agency (ECHA-EINECS-ELINCS-NLP-COSING)	EUROPE	✓
Japanese Existing and New Chemical Substances Inventory (ENCS)	JAPAN	×
Korea Existing Chemicals Inventory (KECI)	KOREA	✓
New Zealand Inventory (NZIoC)	NEW ZEALAND	/
Philippines Inventory of Chemicals and chemical Substances (PICCS)	THE PHILIPPINES	/
Toxic Substances Control Act (TSCA)	USA	×
Taiwan Chemical Substance Inventory (TCSI)	TAIWAN	1

SECTION 16: ADDITIONAL INFORMATION

16.1 QUALITY STATEMENT

NATIVE EXTRACTS Pty Ltd specialises in the manufacture and supply of the highest quality, pure, naturally derived phyto-active compounds in hydrophilic extracts, seed oils and pure natural powders; for use in the Cosmetic, Pharmaceutical and Nutraceutical industries globally. Our company's objective is to manufacture and supply the highest quality and purity of natural ingredients across multiple delivery formats that meet the application/formulation objectives and specifications of our customers. Our commitment to quality extends beyond our products and applies to our blends, services, workplace, environmental practices and partnership and relationships engaged with commercial growers and Indigenous communities.

Any quality problems arising will be identified and solved with speed, technical efficiency and economy, stakeholder engagement – focusing our human and technical resources internally and externally to the prevention of quality deficiencies to meet our company goal of "right first time, every time".

The successful operation of our QMS relies on the cooperation, participation and engagement of our personnel across all areas of the company. Our commitment to quality underpins our continued success, the satisfaction of customers and staff, our pursuit to achieve new scientific discoveries and new benchmarks in performance ingredients. We are committed to improving our performance in every aspect of our business.

NATIVE EXTRACTS will to provide high and consistent quality in Botanical extracts and naturally derived phyto-active ingredients, evolving the botanical extract from inferior processes and synthetic standardisation to the delivery of stable, active True to Nature phyto-activity, influencing new innovation in natural product development, new advances in consumer experiences, influencing the emergence of new primary industry partnerships, and participating in socially and environmentally responsible practices.

Our commitment is to safety and accurate work to ensure our ingredients conform to various regulatory bodies locally and internationally and are safe to our customers, their clients and the environment. All work is done in conformance to NATIVE EXTRACTS' QMS, the applicable technical and administrative operating policies and procedures of NATIVE EXTRACTS, legal and regulatory requirements, and specific customer requirements.

Through front-line input and management leadership, we will continue to improve our people and processes to anticipate, meet, and exceed the needs of our customers. We support the continually improving quality of our customer's maintenance and other technical operations through the services we provide.

16 2 ANIMAL TESTING POLICY DECLARATION

NATIVE EXTRACTS Pty Ltd does not test raw materials on animals, neither initially nor as a routine test. The product suppliers for NATIVE EXTRACTS Pty Ltd do not test their products on animals, neither initially nor as a routine test.

None of NATIVE EXTRACTS Pty Ltd finished extracts are tested on animals, either initially or as a routine test.

16 3 DISCLAIMER

This Safety Data Sheet was prepared according to: Safe Work Australia's Code of Practice for the Preparation of Safety Data Sheets for Hazardous Chemicals, (Publication date: 23/12/2011) and Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (NOHSC:1008(2004)).

The information contained in this Safety Data Sheet is obtained from current and reliable sources. NATIVE EXTRACTS Pty Ltd provides the information contained herein in good faith but makes no representation as to its comprehensiveness or accuracy. This Safety Data Sheet summaries our best current knowledge of the health and safety hazard information of the product, but does not claim to be all-inclusive. This document is thus, intended only as a guide to the appropriate precautionary handling of the material by properly trained personnel using this product.

Individuals receiving this information must exercise their independent judgment in determining its appropriateness for a particular purpose. As the ordinary or otherwise use(s) of this product is outside the control of NATIVE EXTRACTS Pty Ltd, no representation or warranty, expressed or implied, is made as to the effect(s) of such use(s), (including damage or injury), or the results obtained. NATIVE EXTRACTS Pty Ltd expressly disclaims responsibility as

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to the ordinary or otherwise use(s). Furthermore, nothing contained herein should be considered as a recommendation by NATIVE EXTRACTS Pty Ltd as to the fitness for any use. The liability of NATIVE EXTRACTS Pty Ltd is limited to the value of the goods and does not include any consequential loss. NATIVE EXTRACTS Pty Ltd shall not be liable for any errors or delays in the content, or for any actions taken in reliance thereon.

NATIVE EXTRACTS Pty Ltd shall not be responsible for any damage resulting from use of or reliance upon this information. The user of the product is solely responsible for compliance with all laws and regulations applying to the use of the products, including intellectual property rights of third parties.

MANUFACTURED PRODUCTS INGREDIENTS DISCLAIMER

As the availability of ingredients and raw materials is not always certain whether due to changes in nature or otherwise, NATIVE EXTRACTS Pty Ltd reserves the right to substitute alternate ingredients/raw materials in the manufacture of its products in order to maintain supply to its customers. Customers should always refer to the ingredients label as affixed to each product or to specification sheets, which are current at all time of supply of the product.

16.5 LABELLING DISCLAIMER

NATIVE EXTRACTS Pty Ltd is a manufacturer of extracts. If you intend to re-label our products under your own name/brand for the purpose of on selling or retailing, we thoroughly recommend that you keep up to date with constant changing labelling laws.

Please visit www.acco.gov.au or www.nicnas.gov.au, NATIVE EXTRACTS Pty Ltd cannot be held responsible for consequential loss/product recall due to incorrect labelling.

16.6 ACRONYMS

<	Less than
>	Greater than
°C	Degrees Celsius

ACCC Australian Competition and Consumer Commission

ADG Australian Dangerous Goods

AICS Australian Inventory of Chemical Substances

ACGIH American Conference of Government Industrial Hygienists

AS Australian Standards 800 Biochemical Oxygen Demand

CAS Chemical Abstracts Service (Registry Number)

Cm³ Cubic centimetres

COD Chemical Oxygen Demand

Cosing The European Commission database with information on Cosmetic Ingredients and

Substances

DG Dangerous Goods EC European Commission

EC50 EC stands for the effective concentration. EC50 refers to the concentration of a toxicant,

which includes a response halfway between the baseline and maximum after a specified

EINECS European Inventory of Existing Commercial Chemical Substances (Identifying Number)

EFFA European Flavour Association ĘU Europe/European Union

g GHS The Globally Harmonised System of Classification and Labelling of Chemicals

GMO Genetically modified organism

Hazchem Code Emergency action code of numbers and letters that provide information to emergency

services especially fire fighters

he Hour

HSIS-The Safe Work Australia Hazardous Substances Information System

HSNO Hazardous Substances Approval Code IATA The International Air Transport Association ICAD The International Civil Aviation Organisation **IFRA** The International Fragrance Association International Maritime Dangerous Goods IMDG

INCI The International Nomenclature of Cosmetic Ingredients

ISO International Organisation for Standardisation

Κg

LČSO LC stands for lethal concentration, LC50 is the concentration of a material in air which

causes the death of 50% (one half) of a group of test animals. The material is inhaled over a set period of time, usually 1 or 4 hours. This is normally quoted in mg/kg body

weight.

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LD50 LD50 stands for Lethal Dose. This is the amount of a material, given all at once, which

causes the death of 50% (one half) of a group of test animals. This is normally quoted in

mg/kg body weight.

LDLo LDLo stands for Lethal Dose Low, the minimum amount of a material which tests have

shown will be lethal to a specified type of animal. This is normally quoted in mg.kg body

weight.

Lt Litre Max. Maximum Milligram Mg Min. Minimum ml Millilitre M_3 Cubic metre mm Millimetre

mm Hg Millimetre of Mercury Not Applicable N/A

NICNAS The National Industry Chemicals Notification ants Assessment Scheme (AUSTRALIA)

NIOSH The National Institute for Occupational Safety and Health (USA)

NOHSC National occupational Health and Safety Commission (AUSTRALIA)

n.o.s. Not otherwise specified NZS New Zealand Standards

NZIoC New Zealand Inventory of Chemicals

OECD Organisation for Economic Co-operation and Development (Test Method number)

OSHA The Occupational Safety and Health Administration (USA)

PFI Permissible Exposure Limit

Ppb Parts per billion Ppm Perts per million

RTECS The Registry of Toxic Effects of Chemical Substances

SCCNFP Scientific Committee on Cosmetic Products and non-Food Products (EUROPE)

SDS Safety Data Sheet

STEL. Short Term Exposure Limit

Subsp. Subspecies

SUSMP Standard for the Uniform Scheduing of Medicine and Poisons (AUSTRALIA)

TD stands for Toxic Dose. TD is the amount given all at once, which causes the untoward TD

symptoms in the majority of persons, or in the majority of a group of test animals. This is

normally quoted in mg/kg body weight.

TGA Therapeutic Goods Administration (AUSTRALIA)

TLV Threshold Limit Value TWA Time Weighted Average UK United Kingdom UN United Nations

USA The United States of America

Microgram μĝ μ L Micro litre

DATA SOURCES

AICS; Australian Code for the Transport of Dangerous Goods by Rail and Road; Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (NOHSC:1008(2004)); Work Safe Australia WHS Regulations; Cosing; Supplier Documentation; EFFA; HSIS; IATA Dangerous Goods Regulations; IFRA; IMDG Code; The International Cosmetic Ingredients Dictionary and Handbook, NICNAS, SUSMP, NZIoC, NOHSC Australia

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