Safety Assessment of Vanilla-Derived Ingredients as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: February 21, 2020
Panel Date: March 16-17, 2020

The Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.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 Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Date: February 21, 2020

Subject: Draft Final Report on *Vanilla*-derived Ingredients

Enclosed is the Draft Final Report on 9 *Vanilla*-derived ingredients (*vanill032020rep*). This family comprises cosmetic ingredients that are derived from two vanilla species, *Vanilla planifolia* and *Vanilla tahitensis.* At the December 2019 Panel meeting, the Panel issued a Tentative Report for public comment with the conclusion that the following 7 vanilla-derived ingredients are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Vanilla Planifolia Fruit Extract
Vanilla Planifolia Fruit Oil
Vanilla Planifolia Fruit Water
Vanilla Planifolia Seed
Vanilla Planifolia Seed Powder
Vanilla Tahitensis Fruit Extract
Vanilla Tahitensis Seed

The Panel also concluded that the available data are insufficient to make a determination that Vanilla Planifolia Flower Extract and Vanilla Planifolia Leaf Cell Extract are safe under the intended conditions of use in cosmetic formulations. The data needed to determine the safety of these two ingredients (previously requested) comprise:

- Method of manufacture and impurities
- Composition
- Concentration of use
- 28-day dermal toxicity
    - Depending on the results, other toxicological endpoints may be needed (e.g., genotoxicity and DART)

To date, there has been no response to this data request.

Comments on the safety assessment that were received from the Council prior to the December 2019 Panel meeting (*vanill032020pcpc1*) and after announcement of the Tentative Report (*vanill032020pcpc2*) are also enclosed and have been addressed.

Also included in this package for your review are the CIR report history (*vanill032020hist*), flow chart (*vanill032020flow*), literature search strategy (*vanill032020strat*), ingredient data profile (*vanill032020prof*), 2020 FDA VCRP data (*vanill032020FDA*), and minutes from previous Panel meetings (*vanill032020min*).

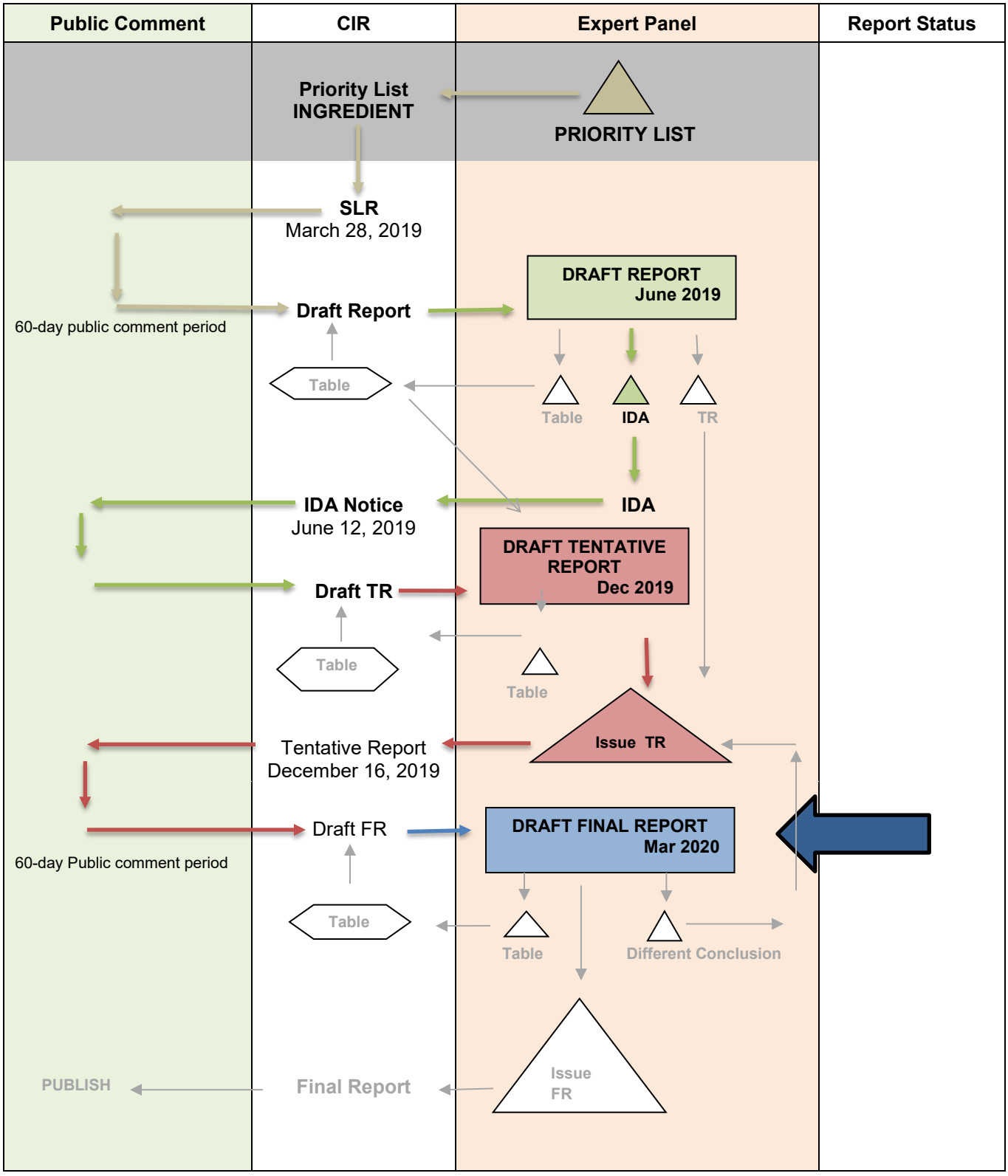
When compared to 2019 FDA VCRP data, 2020 FDA VCRP data do not indicate any significant changes in the use frequencies of vanilla-derived ingredients. In 2019, Vanilla Planifolia Fruit Extract was being used in 370 product formulations, but the use frequency only increased to 383 in 2020. Similarly, changes in use frequencies that are being reported for any of the remaining vanilla-derived ingredients are rather small, and, thus, are not noteworthy.

After reviewing these documents, the Panel should be prepared to issue a Final Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Vanilla-derived Ingredients

MEETING March 2020



CIR History of:

Vanilla-derived Ingredients

A Scientific Literature Review (SLR) on Palm Tree-Derived Ingredients was issued on March 28, 2019. Comments and unpublished data were received from the Council before/after announcement of the SLR.

Draft Report, Teams/Panel: June 6-7, 2019

The draft report also contains the following unpublished data that were received from the Council:

(1) Use concentration data from a Council survey
(2) Method of manufacture and composition data on 2 Vanilla Tahitensis Fruit Extract trade name materials (containing 0.80% and 1.3% Vanilla Tahitensis Fruit Extract, respectively)
(3) Safety test data on 0.80% Vanilla Tahitensis Fruit Extract trade name material : ocular irritation (in vitro), skin irritation (ex vivo, human skin samples), skin irritation (human), skin sensitization (human), and phototoxicity (in vitro)
(4) Genotoxicity data (in vitro) on a 1.3% Vanilla Tahitensis Fruit Extract trade name material

An insufficient data announcement (IDA) with the following data requests on Vanilla Planifolia Flower Extract was issued at this meeting and announced on June 12, 2019.

- Composition
- Method of manufacture and impurities
- Concentration of use
- 28-day dermal toxicity
    - Depending on the results, other toxicological endpoints may be needed (e.g., genotoxicity and DART)

Draft Tentative Report, Teams/Panel: December 9-10, 2019

To date, there has been no response to the IDA that was issued at the June 2019 Panel meeting. However, a summary of the human repeated insult patch test on a leave-on product containing 0.02% Vanilla Planifolia Fruit Extract (*vanill122019data1*) was received from the Council.

The Panel issued a Tentative Report for public comment with the conclusion that the following 7 vanilla-derived ingredients are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Vanilla Planifolia Fruit Extract
Vanilla Planifolia Fruit Oil
Vanilla Planifolia Fruit Water
Vanilla Planifolia Seed
Vanilla Planifolia Seed Powder
Vanilla Tahitensis Fruit Extract
Vanilla Tahitensis Seed

While the available human skin sensitization data on Vanilla Planifolia Fruit Extract, Vanilla Tahitensis Fruit Extract, and vanilla extract are negative, final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern. Thus, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

However, the Panel also concluded that the available data are insufficient to make a determination that the following 2 ingredients are safe under the intended conditions of use in cosmetic formulations:

Vanilla Planifolia Flower Extract
Vanilla Planifolia Leaf Cell Extract

The data needed to determine the safety of these two ingredients comprise:

- Method of manufacture and impurities
- Composition
- Concentration of use
- 28-day dermal toxicity o Depending on the results, other toxicological endpoints may be needed (e.g., genotoxicity and DART)

The Panel was not concerned about the positive (++) photopatch test reactions to vanilla extract in a photodermatitis patient, because the strength of the reactions at photoirradiated and non-irradiated sites were the same. Therefore, it was agreed that the observed test results were not due to a photosensitization reaction.

Draft Final Report, Teams/Panel: March 16-17, 2020

Comments on the draft tentative report were received from the Council prior to the December 2019 Panel meeting. Comments on the tentative report that was announced were also received from the Council. All comments have been addressed.

To date, there has been no response to the data requests on Vanilla Planifolia Flower Extract and Vanilla Planifolia Leaf Cell Extract.

Vanilla-derived Ingredients Data Profile* –March 16-17, 2020 Panel – Wilbur Johnson																															
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Vanilla Planifolia Fruit Extract	**X**	**X**	X																					X						
Vanilla Planifolia Flower Extract	**X**																													
Vanilla Planifolia Fruit Oil	**X**																													
Vanilla Planifolia Fruit Water	**X**																													
Vanilla Planifolia Leaf Cell Extract	**X**																													
Vanilla Planifolia Seed																														
Vanilla Planifolia Seed Powder	**X**																													
Vanilla Tahitensis Fruit Extract	**X**	**X**													X				**X**		**X**			**X**	**X**	**X**				
Vanilla Tahitensis Seed																														

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

[Vanilla-Derived Ingredients–1/2-4/2019; 10/25/2019;2/06/2020]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
VANILLA PLANIFOLIA FRUIT EXTRACT	8024-06-4; 84650-63-5	Yes	25/3	0/0	10/0	Yes (Vanilla, both species)	No	Dossier on Vanillin	No	No	No	Report on White Vanilla available	No	No	Vanilla Bean pesticide residues	No	No	Yes
Vanilla Planifolia Flower Extract (Search Flower)	8024-06-4; 84650-63-5	Yes	16/0 66/5	0/0	10/0		No		No	No	No		No	No		No	No	Yes
Vanilla Planifolia Fruit Oil (Search Fruit)	8024-06-4; 84650-63-5	Yes	2/0 7/1	0/0	10/0		No		No	No	No		No	No		No	No	Yes
Vanilla Planifolia Fruit Water	8024-06-4; 84650-63-5	Yes	18/0	0/0	11/0		No		No	No	No		No	No		No	No	Yes
Vanilla Planifolia Leaf Cell Extract (Search Leaf)	8024-06-4; 84650-63-5	Yes	0/0 100/8	0/0	10/0		No		No	No	No		No	No		No	No	Yes
Vanilla Planifolia Seed	8024-06-4; 84650-63-5	Yes	2/1	8/3	10/0		No		No	No	No		No	No		No	No	Yes
Vanilla Planifolia Seed Powder	8024-06-4; 84650-63-5	Yes	9/0	0/0	10/0		No		No	No	No		No	No		No	No	Yes
Vanilla Tahitensis Fruit	94167-14-3	Yes	4/0	0/0	10/0		No		No	No	No		No	No		No	No	Yes
Vanilla Tahitensis Fruit Extract (Search Vanilla Tahitensis)	94167-14-3	Yes	3/0 88/25	0/0	10/0		No		No	No	No		No	No		No	No	Yes
Vanilla Tahitensis Seed	No CAS	Yes	4/0	0/0	10/0		No		No	No	No		No	No		No	No	Yes

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
RIFM (the Research Institute for Fragrance Materials) should be contacted

Qualifiers

Absorption	Genotoxic	Sensitization
Acute	Irritation	Skin
Allergy	Metabolism	Subchronic
Allergic	Mutagen	Teratogen
Allergenic	Mutagenic	Teratogenic
Cancer	Penetration	Toxic
Carcinogen	Percutaneous	Toxicity
Chronic	Pharmacokinetic	Toxicokinetic
Development	Repeated dose	Toxicology
Developmental	Reproduction	Tumor
Excretion	Reproductive	

JUNE 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – June 9, 2019

DR. BELSITO: Okay. So we're going onto the vanilla ingredients. There are nine vanilla-derived ingredients; five from Vanilla planifolia, which include fruit extract, flower extract, fruit oil, fruit water, and leaf cell extract, and four from Vanilla -- oh, and seed, seed powder, fruit extract, and seed -- sorry -- and the fruit extract and seed from Vanilla tahitensis.

We got quite a bit of data. It's mentioned that the fruits from both of these vanilla strains are used only as fragrances. RIFM has not reviewed them as of yet.

MR. JOHNSON: They reviewed the vanilla tincture.

DR. BELSITO: Tincture.

MR. JOHNSON: There's a monograph on that.

DR. BELSITO: Right. But not the fruit extract.

MR. JOHNSON: Right.

DR. BELSITO: And we got quite a bit of data. We don't have developmental and reproductive toxicity. Do we need that?

DR. LIEBLER: Repro.

DR. SNYDER: Yeah, I didn't flag that. This is GRAS, right?

DR. KLAASSEN: Yes. Yes, I don't think we need it.

DR. BELSITO: Okay. And genotox, we have Ames, but no mammalian. And we have no carcinogenicity studies.

DR. KLAASSEN: Well, I guess -- again, I think because it's GRAS, I can get along without it.

DR. LIEBLER: Right. My comment was minimal but acceptable.

DR. BELSITO: Okay. But are they all GRAS? The extract is, but --

MS. FIUME: PDF page 13 states which are GRAS, non-cosmetic use.

MR. JOHNSON: And there's a differentiation between GRAS for animal drugs and feed versus GRAS for human food consumption.

DR. BELSITO: Yeah. And it's really just the seed that's GRAS, right?

DR. LIEBLER: Is the seed and the bean the same thing?

MR. JOHNSON: It's my understanding that the seeds are inside of the bean.

DR. LIEBLER: So, would the bean encompass the seed? Or vice versa?

MR. JOHNSON: That's my understanding.

MS. KOWCZ: I think so, because the seeds are in the bean.

DR. LIEBLER: The seeds are in the bean?

MS. KOWCZ: Yeah.

DR. LIEBLER: Because I thought one characteristic of this package was the composition and methods of manufacturer were like a poster child of excellence for a botanical ingredient. I mean, this was a really --

DR. BELSITO: Except for the flower. We don't have any connection on the flower.

DR. LIEBLER: Yeah, except for the flower, I suppose. But really, this was so well documented. I have no concerns. We had the leaf, but not the flower. Are there uses on the flower?

MR. JOHNSON: PDF page 27. The flower extract.

DR. LIEBLER: 58 uses, but no concentration use.

MR. JOHNSON: No use concentration data.

DR. BELSITO: Ah, so, doing a quick Google search, Dan. This is what vanilla bean looks like, those long stringy things.

DR. LIEBLER: Oh, yeah. We get them from the spice place.

DR. BELSITO: And the seeds are in the bean.

DR. LIEBLER: Hmm. Okay.

DR. BELSITO: Okay. We don't have any composition for the flower. So, are we going insufficient for composition?

DR. LIEBLER: On the flower?

DR. BELSITO: On the flower.

DR. LIEBLER: Because I think that's the only one we don't have documentation on.

DR. BELSITO: Yeah. So, I said safe as used when formulated to be non-sensitizing, again, particularly given the studies with Balsam of Peru showing cross-reactivity with other fragrance materials. And we need the plant and the respiratory boilerplate in the discussion. And flower is insufficient for composition.

DR. LIEBLER: Okay. Yeah. And method of manufacturer for the flower.

MR. JOHNSON: When you have a chance, Dr. Belsito, please mention those again.

DR. BELSITO: The flower is insufficient for composition and method of manufacture. And the others are safe as used when formulated to be -- whatever the botanical boilerplate we use for sensitization. Then, in the discussion, the usual boilerplates for plant products and inhalation.

Let's see one thing. It has cinnamates, which is probably why it cross-reacted with Balsam of Peru, which has a lot of cinnamates. It has benzyl alcohol which, I believe, has a RIFM standard. Right? Isn't benzyl alcohol the standard, Dan? Do you remember?

DR. LIEBLER: I don't remember that.

DR. BELSITO: It has benzaldehyde.

DR. LIEBLER: It's got benzaldehyde. It's got several aldehydes.

DR. BELSITO: Right.

DR. LIEBLER: It's got phenylacetaldehyde. It's got, as you mentioned, the cinnamyls. It's got linalool oxide, limonenes, furfural.

DR. BELSITO: Right.

DR. LIEBLER: So, a number of chemicals that, in principle, could be protein reactive.

DR. BELSITO: Again, could cause issues when formulated with other botanicals that contain those as well.

DR. LIEBLER: Yeah. Correct.

DR. BELSITO: So, I don't remember exactly how we used that sensitization boilerplate for botanicals. But it's the same boilerplate that should be used.

MR. JOHNSON: I'd just like to call the Panel's attention to PDF page 28, that last study in the table. It indicated a positive for a photopatch test reaction. Is there any concern about that in that case report?

DR. BELSITO: Yeah. I think I commented on that. Let me see. I apologize. This is one I did on paper. I really couldn't make much of it. I'm looking at the constituents. The only one that would raise any issues would be benzophenone-3, which is a sunscreen but has been reported to cause photoallergy. But I don't see that as an issue. I didn't make much of it.

The other thing, too, Wilbur, is that it says patch test results for vanilla extract and vanilla fruit positive (++ reaction) on day 2 and 4. And photopatch tests were also positive (++). That was my point. When you get the same degree of reactivity on patch and photopatch, it's not a photosensitizer. It's just a sensitizer. To be a photosensitizer, you'd have to see it more strongly positive on the photo side than on the non-photo side.

Anything else?

MS. FIUME: Just to clarify, for the IDA, it's just composition and method of manufacture on the flower. And that's all that --

DR. BELSITO: Yeah. And if significantly different, other endpoints may be needed.

MS. FIUME: Okay.

MR. JOHNSON: That's on the flower extract?

DR. BELSITO: Right. Flower extract. So, in the discussion, we need the plant boilerplate. We need the respiratory boilerplate. We need why we're not concerned about DART, and --

DR. SNYDER: Heavy metal pesticides.

DR. BELSITO: Yeah. Well, that's the botanical. And then we also need why we're not concerned about lack of DART data and why we feel we don't need a mammalian genotox.

DR. SNYDER: Right.

MR. JOHNSON: Why don't you need development and reproductive tox data?

DR. BELSITO: Well this is GRAS.

DR. LIEBLER: GRAS.

DR. SNYDER: We typically don't ask for that when we have widespread GRAS uses, particularly food safety.

DR. BELSITO: Anything else in the discussion that we need to put? Dan? Curt? You're all set, Wilbur?

MR. JOHNSON: Yes, I am.

Marks Team - June 9, 2019

DR. MARKS: Last ingredient, unbelievable. It's 2:00. I don't know, team. Do you want to spend a couple hours on this one?

DR. SLAGA: I like vanilla ice cream.

DR. MARKS: Yes. So there are nine vanilla derived ingredients. If I read this correctly, these are beans from orchids. Is that right?

MR. JOHNSON: Yeah.

DR. MARKS: Yeah. I didn't know that. Any rate, this is a first review of these nine ingredients. Fruit is a fragrance and not included in this report. So that's why. There are two species -- planifolia and tahitensis.

So first, Ron and Tom, do you like the nine ingredients? It's hard to get away from them. Where are my notes on it? Any rate, are the ingredients okay? It's hard to say they aren't, because they're all from the vanilla. And what are the needs?

DR. SHANK: Well, is vanilla fruit, which is the same as bean and seed, are those GRAS? I would think those extracts would be GRAS.

MR. JOHNSON: There's a statement in the non-cosmetic use section relating to that -- statements relating to that.

DR. SHANK: Okay. Let me -- because I --

DR. MARKS: I knew GRAS was going to come up on this. Just to kind of give you a hint, our team will move --

MR. JOHNSON: PDF 13.

DR. MARKS: I have an insufficient data announcement because I want some sensitization data for the extracts. While you're looking that up, Ron, there are case reports of allergic contact dermatitis to vanilla. There are positive patch tests of vanilla extract. So I would want to see sensitization data for the extracts, and I would do flower, leaf cell, fruit, and also the seed, and then, not an extract but the seed powder. So I want to see a fair amount of sensitization data. But I'd be interested in your response.

DR. SLAGA: They're GRAS in humans and also used in animals, so there's two aspects.

DR. SHANK: Where does it say the GRAS?

MR. JOHNSON: In the non-cosmetic part. PDF 13. That's it.

DR. BERGFELD: Did you say the fruit, as well? Was the fruit one that you needed sensitization?

DR. MARKS: Yes. I wanted to see that because what really alerted me was a combination of the case reports.

DR. BERGFELD: These are aromatic, so do we think that RIFM has any stuff on it?

MS. FIUME: Wilbur, you requested from RIFM, right? Did you ask RIFM?

MS. JOHNSON: Yeah. Actually, there is a monograph on vanilla tincture, and those data are in the safety assessment. What RIFM had said, it is their plan to review the safety of the vanilla derived -- those that are fragrance materials.

DR. BERGFELD: Right. Did they say which ones that were fragrances?

MR. JOHNSON: No, they weren't specific in terms of which --

DR. BERGFELD: So that is pending?

MR. JOHNSON: Yes.

DR. BERGFELD: I would think that would be another reason to hold and see what they have. And I thought the cross-reactivity would also prove whether planifolia and tahitensis --

DR. MARKS: Mm-hmm.

DR. BERGFELD: -- food is interesting. So Wilbur, we eat all this? We eat all these parts of the plant?

DR. MARKS: Well, that's what Ron Shank is trying to --

MR. JOHNSON: I'm not sure about all of it.

DR. SLAGA: Between humans and animals, I think we eat them all.

DR. BERGFELD: We eat more? Animals eat some, too.

DR. SHANK: Not the leaf or the flower. I don't see that.

DR. ANSELL: So, Wilbur, you were on to RIFM, and they are going to be --

MR. JOHNSON: They said that they're going to be reviewing the vanilla.

DR. MARKS: Are they going to review anything other than the fruit?

MR. JOHNSON: I'm not certain.

DR. MARKS: Because isn't that the only fragrance among these ingredients? Because that's the one that's been excluded.

MR. JOHNSON: Yes.

DR. ANSELL: But we actually eat the seed.

DR. BERGFELD: Well, they talk about aromatic all through here.

DR. SHANK: Well, the flower probably has a fragrance component.

DR. MARKS: They all have a fragrance component.

MR. JOHNSON: The fruit is the one that's listed in the dictionary as a fragrance material.

DR. MARKS: Where is Bart with his pictures? Because I'd like to see a picture of this. What is actually vanilla. We talk about a fruit. We talk about a leaf. There's also a seed.

MR. JOHNSON: It's a vanilla bean. I think that they use the whole thing.

DR. ANSELL: When you buy it in the store, it looks like the whole bean.

DR. BERGFELD: A pod that has seeds in it.

MR. JOHNSON: It has seeds on the inside of it, yeah.

DR. ANSELL: Yeah. You kind of scrape it into whatever you want.

DR. MARKS: So that would make sense for the seed powder. Are they talking about the beans inside is the fruit?

DR. BERGFELD: Well, the seed and the bean --

MR. JOHNSON: The seed's on the inside.

DR. BERGFELD: Where's the bean?

MR. JOHNSON: The bean is on the outside, and the seeds are on the inside. It's pulled apart --

DR. BERGFELD: The seeds are inside the bean?

MS. FIUME: So it's a pod. The bean is a pod.

DR. MARKS: There you go.

DR. BERGFELD: Is that called the bean -- that pod?

MR. JOHNSON: Yes. Vanilla bean.

DR. MARKS: So it's easy what the flower is, and it's easy what the leaf is. So what does the fruit represent?

MS. FIUME: Let me see. Vanilla fruit.

MR. JOHNSON: I think it's the whole bean.

DR. SHANK: The whole thing. The pod with the seeds in it.

DR. MARKS: If that's the case, then it makes it -- then it's either an IND or you hold off until -- then you can get rid of anything that says fruit on it in here -- fruit oil, fruit extract -- because that's all going to be reviewed by RIFM, if they're doing the fruit.

DR. BERGFELD: The fruit -- is part of the plant -- it's not the bean?

MS. FIUME: That's what I'm trying to find.

DR. MARKS: But then we still have leaf, flower --

MR. JOHNSON: That's my understanding that that's considered the fruit, the whole bean.

DR. MARKS: Presumably, the seed is part of the fruit.

MR. JOHNSON: Vanilla bean.

MS. FIUME: Vanilla is the fruit of an orchid plant, which grows in the form of a bean pod.

DR. BERGFELD: So fruit and bean are the same?

DR. MARKS: No.

MS. FIUME: Fruit and bean pod, I believe.

DR. BERGFELD: It's bean pod? But we only have bean here, so what does that mean?

DR. MARKS: The bean would be a subset of the fruit, because the fruit includes everything in that picture -- that pod, the whole deal -- is how I interpret it.

MR. JOHNSON: That's my understanding.

DR. MARKS: So now, we're left with just -- and if RIFM is going to take care of the fruit, I would think we wouldn't want to do anything relevant to that. And then, the question is, if we're doing the flower -- well, it's worth it. There are 58 uses.

DR. ANSELL: So to make custard, the bean is usually cut in half, allowed to steep. Vanilla seeds then are scraped out and added to the custard. The leftover pod can be rinsed and dried and then added for vanilla flavoring.

DR. BERGFELD: So the pod can be used for vanilla flavoring, too?

DR. ANSELL: I think the whole thing.

MR. JOHNSON: Now, it's my understanding that's RIFM's plan. It's not like they said definitely, but that's their plan to review the --

DR. MARKS: Even though -- since the fruit is a fragrance, I would extent that to any part of the fruit. Then it really comes under the purview of RIFM, since it's a fragrance. Unless it has another use.

MS. FIUME: And these ingredients do have other -- they don't have fragrance listed. They have other uses listed, other functions and not fragrance.

DR. MARKS: So why was the fruit excluded, then, in this?

MR. JOHNSON: That was the reason -- because we thought it was under RIFM's purview to review it.

DR. MARKS: But does the fruit have other uses, too? Skin conditioning, whatever that means -- which we see a lot. And then it also -- it's an abrasive and one of is reported functions of antioxidant and skin protectant. Hmm.

DR. ANSELL: The fact that it has other uses listed is permissive, but it's not obligatory that we undertake a safety assessment if we know RIFM is undertaking a safety assessment of exactly the same materials. I think we should --

DR. MARKS: Table it. That's one way to do it.

DR. ANSELL: Well, yeah. Or at least --

MS. FIUME: But actually -- because the fruit versus an extract would be different, right? Because you have to worry about what the solvents are, as well, when you're looking at the extracts when considering safety?

DR. ANSELL: But we don't know what RIFM's doing.

MS. FIUME: They're doing -- they said the fruit.

MR. JOHNSON: That's my understanding is that's their plan to do it. They've already issued a monograph on vanilla tincture, and those data are summarized in this safety assessment.

DR. ANSELL: Well, I don't see fruit as --

MS. FIUME: Fruit has been pulled out because it's only a fragrance. Its only reported function is fragrance. So the fruit is not included in the safety assessment.

DR. ANSELL: Right. But I'm struggling with what's the difference between the pod and the fruit, since the fruit is the seed carrier and the pods are where the seeds are --

DR. MARKS: Oh, I hear you loud and clear. I would take everything that has fruit in the ingredient name -- fruit extract, fruit oil, fruit water, fruit -- and there are two different species. You got into solvents, Monice. How about if it's Planifolia fruit extract versus the Tahitensis fruit extract?

MS. FIUME: So I believe both fruits from both species are being reviewed.

MR. JOHNSON: That's right.

MS. FLUME: Or the plan is to have them be reviewed by RIFM.

MR. JOHNSON: But that's not carved in stone. But I was informed that that was the plan -- RIFM's plan.

MS. FIUME: The intention.

MR. JOHNSON: Right.

DR. MARKS: And then, obviously, the takeoff for us would be, based on their findings, if it's safe -- and of course, even though we don't have GRAS for all of these, it would be pretty straightforward to go to the flower and the leaf, perhaps -- leaf cell extract. You did a nice summary here, Wilbur.

MR. JOHNSON: Thank you.

DR. MARKS: Team, what do you want to -- in some ways, I would table it -- await the RIFM. We have two RIFM panel members on the CIR, so we can hear what they have to say, in terms of -- IND with the sensitivity. We haven't settled. I said what I wanted to see from sensitivity data versus table it and wait for RIFM.

MR. JOHNSON: They issued an IDA, just for your information.

DR. MARKS: And then, if we do an IDA -- an insufficient data announcement -- besides the sensitization, Ron, are you satisfied that we don't need tox, based on the GRAS we have already?

DR. SHANK: Correct, for the fruit.

DR. MARKS: For the fruit, but not for the --

DR. SHANK: Not for the flower or the leaf. We don't have any information on the flower or leaf, that I can recall.

DR. ANSELL: So there's the leaf cell extract. Everything else is fruit and flower.

DR. MARKS: Yeah. Basically, if we say that the fruit is going to be the driver for all these other fruit ingredients, really, we're down to the flower extract and the leaf cell extract that are going to be the main ones we focus in at CIR, even though there are other uses.

So the flower and leaf, do you want a 28-day tox? You want everything on it, Ron?

DR. SHANK: Yeah. The usual composition. Please the chemists. 28 dermal. These will be mixtures, so you can't do absorption. So that's why you want the 28 dermal.

DR. MARKS: Do we assume it's absorbed, and we need DART?

DR. SHANK: Genotox and DART.

MR. JOHNSON: Is that genotox and DART depending upon the results of the 28-day dermal test, or are those items --

DR. SHANK: Usually, we ask for the 28 dermal first, because those are relatively cheap and fast, before you do the DART studies. Those are expensive.

DR. MARKS: It's hard for me to believe that some chef doesn't put these petals on foods.

DR. BERGFELD: Edible orchids, we've seen that.

DR. MARKS: But we need to have some sort of confirmation that they are used as foods, and we don't have that at this point.

MS. FIUME: Right. Because is it the same genus species, or is it a different orchid that is used as the edible flowers?

DR. BERGFELD: Maybe.

MS. FIUME: Because these genus and species are the only ones that produce the pods.

DR. BERGFELD: I was wondering if you looked at the fruit extract in the memorandum from Bart and Carol Eisenmann where they take the pod of the Tahitensis vanilla and mix it with propylene, glycol, water, filtration. And they get 0.8 percent vanilla fruit extract. So we do have what is in it --

DR. SHANK: For fruit.

DR. BERGFELD: Fruit. And the next page, they take that same ingredient that is 0.8 percent, and they do some patch testing. And these are basically -- let's see -- the 48-hour patch, non-irritating in human RIPT at 5 percent non-irritating, non-sensitizing. And the phototox is in here. Did not show any toxicity at the highest test concentration and no phototox potential on the fruit extract.

And then they had an ex vivo cutaneous tolerance using some skin -- experimental conditions: human samples 10 percent, which I assume was a --

DR. MARKS: Which page are you on?

DR. BERGFELD: It follows this.

MR. JOHNSON: Unpublished data.

DR. BERGFELD: This is Bart's memorandum and Carol Eisenmann's. So we do have some human testing, and we know that at 0.8 percent --

DR. MARKS: I didn't have those same -- I have on the fruit extract 10 percent was not an irritant. That's way above the use concentration of leave-ons at 0.33. I had at the 0.04 percentage on human sensitization testing was okay. It sounded like he used a higher concentration.

DR. BERGFELD: 5 percent.

DR. MARKS: Yeah. But was it 5 percent diluted?

DR. BERGFELD: Yeah. 5 percent is in distilled water and 0.02 mils applied to disk at filter table. I'm not sure what that translates to --

DR. MARKS: Under inclusion patch, huh. Why didn't I pick that up? Where did I get the 0.4 percent? That was 15. Let me go and see.

DR. BERGFELD: Well, under the maximum concentrations of use, 0.14.

DR. MARKS: 80 percent. Oh, yeah. Here it is. Go on page 15, Wilma.

DR. BERGFELD: Okay.

DR. MARKS: And then under human sensitization, you notice that, in the parentheses, it gives you the tested at 5 percent effective concentration of the extract 0.04 percent. So that's how I got the 0.04. I didn't use the 5 percent, so I assume it's 5 percent of that 80 percent fruit extract up above. So I used the 0.04 percent, which is considerably less than what is used.

DR. BERGFELD: I don't know. Here's the use tablet. It's used a 0.36 and 0.33.

DR. MARKS: And this is 0.04, so it's about ten times less concentrated in the HRIPT they did.

MS. FIUME: How do you get the ten times?

DR. BERGFELD: 0.4 and we have here under use 0.036. So it's basically 0.4 --

MS. FIUME: 0.04.

DR. MARKS: 0.04, so ten times that would be 0.4. And its use concentration is 0.33. That's how I got the ten times. Am I calculating correct, Monice?

DR. BERGFELD: I don't know. I'm not used to calculating --

MS. FIUME: I believe so, because it's ten hundredths, so it would be about a ten-fold difference.

DR. SHANK: They're small values of ten.

DR. MARKS: Yeah. Sensitization for the extracts. So I wanted to still see the extract at the concentration. I think if we get into -- as we've discussed many times, we're back to getting sensitization data for the flower and the leaf cell.

That alone, if we put the fruit and the seed into the fruit review by RIFM, that may answer the question of what they do. But I think we're still -- are we going to move forward with that insufficient data announcement versus table it until the RIFM review of the fruit is done? Do you have a preference, and is there another option? We're going to be moving -- our team moves tomorrow for how to proceed forward with these ingredients.

DR. ANSELL: I wouldn't concern moving forward with an insufficient request for additional data without a clear idea as to what ingredients are actually going to be in this review. I think that would be potentially confusing or demotivating, perhaps.

DR. MARKS: That's why I put table it, because the RIFM -- in point of fact, most of these are derivatives of the fruit. And I would think if you had a clear -- if the fruit is cleared by RIFM, then the only thing left is flower and leaf.

DR. ANSELL: Well, I'm also not sure that the leaf would fit in because it's a cellular extract of culture of leaf cells. I'm not sure that would fit in this family to begin with.

DR. MARKS: Now you're into are the ingredients okay. Yeah. That's interesting. So then, I think it would, but that's just -- it's plant derived. And normally, yeah -- chemically, if it's not in the same class -- so you're saying, biologically, this isn't the same as a leaf.

DR. ANSELL: I'm not sure that we have a sufficient understanding of what the family is to go in and ask industry -- to ask the manufacturers -- certainly not to develop data at this point.

MS. FIUME: So my concern would be we don't have a definitive answer from RIFM that the fruit is going to be reviewed or when. It most likely will be reviewed, but we don't have a timeline of when. And there's 370 uses on the planifolia fruit extract. So, one, should that be tabled, not knowing when or if RIFM is going to review the fruit itself?

DR. ANSELL: Well, we're not tabling it for RIFM's review. We're tabling it because we don't know if RIFM is going to do it or not.

MS. FIUME: Right. Well, that's sort of the same, right? If they might do it or are they doing it.

DR. ANSELL: Well, if they say yes, then yeah.

MS. FIUME: They didn't. They said most likely, but they've been asked. It's going to most likely be reviewed, but they didn't say it is going to be reviewed or have a timeline of when the review would happen.

We've reviewed ingredients before that have -- would be under RIFM purview for the fragrance portion but CIR purview for the other reported functions, especially if the review hasn't happened yet by RIFM.

DR. ANSELL: Yeah. Certainly, we could if we wanted to, but I don't think we should have competing reviews. And I think it's just a question that we're not going to have an answer to by tomorrow.

MS. FIUME: I guess I'm still confused what answer you're looking for, Jay.

DR. ANSELL: Are they or aren't they? If they are, then --

MS. FIUME: They haven't given us -- Wilbur, do you have what the response was?

MR. JOHNSON: I'm looking for the memo right now.

DR. BERGFELD: I think we made a stride forward, understanding what the bean was.

DR. MARKS: Definitely.

MS. FIUME: I was just amazed that I didn't know it was an orchid either until I read this review.

DR. MARKS: I think that was insufficient data that Bart didn't show a picture of it for this ingredient. It probably wasn't a priority.

MS. FIUME: I'm sure it was in the priority list.

DR. BERGFELD: Is it in here? Sometimes there's pictures in here.

DR. ANSELL: It wasn't in this one, but would it would have been in the --

DR. MARKS: No, he has soy. There's a nice picture of soybeans. Well, I should say soy fruit in this case because it includes the -- let me see. Hold on a second.

MS. FIUME: It's showing the flower.

DR. MARKS: Oh, yeah. See. No, look right behind the flower.

MS. FIUME: Oh, those look like the pods.

DR. MARKS: Is that an early pod? I think it is.

MS. FIUME: I think you're right.

DR. BERGFELD: There's a pod right there, next to the flower.

DR. MARKS: I take that back. Bart did show us the picture, if I'd only looked at it. Okay. So what do you think? Tomorrow, shall I start the discussion we were -- we had a robust discussion of whether or not to issue an insufficient data announcement versus tabling these ingredients until RIFM has reviewed the fruit? And that way we'll know more carefully which ingredients we should review? And then see how that discussion goes?

DR. BERGFELD: But you can also say the intent is to review the aromatic fruits. We would be left with the leaf and the flower.

DR. MARKS: There it is. There's the leaf, and there's the flower.

DR. ANSELL: So we're saying that's in this report? I'm looking for the picture.

DR. MARKS: It's right here. It's in Bart's annotated notes. You probably don't get those, do you? This is how the cover looks, Jay.

DR. ANSELL: No.

DR. MARKS: He sends this to both teams, in the order in which we review the ingredients, which just actually started happening -- he used to send it just to the readers. Now, he sends it to everybody, which I think is good. Then, he hides a few links in there so that he can see whether you really read his notes or not.

If you had your druthers, Tom and Ron, do you want to table it, or do you want an insufficient data announcement?

DR. SLAGA: How about an insufficient? I don't think tabling it we're going to get any answers for a period of time, so --

DR. BERGFELD: So proceed with the leaf and the flower?

DR. SLAGA: Yeah.

DR. MARKS: And we're not going to do the other fruit components because we assume that's going to be covered by -- and with that in mind, I can pair down my sensitization to only the extracts of the leaf cell. And why don't I add powder?

DR. SHANK: We have no concentrations of use.

DR. MARKS: Yeah. I know.

DR. BERGFELD: How about composition?

DR. SHANK: There is composition.

MS. FIUME: There is composition.

DR. SHANK: A little bit.

DR. BERGFELD: Is it enough to say it's in there without saying how much?

DR. SHANK: Need more.

DR. MARKS: I'm going to put sensitization.

DR. BERGFELD: The volatile aroma of the vanilla beans -- I think the whole thing smells.

DR. MARKS: Okay. So with that -- unless Ron, you have a different comment. We didn't read Ron Hill's yet. I'm going to move tomorrow that we issue an insufficient data announcement, that we're going to, at this point, limit the ingredients to two: the flower and the leaf. And we want concentration of use, composition, 28 day dermal, genotox, DART, and sensitization data.

And then we'll see where it goes. That should be a fun discussion tomorrow. I'll mention we did discuss tabling it until the RIFM review, but we felt let's move forward with an insufficient data announcement. Either way, it's not the final one. But I think it will be interesting to see. And Wilbur, don't give us a heads up tomorrow. We don't want to be too biased about what the Belsito team's going to be doing.

MR. JOHNSON: Okay.

DR. MARKS: Particularly since they're RIFM members.

DR. SHANK: Dr. Hill's remarks is just the cleanup and distillation are still pending, so I'm not quite sure. Cleanup distillation of my input for meeting use still pending. I'm not sure what that means.

DR. BERGFELD: He didn't get to it.

DR. MARKS: Okay. Any more comments?

MS. FIUME: Can you just clarify for me one more time why we're pulling those ingredients out when they have reported functions that are not fragrances? Because that's a little different than what we've done in the past. Even though the fruit might have the fragrance as a reported function, whether we agreed with what the dictionary says or not, a lot of times we have gone by what is in the dictionary.

So if these have reported functions that are not fragrance, is it just waiting to see if we get additional sensitization data if they finally review the fruit, or is it whether or not these ingredients should be reviewed by CIR, if you pull out the fruit and seed ingredients? I'm just trying to get an understanding so that we know tomorrow why we would remove those from the report.

DR. MARKS: At least my reasoning is that, if and when RIFM does review the fruit, that, at a minimum, we could read across for all these fruit derived ingredients. And we could come back and reopen it at that point, if we have that. But we could move forward at least with the flower and leaf because we don't expect what RIFM does is going to be relevant to -- it will be relevant tangentially but not truly clear -- the flower and leaf. Because we have a lot of data needs.

So that's my reasoning. But Ron and Tom? That's how I would do it, is why ask for all these fruit -- like the fruit water or fruit extract, seeds, since we include the seed in the fruit, the seed powder, fruit extract, when presumably that's all going to be done by RIFM sometime in the future as part of their fruit review.

DR. SHANK: It doesn't seem there are any alerts on the vanilla family.

DR. MARKS: Other than there are a series of case reports of allergic contact dermatitis, so the sensitization is an issue. That was on page 28. There are a fair -- and the patch tests were positive.

So that, to me, is the alert. Was it 28? Yeah. Case reports. It varies, but a lot of it -- well, not a lot of it but several are in the food industry -- a baker, a bread factory worker.

DR. BERGFELD: These are patients.

DR. MARKS: Yeah. I know.

DR. SHANK: These are just individuals.

DR. MARKS: Oh, I agree. But to me, that's enough of an alert that I would want to see -- if we were going to do the vanilla extract, I would want to see some sensitization data in terms of, okay, is the guinea pig -- presumably it's a sensitizer, local lymph node. Is it a strong sensitizer, moderate? And do an HRIPT. To me, that was enough of a clinical alert, Ron. That's why I --

DR. SHANK: Okay. Could this wait a year or two, if we were -- if the panel reviews it?

DR. BERGFELD: Or do you want to ask for the lymph node assay?

DR. MARKS: We essentially are doing that for the --

DR. SHANK: If you're going to do the fruit, then do the whole list of ingredients.

DR. MARKS: Yes.

DR. SHANK: And say it has uses other than fragrances, so we're reviewing it.

DR. MARKS: That's back to what Monice --

DR. SHANK: Right. Has RIFM ever objected to CIR reviewing something?

MS. FIUME: Oh, it's not whether they object or not. It's just to avoid a duplication of effort, if something is purely a fragrance ingredient, that we're not also performing --

DR. SHANK: Okay. But this is more than just a fragrance ingredient.

DR. ANSELL: Yeah. But is the cosmetic review going to be substantively different than the fragrance review, with maximum use concentrations of fragrance levels?

MS. FIUME: Yes. The benzyl salicylate is an example. There's a whole RIFM dossier on benzyl salicylate, but it had functions that are other than fragrance. So CIR also reviewed benzyl salicylate. So it's not that we never review the same ingredient. It's just that --

DR. SHANK: We used RIFM's data.

MS. FIUME: We did use their data, but we did review it as well to come up with the review for use in cosmetics, which is what -- that's why I'm trying to see how the difference plays out. Because this would have use in cosmetics versus a fragrance use.

So that's what I was trying to understand because this seems a little different than what we've done in the past. So I was just trying to get an understanding.

DR. ANSELL: It's just a tiny issue. If the benzyl salicylate was under review when we undertook it, I think we could make the same argument that we don't need two expert panels reviewing the same material at the same time.

When we have the fragrance data, it may well inform the cosmetic use discussion or not. And I'm sure that RIFM would use a CIR review, if it were available, to see the data.

It's the concurrency, I think, which is making this somewhat different. It's that we didn't -- if they're going to do it -- so that's why I was suggesting tabling it. It's just going to be hard to go out to people and say send data to both groups at the same time because they're reviewing the same material at the same concentrations at the same time. And I think we would rather you guys used your time --

MS. FIUME: Did they give a timeline, Wilbur?

MR. JOHNSON: This was the email relating to vanilla tahitensis fruit. And Kristen said that they probably will review it. But as they are just starting to pilot some naturals, I don't think it will be done within a year.

DR. ANSELL: Well, it's not going to be done by this group within a year either.

MS. FIUME: I think, Jim, as you said, it will make for an interesting conversation tomorrow to see what --

DR. MARKS: Oh, absolutely. Well, to me, the -- I need to go back, but maybe you know off the top of your head. The reason it was included in the priority list was frequency of use. There were no other alerts?

So even though there's been case reports of allergy, it's not something that I look at, certainly, in the same way I would look at MI, methylisothiazolinone and methylchlorisothiazolinone. So, Tom, I think I still will move forward with your suggestion, an insufficient data announcement.

DR. SLAGA: And if we end up tabling it, we end up tabling it.

DR. MARKS: And then, I said we did discuss tabling it. I probably will discuss both but make the motion insufficient data announcement. And we'll see what the Belsito team comes back. And I'm sure it will be an easy resolution. I don't think anybody strongly feels one way or another. And we're going to focus on the flower and the leaf if we do move forward with an insufficient data announcement.

If it's tabled, then that becomes somewhat of a moot subject. We'll wait until that report. Then we'll see if we can do read across for all the fruit components. It would make it easy. And we still will have the needs for the flower and the leaf.

Does that sound reasonable, Tom and Ron?

DR. SLAGA: Yeah.

DR. SHANK: Yes.

MR. JOHNSON: So I just want to confirm, Dr. Marks, the IDA is on the flower extract and the leaf cell extract? Only just those two?

DR. MARKS: Yes. That's what we will propose. We'll see because we're taking all the fruit ingredients, and we're going to, essentially -- even though they have non-fragrance uses, we're going to see what RIFM has to say about the fruit. And then we can utilize data from the RIFM review in our review if we go back and do all the rest.

If the consensus is to table it, then we'll just table it and have a heads up what the needs are for flower and leaf going forward.

MR. JOHNSON: Dr. Marks, I might add that, as I said, there are data on vanilla tincture in the report. Are those data relevant in any way in relation to the other ingredients in this review?

DR. MARKS: So the first question would be what's the vanilla that's tinctured? Where is that? Is that from the fruit? Is it from the flower, or is it from the whole plant plus the fruit just mushed up?

So I would think it would be relevant in that respect. If it said vanilla leaf tincture, that would be much more specific and helpful -- or vanilla flower tincture or vanilla bean.

DR. ANSELL: I think tincture is the flavor. Isn't that what you buy?

DR. BERGFELD: You're actually right. It's in the little brown bottle.

MS. FIUME: Oh, is that what that is?

DR. ANSELL: And they won't sell it to kids because people used to drink it for the alcohol.

DR. SLAGA: Vanilla flavored alcohol.

DR. MARKS: Well, Wilbur, that will be homework. Any other comments? Anything we've overlooked, Tom, Ron?

DR. SLAGA: That's good.

DR. MARKS: Okay. I think tomorrow is going to be exciting.

DR. BERGFELD: Lively.

DR. MARKS: And if vanilla is the most contentious ingredient we discuss, it will be "easy," quote/unquote.

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DR. MARKS: Yes, this is the first time we've seen the vanilla ingredients, there are nine ingredients. The vanilla fruit is a fragrance and was not included in this draft report. Because this would come under the purview of RIFM, and I'll be very interested in hearing Dan and Don's input on these ingredients. Because our team, first of all, sort of struggled with to begin with defining what the fruit is. And, then with that in mind, if all the fruit derived ingredients here like, the fruit extract, the fruit water, and the two different species, will that all be a read-across from a safety report from RIFM.

And so, we came down to potentially two alternative ways to move forward. One, in an insufficient data announcement, with it needing for the flower and leaf, concentrating on those two ingredients, the concentration --

DR. BELSITO: Flower and --

DR. MARKS: And leaf. And everything with fruit, postpone or don't tack on until we see the RIFM review. Where the others were tabled until we see the RIFM review and then go back and look at all these ingredients with the knowledge of the RIFM review conclusion. So we were torn between an insufficient data announcement, versus, just tabling and waiting until the RIFM review is done.

And then if we did do an insufficient data announcement, we would concentrate again on the flower and the leaf and have a lot of needs there. Concentration in use, composition, 28-day dermal, genotox, DART and sensitization data, since there are case reports with positive reactions to vanilla extract.

So, I'd be very interested, Don, in your team's input and how you move forward. As you can see we had two alternative potential ways to move forward. We were sort of struggling with how to handle it. Actually, this group of ingredients probably tied up as much time as any of our ingredients yesterday. Did I characterize that right, Ron and Tom?

DR. SHANKS: Yes.

DR. GREMILLION: Yes.

DR. BERGFELD: Don?

DR. BELSITO: RIFM wrote a monograph many years ago on vanilla tincture. The naturals, as we call them rather than botanicals, the complex mixtures that come from plants, we're only beginning to review. And I doubt that you are going to get to vanilla very quickly. So if you're going to wait for RIFM's review, it'll probably be in the next 15 years -- I'm kidding -- the next several years.

DR. MARKS: Right.

DR. BELSITO: We are trying to move quickly.

So, I don't think that we should wait for that review. What I can tell you is that we looked at this, and I'll let Dan comment. He did not have concerns with the leaf cell extract. We thought the flower extract was insufficient for composition and method of manufacturing. And if the composition was significantly different, other toxicological endpoints might be needed.

All of the others were safe as used when formulated to be non-sensitizing because they do contain a number of materials that could approach RIFM's limits for specific ingredients, such as Limonene, Linalol, the cinnamates, et cetera. So, sort of our botanical boilerplate with sensitization.

And, I'll let Dan comment on why he felt that -- I mean we have an incredible amount of data on the fruit very clearly showing composition. Dan, why did you not have problems with the leaf?

DR. LIEBLER: First of all, I want to echo that this is just, for botanicals for us, this is a fabulous level of characterization overall across the -- but the big hole was the flower, which we really had nothing on.

And then the leaf cell extract, on PDF 11, the first paragraph, has in parenthesis a very brief description of how it's prepared, but it's very similar to the other extracts. It was not unusual for, you know, for a botanical extract, essentially a methanolic buffer extract. And then, pretty good description of what's in it. And that was pretty consistent with what's in the other ingredients we see from vanilla. So, I was okay with the leaf cell extract for that reason. The flower basically had nothing. And so, I think that just fills in a little bit around what Don just told you.

DR. BERGFELD: Ron Shank?

DR. SHANK: For the leaf extract you're basing it strictly on that list of components? There's no other data.

DR. LIEBLER: And the brief mention of how it's a methanolic buffer extract.

DR. SHANK: Okay, but there's no safety data, just the chemical composition.

DR. LIEBLER: Right. I'm only referring to composition and method of manufacture here, okay? So, the question of whether or not the other data -- were you talking about whether the other data supports the safety of the leaf extract, all the safety data?

DR. SHANK: No, from the fruit?

DR. LIEBLER: Right.

DR. SHANK: No.

DR. LIEBLER: Okay. So I thought that we were just talking about whether or not we were sufficient for method of manufacture and composition.

DR. SHANK: Sufficient for that.

DR. LIEBLER: Yes.

DR. SHANK: But not necessarily adverse reactions.

DR. LIEBLER: Uh-huh.

DR. BELSITO: Dan, didn't you think we could read across from the composition given to the safety data for the other -- for the fruit?

DR. LIEBLER: I was inclined to do so. I would admit that the composition data aren't as thorough as the data for the other fruit seed components. It appears similar based on what we do have.

DR. SHANK: Okay.

DR. BERGFELD: Tom, any comment?

DR. GREMILLION: No. I stick with Ron.

DR. BERGFELD: How about, Paul?

DR. SNYDER: No comment.

DR. BERGFELD: Curt?

DR. KLAASSEN: I'm fine.

DR. BERGFELD: So, the conclusion being proposed by you, Jim -- or you have no conclusion.

DR. MARKS: Well, I think, based on the discussions it's going to be an insufficient data announcement. And then the question is what data do we need. Unless you say safe for, and insufficient for, say the flower. But, we usually give industry time to respond and after the first review, to provide data.

Did I interpret that right, Don? Basically you feel it's safe including the leaf as a read-across because we have well define composition of leaf. We have enough data for the fruit to read across all these fruit ingredients, and so we're really left with the flower as the insufficient data. Did I interpret that correct?

DR. BELSITO: Yes.

DR. MARKS: And that's fine. If you want I'll move that we have an insufficient data announcement and then the insufficiencies we just talked about.

DR. BERGFELD: Is that agreeable?

DR. BELSITO: It's fine.

DR. BERGFELD: It's fine. So, are you going to propose that as an insufficient? I'd like a vote on that since the discussion is sort of wide ranged.

DR. BELSITO: Well, I just want to clarify what's insufficient. Our team said it was just the composition of the flower and method of manufacture. You had a much longer list.

DR. MARKS: Yeah, then we went on with the 28-day dermal, genotox, DART and sensitization data, on the flower.

DR. BELSITO: Okay.

DR. BERGFELD: Is that agreeable?

DR. BELSITO: We just said, depending upon the data the toxicological endpoints where we need it.

DR. BERGFELD: Okay, say - okay.

DR. LIEBLER: Yeah, it's interesting that the flower extract and the leaf cell extract collectively have a little over 60 uses, and no report of concentrations.

DR. BERGFELD: Okay. I'm just going to call the question, do everyone agrees with this going out as insufficient specifically on the flower with what has been stated regarding the insufficiencies? May I see a show of hands of agreement? Thank you.

DR. MARKS: And then just one other point I'd like to get your input, Don; there are case reports of allergic contact dermatitis and positive patch test to the vanilla extract. How are we going to handle that in the final report, are we going to have a non-sensitizing conclusion, "also formulate to be non-sensitizing?"

DR. BELSITO: We already do because of the botanical boilerplate.

DR. MARKS: Right. Okay. Good.

DR. BERGFELD: Okay Wilbur has something.

DR. BELSITO: And you, I mean, you saw that balsam of Peru cross reactivity probably coming from all the cinnamates.

DR. MARKS: Right.

DR. BELSITO: So this has a lot of fragrance-like materials that could be combined with other botanicals that create issue.

DR. LIEBLER: Yeah.

DR. BERGFELD: Wilbur?

MR. JOHNSON: Yeah, I just want to make sure. 28-day dermal toxicity data, is that one of the items in the request? Or are you going to say, based upon the composition, additional toxicity data may be needed?

DR. BELSITO: I don't really care. I mean, we can list all the data or we can say additional. I mean, I don't know that we know what we need until we see it. But, I mean, we could ask for 28-day dermal and if absorbed, then reproductive and genotox may be needed. I mean, I like the idea of just saying other toxicological endpoints and not boxing myself into something specific.

DR. BERGFELD: Ron Shank, you want to comment on that?

DR. SHANK: No.

DR. BERGFELD: Jim, do you want to comment on it?

DR. MARKS: No, this is early in the process, so we'll --

DR. BERGFELD: But what are we going to ask for, though?

DR. MARKS: I think just as Don --

DR. BELSITO: Method of manufacture, impurities, composition, and concentration of use, and if significantly different, other toxicological endpoints -- or depending upon the results, other toxicological endpoints may be needed.

DR. BERGFELD: Anyone wants to add to that?

DR. SLAGA: Well, you say other toxs, but the first part that you mentioned, method of manufacture and impurities, that's not a toxicological endpoint. So you can't say "other".

DR. BERGFELD: "And"?

DR. BELSITO: Depending upon those results --?

DR. SLAGA: Right, we need "the" toxicological endpoints, not "other".

DR. BELSITO: I guess I was referring to -- yeah, fine.

DR. BERGFELD: Okay, that's been corrected. Ron?

DR. SHANK: Why not ask for a 28-day dermal toxicity? Added to your list of insufficiencies. You're not asking for any toxicological data.

DR. BELSITO: Whatever you'd like, Ron.

DR. SHANK: That's what I would like.

DR. BELSITO: Fine.

DR. BERGFELD: Thank you. Done, okay?

DR. SHANK: Okay.

DR. BERGFELD: Any other comments? Paul? Dan? Curt? No? Okay, we're moving on.

DECEMBER 2019 PANEL MEETING –SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team –December 9, 2019

DR. BELSITO: Vanilla. So at the June meeting, we issued another IDA. We wanted for the flower extract composition, manufacturing, impurities, concentration of use, 28-day dermal. Depending upon that, other endpoints. There was no response.

We had a summary of an HRIPT and a leave-on product endpoint of 0.025 percent fruit extract, which we didn't ask for. And that the rest of the ingredients, other than the flower extract, were safe as used.

DR. LIEBLER: Don, I have a little mea culpa here, I think. On the last time we talked about this, I said that the leaf ingredients could be read across from the -- that the leaf ingredients would allow us to read across to the fruit ingredients for safety assessment.

But when I actually took another look at Table 8, which is the leaf ingredient composition. All it is, is a list of a few carotenoids. It's not really a full list of ingredients. It's not even a list of representative major ingredients that would really support what I would --

DR. BELSITO: Which PDF again?

DR. LIEBLER: I'm on PDF 25 right now, which is composition. I'm under vanilla planifolia leaf cell extract.

DR. BELSITO: Right.

DR. LIEBLER: And sun leaf, shade leaf. That was Table 8. And I had been suggesting -- I looked at the minutes from the last meeting. I had suggested that that information would allow us to read across to the fruit and use the fruit data to clear the leaf.

But as I look back at this, you know, I was surprised that I had accepted that, because the data on the leaf are not really good enough to allow us read across to the fruit. So, sorry to have missed the ball last time, but I don't think the composition data are sufficient for leaf cell culture to read across to the fruit ingredients. So, the leaf and the flower are insufficient for the same reasons.

And again, I apologize for missing that last time, but it just doesn't work.

DR. BERGFELD: Could we assume that the leaf is never equal to the flower? Like it seems to in all the other botanicals, that's true?

DR. LIEBLER: Yeah. I think that's true and that just -- it doesn't help the leaf.

DR. BERGFELD: Yeah.

DR. LIEBLER: It just adds another reason why it's a problem.

DR. BELSITO: So, safe as used. The flower, I guess, is safe as used. What are the ingredients we're looking at here?

So we're looking at fruit flower, fruit leaf, seed, fruit seed. So, we're saying the flower and the leaf are insufficient for composition, method of manufacture and concentration of use. Do we need concentration of use? Let's look. So, flower extract.

DR. LIEBLER: Flower extract has no concentrations that --

DR. BELSITO: Yeah, we know that. That was our last go around. But now if we're saying leaf is insufficient, what is it insufficient for?

DR. HELDRETH: Yeah, there's no concentration of use reported for leaf.

DR. BELSITO: Just leaf?

DR. HELDRETH: Just five uses.

DR. LIEBLER: And that's the leaf cell extract, right?

MR. JOHNSON: Right.

DR. HELDRETH: That's correct.

DR. LIEBLER: So, we would have been insufficient for that anyway, but I was adding onto the insufficiencies all the other things, because it's not equivalent to the fruit.

DR. BELSITO: Okay. So, the fruit, the fruit oil, the fruit water, the seed, the seed powder, the fruit extract and the seed are safe as used when formulated to be non-sensitizing. The flower extract, and the leaf cell extract are insufficient for composition, method of manufacturing, impurities, concentration of use and 28-day dermal. Depending upon the results, other tox endpoints. Yes?

DR. LIEBLER: Right.

MR. JOHNSON: Yeah, I'd like to call the panel's attention to PDF page 28. The dermal irritation and sensitization studies. The human subheading and vanilla extract under the human subheading.

DR. BELSITO: Um hmm.

MR. JOHNSON: The test concentration should be ten percent in petrolatum, for the vanilla extract.

DR. BELSITO: Um hmm.

MR. JOHNSON: And the number of subjects tested in that particular study should be 5 and not 25.

DR. LIEBLER: Who does a study with five subjects?

MR. JOHNSON: Well, actually it was sort of like a preliminary study for the sensitization study.

MS. EISENMANN: This is the RIFM study. This is old.

MR. JOHNSON: Actually, it was a preliminary test before the actual sensitization.

DR. BELSITO: This was irritation, Dan.

MR. JOHNSON: Right, right. And the sensitization study is on PDF page 28.

DR. LIEBLER: Okay.

MR. JOHNSON: Vanilla extract. And so, it should be 10 percent in petrolatum as the test concentration for that one as well.

DR. BELSITO: Wilbur, on PDF Page 31, the first -- the end of the paragraph in the discussion --

MR. JOHNSON: Yes.

DR. BELSITO: -- where you're talking about the tests and the photo studies. It says, "The panel was not concerned about the positive (++) photopatch test reactions to vanilla extract on days two and four that were observed, because the strength of the reactions were the same on both days." That's not why we're not concerned.

We're not concerned because the strength of the reactions were the same on the irradiated and the unirradiated site, so it wasn't photo-allergenic, it was purely an allergic response. So, "because the strength of the reactions was the same on the irradiated and unirradiated sites," rather than on both days.

Okay. Anything else? No? Okay.

MR. JOHNSON: One more thing, Dr. Belsito. I guess with respect to those ingredients that are under the safe categorization. They're similar enough to be grouped together, you know, for that type of conclusion. What is that based on?

DR. BELSITO: Dan?

DR. LIEBLER: Say it again, Wilbur.

MR. JOHNSON: The ingredients that fall under the safe when formulated to be non-sensitizing category, those are similar enough to be categorized as such. So, what is that similarity based upon?

DR. BELSITO: Composition.

DR. LIEBLER: Maybe you should say that. I just closed the report so I'm trying to --

DR. SNYDER: I think, Wilbur, the logic is going to be the same as we used in the last botanical.

MR. JOHNSON: So no sensitizing constituents?

DR. SNYDER: The compositions would -- anticipated to be the same. And the data that we have appears to show similarity across the two species.

MR. JOHNSON: So similar, okay.

DR. LIEBLER: Thanks, Paul.

MR. JOHNSON: Thank you.

Marks Team -December 9, 2019

DR. MARKS: Okay. Next is vanilla. So this is a draft tentative report on the vanilla derived ingredients. There are nine ingredients. An insufficient data announcement was requested, at the June meeting of this year, for the flower extract. And those needs were listed in Wilbur's memo: composition met, the manufacture, concentration of use, 28-day dermal depending on the results. And there's been no response.

So at this point, we should be moving on to a tentative report. And I have that we could move forward with fruit, leaf and seed ingredients, eight of them safe when formulated to be non-sensitizing, insufficient for the flower extract. The needs are listed below.

There was quite a bit of discussion in the minutes, anybody, when you look at that. And then obviously, it's the discussion Wilbur put together on page 31, should that be edited?

So Ron, Tom, and then Lisa, do you like that conclusion? Can we go forward with eight of the ingredients safe when formulated to be non-sensitizing, and just insufficient for the flower extract?

DR. SHANK: Yes.

DR. PETERSON: Yup.

DR. SLAGA: Um-hmm.

DR. MARKS: Okay. And Page 31, discussion? And I'll be seconding this tomorrow. So presumably, that's -- any comments about the discussion? Ron, Tom, or Lisa --

DR. SHANK: It's good.

DR. MARKS: -- at this point. It looks good? Tom?

DR. SLAGA: Nope.

DR. MARKS: Okay.

MR. JOHNSON: I have one concern. I'll call the Panel's attention to PDF Page 28.

DR. SHANK: 28?

MR. JOHNSON: Yes. Under the human section, the vanilla extract subheading, actually the test concentration -- in the paragraph beginning with, "Prior to initiation" -- the test concentration is 10 percent in petrolatum. So, the text will be revised to indicate that.

DR. MARKS: I'm not sure -- so I'm on 28.

DR. SHANK: I haven't found that yet.

MR. JOHNSON: Right before the sensitization section, under human, vanilla extract, that subheading.

DR. MARKS: Oh, okay.

MR. JOHNSON: So, I say concentration not stated, but the concentration data were provided. And it was tested at concentration of 10 percent in petrolatum.

DR. MARKS: And it was fine?

MR. JOHNSON: Yeah. And also, in this particular study, five subjects were tested, not 25. So, 25 is a mistake.

DR. MARKS: Okay.

MR. JOHNSON: And also, in the sensitization section, under the vanilla extract subheading, that concentration should be 10 percent in petrolatum also.

DR. MARKS: Okay. So, that's -- 10 percent. Okay. Again, that was no evidence of sensitization?

MR. JOHNSON: Yes.

DR. MARKS: Okay.

MR. JOHNSON: And also, I'd like to call the panel's attention to --

DR. MARKS: None of these change the bottom line on these, and it was neither an irritant or a sensitizer, right, Wilbur?

MR. JOHNSON: Right. Right. And I'd like to call the Panel's attention to PDF Page 42, Table 10, and the last entry in Table 10.

Now, the discussion -- with respect to that phototoxicity evaluation -- the discussion indicates that the same reaction was observed on days two and four.

DR. MARKS: Um-hmm.

MR. JOHNSON: But the table also indicates that the same reaction was observed at the site that was irradiated, as well as the one that was not irradiated. So, should that be mentioned in the discussion as well? Because we only say that the same reaction was observed on days two and four.

DR. MARKS: If you want to clarify, you say the photopatch tests were also positive. That would indicated, when you do the photopatch test, that your routine patch -- that's without the light -- would be negative. And then with the light, it's going to be positive. So, it implies that; but if you want to be more specific, that's fine.

MR. JOHNSON: Just to say that the same reaction was observed as the non-irradiated site, versus the irradiated site.

DR. SHANK: So, that's not a positive result?

DR. MARKS: No. That's correct. None of that changes. We didn't have phototoxicity as an alert. And Ron, you're right, I misheard. I thought you said that the non-irradiated site was negative; but it was positive?

DR. SHANK: Um-hmm.

MR. JOHNSON: Right.

DR. MARKS: Yeah. Okay.

MR. JOHNSON: They both got the same reaction.

DR. MARKS: Yeah. That's exactly correct. It would be considered -- if they're both the same, it's considered allergic contact dermatitis.

If the photo irradiated site is enhanced, then it's thought to be a combination of both allergic contact and photoallergic contact. But if they're the same intensity, then it would be considered allergic contact.

MR. JOHNSON: What is the meaning of observing that same reaction on both days two and four, the significance of that?

DR. MARKS: I would say there it would be that when you have a persistent reaction it's more likely an allergic reaction. Whereas if it's an irritant, it tends to fade on the more delayed readings on day four. If the reaction was diminished, it may not be a true allergic reaction. That's the general thought of that.

DR. SHANK: Or they didn't look on day three.

DR. MARKS: No, typically, you don't look at day three.

DR. SHANK: See.

DR. MARKS: So, yeah. But I don't think any of that -- all those editorial -- I'll put editorial -- are significant when it's change in concentrations, really change our conclusion here.

DR. SHANK: Right.

DR. MARKS: Okay. Anything else, Wilbur?

MR. JOHNSON: No, that's all, Dr. Marks. Thanks.

DR. SHANK: Do you have to put formulated to be non-sensitizing?

DR. HELDRETH: That's what I was going to ask. Because if you look at Wilbur's draft discussion, that first paragraph gives all the verbiage we would put in for a report that has that caveat in the conclusion.

DR. MARKS: Um, well --

DR. SHANK: Sorry.

DR. MARKS: No, that's okay. That's what we've been putting in, even though it's in the discussion in that first paragraph, Bart.

I'm fine with leaving it out. But, you know, we've been doing this now with these botanicals, as I mentioned earlier, to CYA. I don't know. What's your sense, Ron?

DR. HELDRETH: It's the panel's choice.

DR. SHANK: I don't think it's necessary, but the other team really likes to use that.

DR. MARKS: Yes. We'll see. I think that's what I'll be --

DR. SHANK: I could ruffle their feathers tomorrow.

DR. MARKS: That's why I put it in. I suspect we'll be seconding that tomorrow. I didn't think we wanted to get in a long discussion about it. Tom?

DR. SLAGA: I agree with Ron. Let's see what the other team -- they do change.

DR. MARKS: Well, we'll find out tomorrow. If they change and don't include it, I'm not going to put up a -- sometimes when there's a difference, we have a significant discussion.

If they say, safe without having formulate it to be non-sensitizing, I'm just going to second it. I'm not going to bring up any discussant points. And if they say when formulated to be non-sensitizing, I'm going to second it also and not bring up any discussant points. So, I'm going to be flexible on that one.

DR. ANSELL: It should be an easy one to remember.

DR. MARKS: Pardon me, Jay?

DR. ANSELL: It should be easy to remember. You don't say if they do and you don't say if they don't.

DR. MARKS: Yup. You got it. That's it. Any other comments?

MR. JOHNSON: I do, Dr. Marks.

DR. MARKS: Sure.

MR. JOHNSON: In terms of the safe when formulated to be non-sensitizing conclusion on a number of ingredients, is there any read across that's being taken into consideration? In the absence of data on some ingredients, are you using data on another ingredient to support safety?

DR. MARKS: I think that is aimed at, not so much read across of these vanilla ingredients, but as when you add vanilla with other botanicals. But if you have ingredients within it, that are sensitizing within these vanilla ingredients in the present practice and concentration, we're not concerned about sensitization.

But if you add vanilla, plus soy, plus palm, plus whatever, one of those sensitizers may arise above the concentration, may arise above the level that can cause sensitization. So, that's what it's about in my mind.

MR. JOHNSON: But I guess what I mean is the safe part. Data are not available on all of the ingredients in the report.

DR. MARKS: Right.

MR. JOHNSON: So, for the safe part, I guess you're relying on data on certain ingredients, and the absence of data on the other.

DR. MARKS: Yeah.

DR. JONES: So, my concern is what data are being used to evaluate the safety of those without data, specifically?

DR. MARKS: I think that's why we want the composition; is because we assume that in the ones we don't have the specific data on sensitization, or any of these other toxicologic endpoints. That the composition in the other plant parts are similar, and we would expect their toxicology would be similar.

MR. JOHNSON: I see.

DR. MARKS: That's my reasoning. Now, Tom and Ron?

DR. SLAGA: That's right.

DR. SHANK: No, that's right.

DR. MARKS: Yeah. Okay.

DR. PETERSON: I have just a very minor suggestion. Addition to the methods of manufacture on Page 24, it's mentioned that the pods from Papua New Guinea were different than those from French Polynesia.

And it says what the difference is, but I thought it would be worth saying how the curing process for the French Polynesia should be inserted there, too. That was just a question I had. And I have a note.

MR. JOHNSON: That's the first paragraph?

DR. PETERSON: Yeah, the first one.

MR. JOHNSON: So the curing methodology should be specifically state for both in there?

DR. PETERSON: Yeah. I think one's different, but you don't know what the other one was.

MR. JOHNSON: Right. Okay. Thank you.

DR. MARKS: Okay. So tomorrow, our team will be seconding a tentative report, which has a safe for eight and insufficient for the flower extract. And we will find out tomorrow whether we're going to formulate this to be non-sensitizing or not. Next is glycerin --

Full Panel –December 10, 2019

DR. BELSITO: Okay, so at the June meeting we issued an IDA. We requested data on composition, method of manufacture and impurities, concentration of use, 28-day dermal depending upon the results of the genotox endpoints.

And, after I guess some discussion the panel agreed that available data to support the safety of all the ingredients, except for the vanilla flower extract, which had insufficient data -- anyway long story.

We thought that the vanilla ingredients were safe as used when formulated to be non-sensitizing, except for the flower extract and the leaf cell extract, for which we needed method of manufacture, impurities, composition. And if the composition was significantly different, tox endpoints, concentration of use and a 28-day dermal. Yeah, Dan?

DR. LIEBLER: Yeah, you know, I think I mentioned this yesterday. At the last meeting -- and this a little mea culpa on my part. At the last meeting I suggested that the composition data that we had for the leaf was sufficient to read across to the other vanilla stuff. And I took another look at that, when I reviewed the report this time, and I realized that table was only just a few carotenoids. It wasn't really sufficient to do that.

So, I don't think we have enough data to support the leaf, so I think we're insufficient for the leaf and the flower unfortunately. So, my apologies for missing that but I wanted to catch it this time.

DR. MARKS: Our team seconds that. So, this would be a tentative report.

DR. BELSITO: Um-hmm.

DR. BERGFELD: Going out with safe with two insufficient.

DR. BELSITO: Right.

DR. BERGFELD: All those in favor of that decision, or comment? Unanimous. Any other discussion points that have to go in? Wilbur?

MR. JOHNSON: Yes, I would just like the panel to review the discussion to determine whether or not it needs to be revised in anyway.

DR. MARKS: Well, certainly with the changes we mentioned yesterday and today about the leaf, the discussion will be changed a bit. And I think in our team we did not have any significant edits for the discussion.

MR. JOHNSON: All right.

DR. BERGFELD: Belsito team, any added items to the discussion?

DR. BELSITO: No.

DR. BERGFELD: Wilbur?

MR. JOHNSON: One thing Dr. Belsito did mention in the discussion relating to the phototoxicity test --

DR. BELSITO: Well, I mean, you just misinterpreted it. I mean, and with the changes that the panel was not concerned about positive photo patch test reactions to vanilla extracts on day two and day four -- you had -- because the strength of the reactions were the same on both days.

That's not the reason we weren't concerned. We weren't concerned because the strength of the reactions was the same on the eradiated and the un-eradiated side, meaning that this was an allergic reaction and not a photo allergic reaction.

DR. BERGFELD: So, clarification of the results of the test? Okay?

MR. JOHNSON: Yes, thank you.

DR. BERGFELD: Anything else? Seeing none, call the question, all those in favor then of safe for vanilla? Thank you. With two insufficient. Unanimous. Ron voted?

DR. MARKS: Yeah.

Safety Assessment of Vanilla-Derived Ingredients as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: February 21, 2020
Panel Date: March 16-17, 2020

The Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.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 Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 9 vanilla-derived ingredients. These ingredients are reported to function mostly as skin conditioning agents in cosmetic products. Because final product formulations may contain multiple botanicals, each containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Industry should continue to use good manufacturing practices to limit impurities. The Panel reviewed relevant data relating to the safety of these ingredients in cosmetic formulations and concluded that 7 ingredients are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing. The Panel further concluded that the available data are insufficient to determine that Vanilla Planifolia Flower Extract and Vanilla Planifolia Leaf Cell Extract are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

The safety of the following 9 vanilla-derived ingredients, as used in cosmetics, is reviewed in this Cosmetic Ingredient Review (CIR) safety assessment.

Vanilla Planifolia Fruit Extract
Vanilla Planifolia Flower Extract
Vanilla Planifolia Fruit Oil
Vanilla Planifolia Fruit Water
Vanilla Planifolia Leaf Cell Extract
Vanilla Planifolia Seed
Vanilla Planifolia Seed Powder
Vanilla Tahitensis Fruit Extract
Vanilla Tahitensis Seed

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), 6 of these ingredients function as skin conditioning agents in cosmetic products, 2 are reported to function only as abrasives, and one ingredient is reported to function as an antioxidant and skin protectant (See Table 1).[1] An additional 2 vanilla-derived ingredients that are included in the *Dictionary*, Vanilla Planifolia Fruit and Vanilla Tahitensis Fruit, are only reported to function as fragrance ingredients in cosmetics. It is probable that the safety of these will be reviewed by the Expert Panel for Fragrance Safety; thus, the safety of Vanilla Planifolia Fruit and Vanilla Tahitensis Fruit will not be reviewed by CIR. However, data on these ingredients are included in this report for use in the safety evaluation of the other fruit-derived ingredients (which do not function exclusively as fragrances). (The Research Institute for Fragrance Materials (RIFM) previously issued a monograph on vanilla tincture (ethanol extract)[2])

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

Botanicals, such as *Vanilla planifolia* and *tahitensis*-derived ingredients, may contain hundreds of constituents, some of which may have the potential to cause toxic effects. In this assessment, CIR is reviewing the potential toxicity of each of the botanical ingredients as a whole, complex mixture. CIR is not reviewing the potential toxicity of the individual constituents. Additionally, some of the ingredients reviewed in this safety assessment may be consumed in food, and daily exposure from food use would result in much larger systemic exposures than those from use in cosmetic products. The primary focus of the safety assessment of these ingredients as used in cosmetics is on the potential for effects from topical exposure.

In many of the published studies, it is not known how the substance being tested compares to the cosmetic ingredient. Therefore, if it is not known whether the chemicals being discussed are cosmetic ingredients, the test substances will be identified simply as "vanilla extract;" if it is known that the substance is a cosmetic ingredient, the International Nomenclature Committee (INC) terminology "Vanilla Planifolia…" or "Vanilla Tahitensis…" (e.g. Vanilla Planifolia Fruit Extract) will be used.

CHEMISTRY

Definition

Vanilla planifolia and *Vanilla tahitensis* are 2 orchid species, and *Vanilla tahitensis* is a hybrid between *Vanilla planifolia* and *Vanilla odorata*.[3] The United States (US) Food and Drug Administration (FDA) defines vanilla beans as the properly cured and dried fruit pods of *Vanilla planifolia* Andrews and *Vanilla tahitensis* Moore [21 CFR 193.6].

According to the *Dictionary*, Vanilla Planifolia Fruit Extract is the extract of the fruit (bean) of *Vanilla planifolia*, and Vanilla Tahitensis Fruit Extract is the extract of the fruit (bean) of *Vanilla tahitensis*; vanilla extract is a technical name for both.[1] The FDA defines vanilla extract as the solution in aqueous ethyl alcohol of the sapid and odorous principles extractable from vanilla beans [21 CFR 169.175]. It should be noted that vanillin (4-hydroxy-3-methoxybenzaldehyde) is a prominent component of the volatile aroma of vanilla beans;[4] yet, published studies indicate that it does not exceed 4% of the

total extract content. It should also be noted that neither synthetic vanilla nor artificial vanilla are derived from *Vanilla spp*. Thus, data on synthetic or artificial vanilla are not applicable to the ingredients in this report.

The definitions and functions in cosmetics of the 9 *Vanilla planifolia*- and *Vanilla tahitensis*-derived ingredients reviewed in this safety assessment are presented in Table 1.

Plant Identification

Vanilla tahitensis is mainly cultivated in French Polynesia.[5] *Vanilla tahitensis* is also found, together with *Vanilla planifolia*, in New Guinea (Papua New Guinea and Indonesia). According to another source, *Vanilla tahitensis* samples from Papua New Guinea and *Vanilla planifolia* samples from Madagascar (Bourbon vanilla) are among the vanilla samples that are commercially available.[6]

Physical and Chemical Properties

Physical and chemical properties of a Vanilla Planifolia Fruit Extract trade name mixture are presented in Table 2.[7] Among the properties presented is the solubility of this mixture in water and ethanol.

Method of Manufacture

Vanilla planifolia fruit and Vanilla tahitensis fruit

The curing method for *Vanilla planifolia* and *Vanilla tahitensis* pods from Papua New Guinea is different from that for *Vanilla tahitensis* from French Polynesia, in that it includes a high-temperature, scalding step to stop maturation, followed by drying to ~ 40% water content.[6] In French Polynesia, rather than scalding the vanilla pod after harvesting, the pod is allowed to cure slowly through alternating exposures in the cool shade and warm sun.[8]

Vanilla Tahitensis Fruit Extract

According to one study, *Vanilla tahitensis* pods are harvested at full maturity in a shadehouse.[9] The vanilla pods are then cured according to the traditional Polynesian curing method in order to obtain ~ 50% moisture vanilla pods. Vanilla samples comprising cured vanilla pods are used for extraction (e.g., ethanolic extraction).

An unpublished method of manufacture of a Vanilla Tahitensis Fruit Extract trade name mixture consisting of 64.7% propylene glycol, 34.5% water, and 0.8% Vanilla Tahitensis Fruit Extract was submitted.[10] Therein, pods of *Vanilla tahitensis* are extracted using a mixture of propylene glycol and water. This process (12 h at 105ºC) is followed by filtration, yielding the Vanilla Tahitensis Fruit Extract trade name mixture. A similar production method for another Vanilla Tahitensis Fruit Extract trade name mixture consisting of 68.7% butylene glycol, 30% water, and 1.3% Vanilla Tahitensis Fruit Extract was also submitted.[11] The method is the same (expressed as dry extract, 12 h at 105ºC), except for the extraction of *Vanilla tahitensis* pods with a mixture of butylene glycol and water.

Vanilla Planifolia Fruit Extract

One method of manufacture of Vanilla Planifolia Fruit Extract, found in the published literature, involves an enzyme-assisted process, and is summarized as follows: fresh green vanilla pods are immersed in warm water for 2 to 5 minutes.[12] After cooling to ambient temperature, the beans are pureed in a laboratory grinder and separated into 2 equal portions (100 g each). To the first portion, 1% v/v of a mixture of arabinases, cellulases, hemicellulases, xylanases, and pectinases from Aspergillus was added. Tea leaf enzyme extract (TLEE, 2% v/v) was added to the second portion. Addition of the enzyme mixture/enzyme extract was followed by incubation at 50 °C for 12 h. Ethyl alcohol (equal volume w/w) was added to the reaction mixture for extraction of vanilla constituents. The entire mixture was passed through the improvised filter paper to obtain Vanilla Planifolia Fruit Extract.

Vanilla extract is generally prepared via either the percolation method or the oleoresin method.[13] The percolation method consists of circulating a solvent, an ethanol/water solution (in the range 35 - 50:65:50 (v/v)), over and through the beans under vacuum. The oleoresin method consists of pulverizing whole beans and then circulating ethanol over the beans under vacuum at ~ 45°C. The excess alcohol is removed by evaporation.

Composition

Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract

The composition of a Vanilla Planifolia Fruit Extract trade name mixture is as follows: water (49% to 49.5%), propylene glycol (49% to 49.5%), and Vanilla Planifolia Fruit Extract (1% to 2%).[7] A Vanilla Tahitensis Fruit Extract trade name mixture has been reported to consist of the following: propylene glycol (64.70%), water (34.50%), and Vanilla Tahitensis Fruit Extract (0.80%).[14] Another Vanilla Tahitensis Fruit Extract trade name mixture reportedly consists of: butylene glycol (68.7%), water (30%), and Vanilla Tahitensis Fruit Extract (1.30%).[15]

In a study that was performed between 2005 and 2007, more than 300 Tahitian vanilla samples were collected from vanilla curers who were based on the islands of Tahaa and Raiatea.[5] These 2 islands were the locations of most of the vanilla production in French Polynesia at that time. The samples were analyzed by high performance liquid chromatography,

together with 22 samples of *Vanilla planifolia* and 9 samples of *Vanilla tahitensis* from Papua New Guinea. The volatile aroma content of a *Vanilla planifolia* fruit was found to consist mostly of vanillin (80% of the total quantified volatile aroma content (volatile aroma content is 4% of the total extract); ~ 3% of the total extract composition is vanillin). Anisyl constituents represent 7% of the volatile aroma content. The major anisyl constituents are: anisyl alcohol, anisaldehyde, methyl anisate, and anisyl acetate. This *Vanilla planifolia* fruit extract consists of more than 40% phenolic constituents and 2% aliphatic aldehyde; both values are lower in *Vanilla tahitensis*. The data on *Vanilla tahitensis* fruit extract are included below.

According to the same study (more than 300 Tahitian vanilla samples collected), a *Vanilla tahitensis* fruit extract contains *p*-hydroxybenzyl or vanillyl derivatives, but also consists predominantly of anisyl derivatives.[5] Data on the volatile aroma content of a *Vanilla tahitensis* fruit extract components are as follows: vanillin (25%), anisyl alcohol (30%), anisic acid (15%), *p*-hydroxybenzyl constituents (20%), and protocatechuyl derivatives (5%), for a total volatile aroma content equivalent to 4.7% of the total extract (i.e., vanillin is ~ 1.4 % of the total extract). According to another source, a *Vanilla tahitensis* fruit extract, anisyl constituents represent 70% of the volatile content (~3.3% of the total extract composition).[6] Like *Vanilla planifolia*, the major *Vanilla tahitensis* fruit extract anisyl constituents identified are: anisyl alcohol, anisaldehyde, methyl anisate, and anisyl acetate. *Vanilla tahitensis* fruit extract consists of less than 10% phenolic constituents and 0.5 - 1% aliphatic aldehydes.

Data on the concentration of volatile constituents in Vanilla Tahitensis Fruit Extract (dichloromethane extract) from 3 Polynesian cultivars (Haapape, Tahiti, and Parahurahu) and 2 origins (French Polynesia and Papua New Guinea), and in Vanilla Planifolia Fruit Extract from Madagascar (dichloromethane extract), are presented in Table 3.[6] Data on 4 components (vanillic acid, vanillin, *p*-hydroxybenzoic acid, and *p*-hydroxy-benzaldehyde) extracted from *Vanilla planifolia* fruit and *Vanilla tahitensis* fruit from 6 and 1 geographical regions, respectively, are presented in Table 4.[16] Data on the concentrations of 2- or 4-methoxylated constituents in *Vanilla planifolia* fruit, Vanilla Planifolia Fruit Extract, and Vanilla Tahitensis Fruit Extract are presented in Table 5.[17] Table 6 contains composition data on Vanilla Tahitensis Fruit Extract and Vanilla Planifolia Fruit Extract, resulting from the use of various extractants.[3,5,9,12,18-25]

Vanilla planifolia fruit

In commercial practice, size, shape and color serve as quality criteria for vanilla beans from Madagascar.[26] The commercial grades are described as follows: the black beans are the highest grade and are usually used in the retail market. Second in quality is the red beans, which are divided into split and non-split. These subgroups are further classified by size. The red beans are used for extract preparation. "Cuts" are very small beans or broken material. Most batches of vanilla beans contain 1.2 to 2.2 g vanillin/100 g. Only 15 out of the 55 batches analyzed show a vanillin content of > 2 g/100 g. The average over all in samples was 1.76 g/100 g. The vanillin content (units not stated) for some commercial grades of vanilla beans are: 1.72 to 2.18 g/100g (black beans), 1.38 to 2.45 g/kg (red non-split), and 1.37 to 2.18 g/100 g (red split). All qualities, except cuts, contain batches above and below 2 g/100g vanillin. The average vanillin content decreased from black > red non-split > red split > cuts.

Data on the elemental composition of *Vanilla planifolia* fruit harvested in Indonesia and in Papua New Guinea are presented in Table 7.[27]

Vanilla extract

According to the FDA**,** vanilla extract for use in foods (the total sapid and odorous principles extractable from one-unit weight of vanilla beans in an aqueous alcohol solution) is not less than 35% ethyl alcohol [21CFR 169.175]. Data on the content of vanillin in vanilla extracts from various regions are as follows: 2% (Madagascar), 2% (Réunion), 1.75% (Mexico), 1.75% (Caribbean), 1.70% (Tahiti), 1.75% (Indonesia), 1.5% (Sri Lanka), and 1.5% (India).[13] According to another source, vanilla extract contains alcohol (36%) and vanillin (0.199%).[28]

Vanilla Planifolia Leaf Cell Extract

Young *Vanilla planifolia* leaf extracts (extracted with a mixture of methanol and monobasic potassium phosphate; potential inference to Vanilla Planifolia Leaf Cell Extract) were found to have higher levels of glucose, bis[4-(β-D-glucopyranosyloxy)-benzyl]-2-isopropyltartrate (glucoside A) and bis[4-(β-D-glucopyranosyloxy)-benzyl]-2-(2-butyl)-tartrate (glucoside B), whereas older leaves had more sucrose, acetic acid, homocitric acid and malic acid.[29] A comparison of concentrations of these components was not provided. Results obtained from a partial least square modeling discriminate analysis (PLS-DA) showed that leaves collected in March 2008 had higher levels of glucosides A and B, when compared to those collected in August 2007. However, the relative standard deviation exhibited by the individual values of glucosides A and B showed that those constituents vary more according to their developmental stage (50%) than to the time of day or the season in which they were collected (19%).

Composition data on *Vanilla planifolia* leaf (sun leaf and shade leaf) are presented Table 8.[30] Sun leaves are at the top and outer edges of a plant, and shade leaves are at the bottom or interior of a plant.

Vanilla Planifolia Seed

Thioacidolysis of *Vanilla planifolia* seeds revealed that the lignin in the isolated seed coats was entirely composed of catechyl units, with practically no release of α,β,γ-trithioethyl-propylguaiacol from guaiacyl units, or the syringyl analog.[31] Klason analysis of the seed coat indicated a very high level (~80%) of acid-insoluble lignin polymer. The majority of the remaining material in the seed coat was crystalline cellulose (16%); very little non-cellulosic sugars (2%) were detected. The benzodioxane polymer in the seed coat is derived from the polymerization, almost exclusively, of caffeyl alcohol. Benzodioxanes, resulting from β–*O*–4-coupling of a monomer with a caffeyl unit, were the dominant units in both the seed-coat lignin and a synthetic catechyl dehydrogenation polymer (C-DHP), accounting for over 98% of the total identifiable dimeric units.

Vanilla Planifolia Seed Powder

According to the FDA, vanilla powder (for use in the category of specific standardized food dressings and flavorings) is a mixture of ground vanilla beans (including the seeds and bean husk) or vanilla oleoresin or both, with one or more of the following optional blending ingredients: sugar, dextrose, lactose, food starch, dried corn syrup, and gum acacia [21 CFR 169.179]. Additionally, vanilla powder may contain 1 or any mixture of 2 or more of the following anticaking ingredients: aluminum calcium silicate, calcium stearate, magnesium silicate, and tricalcium phosphate.

Impurities

Vanilla Planifolia Fruit

Residues of the pesticide, quintozene, have been detected in *Vanilla planifolia* fruit.[27]

Vanilla Planifolia Fruit Extract

The impurities content of a Vanilla Planifolia Fruit Extract trade name mixture has been described as less than the quantification limit of 0.01 mg/kg (for pesticide levels) and ≤ 10 ppm (for heavy metals content).[7]

Vanilla planifolia plant

The *Cymbidium mosaic* virus has been detected in *Vanilla planifolia* plants grown in 2 states in India.[32]

Vanilla planifolia leaf

The *Cucumber mosaic* virus has been detected in the leaves of *Vanilla planifolia* plants grown in southern India.[33]

USE

Cosmetic

The safety of the vanilla-derived ingredients is evaluated based on data received from the US FDA and the cosmetics 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.[34] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[35]

According to 2020 VCRP data, Vanilla Planifolia Fruit Extract is reported as being used in 383 cosmetic products (240 leave-on products, 136 rinse-off products, 7 products that are diluted for (bath) use).[34] Of the vanilla-derived ingredients reviewed in this safety assessment, this is the greatest reported use frequency. The 2020 VCRP data also indicate that generic vanilla (not assigned to any ingredient in this report) is used in 20 cosmetic products. The results of a concentration of use survey conducted by the Council in 2017 indicate that Vanilla Planifolia Fruit Extract is used at maximum use concentrations up to 0.33% in leave-on products (face and neck products (not spray)) and maximum use concentrations up to 0.25% in rinse-off products (skin cleansing products).[35] These are the highest use concentrations in leave-on and rinse-off products reported for the vanilla-derived ingredients that are reviewed in this safety assessment. Further use data are presented in Table 9.

According to VCRP and Council survey data, the following 2 ingredients are not currently in use in cosmetic products: Vanilla Planifolia Seed and Vanilla Tahitensis Seed. Only 2 of the 7 ingredients (the fruit extracts) reported to be in use according to the VCRP had concentrations of use reported in the survey.

Cosmetic products containing vanilla-derived ingredients may be applied to the skin or, incidentally, may come in contact with the eyes (e.g., Vanilla Planifolia Fruit Extract at concentrations up to 0.036% in eyebrow pencils). Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract are used in products that come in contact with mucous membranes during product use (maximum ingredient use concentrations of 0.055% (lipstick) and 0.00055% (bath soaps and detergents), respectively). Additionally, Vanilla Planifolia Fruit Extract could be incidentally ingested (maximum use concentrations up to 0.055% (lipstick)). Products containing vanilla-derived ingredients may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

The following vanilla-derived ingredients are reported as used in products that are sprayed: Vanilla Planifolia Fruit Extract (concentrations up to 0.003% in hair spray and 0.013% in body and hand spray) and Vanilla Tahitensis (concentrations up to 0.002% in deodorant spray). In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm, compared with pump sprays.[36,37,38,39] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[36,37] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[37] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

According to 2019 VCRP data, some of the vanilla-derived ingredients are used in baby products, including baby lotions, oils, powders, and creams.[40] It is not known if any of the uses are in powders; the only concentration of use reported for this category (0.001% Vanilla Planifolia Fruit Extract) stated the use was not a powder.[41] In case the other uses are powders, please note that conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[42,43,44]

The vanilla-derived ingredients reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[41]

Non-Cosmetic

In the US, Vanilla Planifolia Seed, Vanilla Planifolia Seed Powder, and Vanilla Tahitensis Seed are generally recognized as safe (GRAS) for use as spices and other natural seasonings and flavorings in food, within the meaning of section 409 of the Federal Food, Drug, and Cosmetic Act [21 CFR 182.10]. Vanilla Planifolia Fruit Extract, Vanilla Tahitensis Fruit Extract, Vanilla Planifolia Fruit Oil, Vanilla Planifolia Fruit Water, Vanilla Planifolia Seed, Vanilla Planifolia Seed Powder, and Vanilla Tahitensis Seed are GRAS in animal drugs, feed, and related products, within the meaning of section 409 of the Federal Food, Drug, and Cosmetic Act [21 CFR 182.20; 21 CFR 582.20].

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion

Vanilla Extract (ethanol extract)

Two normal adults, maintained on a plant-free diet for at least 3 to 5 days, ingested 10 ml of vanilla extract (ethanol extract).[2] At 24 h post-ingestion, conjugated 3-methoxy-4-hydroxybenzylamine was detected in the urine.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Vanilla Extract (ethanol extract)

In an acute dermal toxicity study on vanilla extract (ethanol extract) involving rats, the LD_{50} was determined to be > 2 g/kg.[2] (No details were provided)

Oral

Vanilla Extract (ethanol extract)

An acute oral LD_{50} of > 5 g/kg was reported for vanilla extract (ethanol extract) in a study involving rats.[2] (Details were not provided.)

Short-Term, Subchronic, and Chronic Toxicity Studies

Data on the short-term, subchronic, and chronic toxicity of vanilla-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity (DART) of vanilla-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

Vanilla Tahitensis Fruit Extract

The genotoxicity of a trade name mixture containing 1.3% Vanilla Tahitensis Fruit Extract, 67% butylene glycol, and 30% water was evaluated in the Ames test, in accordance with Organization for Economic Co-operation and Development (OECD) Test Guideline (TG) 471.[45] The assay involved *Salmonella typhimurium strains* TA98, TA100, TA 102, TA1535, and TA1537, and the following doses (per plate) of the test material were evaluated with and without metabolic activation: 0.05 µL, 0.167 µL, 0.5 µL, 1.67 µL, or 5 µL. The solvent served as the negative control and standard mutagens served as positive controls. The test material was found to be non-mutagenic and non-promutagenic in this assay.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of the vanilla-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

DERMAL IRRITATION AND SENSITZATION STUDIES

Irritation

In Vitro

Vanilla Tahitensis Fruit Extract

The skin irritation potential of a trade name mixture containing 0.8% Vanilla Tahitensis Fruit Extract, 64.7% propylene glycol, and 34.5% water (tested at 10%; effective concentration of extract = 0.08%) was evaluated for skin irritation potential using the PREDISKIN™ method (non-validated method).[46] Details relating to the test protocol are not included. Human skin, collected after plastic surgery, was exposed to the test material for 20 h. Skin morphology was then assessed by histological examination. Sodium dodecyl sulfate (20 mg/ml) served as the positive control. The test material did not cause any morphological alterations of human skin samples at the concentration tested, and was considered non-irritating.

Animal

Vanilla extract (ethanol extract)

Undiluted vanilla extract (ethanol extract) was applied for 24 h to intact or abraded skin of rabbits.[2] The test site was covered with an occlusive patch during the application period. The number and strain of animals tested and details relating to the test protocol were not stated. Moderate skin irritation was observed. Irritation scores for intact and abraded skin sites in each animal are not included.

Human

Vanilla Tahitensis Fruit Extract

A trade name mixture containing 0.8% Vanilla Tahitensis Fruit Extract, 64.7% propylene glycol, and 34.5% water (tested at 10%; effective concentration of extract = 0.08%) was evaluated for skin irritation potential in a 48-h, single occlusive patch test involving 22 subjects.[46] The dose per cm^2 of the test material, and further test protocol details, were not stated. The skin was examined at 30 min and 24 h after patch removal. The test material classified as a non-irritant.

Vanilla extract

Prior to initiation of the maximization test involving 25 male subjects that is summarized below, a vanilla extract (ethanol extract, 10% in petrolatum) was applied, under occlusion, for 48 h to the backs of 5 subjects.[47] Because skin irritation was not observed, the decision was made to pretreat the skin with sodium lauryl sulfate (SLS) prior to patch application in the maximization test.

Sensitization

Human

Vanilla Planifolia Fruit Extract

A human repeated insult patch test (HRIPT) involving 108 subjects was used to evaluate the skin sensitization potential of a leave-on product containing 0.02% Vanilla Planifolia Fruit Extract.[48] The 3-week induction phase involved 9 occlusive, 24-h or 48-h patch applications of the product (0.02 g per application). Neither the location of the application site nor the area (cm^2) of application was stated. The induction phase was followed by a 2-week non-treatment period. Next, a challenge patch was applied to a new test site, and reactions were scored at 24, 48, 72, and 96 h. One subject had a low-level reaction (score of ≤ 1) during induction. A low-level reaction was also observed in one subject during the challenge phase. Whether or not the induction and challenge reactions were observed in the same subject was not stated. The author concluded that the product did not induce dermal irritation and sensitization in any of the subjects tested.

Vanilla Tahitensis Fruit Extract

A trade name mixture containing 0.80% Vanilla Tahitensis Fruit Extract, 64.7% propylene glycol, and 34.5% water (tested at 5%; effective concentration of extract = 0.04%) was evaluated for skin sensitization potential in an HRIPT involving 55 subjects.[46] A filter paper disc (7-mm diameter) containing 0.02 ml of the test material was applied, under an occlusive patch (48-h or 72-h application), to the arm for a total of 9 induction applications. Following a 15-day non-treatment period, the challenge phase was initiated. A challenge patch containing 0.02 ml of the test material (same extract concentration) was applied for 48 h to dorsal skin. No irritation or sensitization reactions indicating cutaneous intolerance were observed. The test material was classified as non-irritating and non-sensitizing.

Vanilla extract

The skin sensitization potential of a vanilla extract (ethanol extract,10% in petrolatum) was evaluated in a maximization test using 25 male subjects.[47] Initially, the volar forearm was pretreated for 24 h with 5% aqueous SLS (under occlusion). The test material was then applied to the same site for 5 alternate-day, 48-h periods. After a 10-day non-treatment period, a challenge patch containing vanilla was applied (under occlusion) for 48 h to a new site. Challenge patch application was preceded by a 1-h application of 10% aqueous SLS (under occlusion). Reactions were scored at the time of challenge patch removal and 24 h later. There was no evidence of contact sensitization in any of the subjects tested.

Photosensitization/Phototoxicity

In Vitro

Vanilla Tahitensis Fruit Extract

The phototoxicity of a trade name mixture containing 0.8% Vanilla Tahitensis Fruit Extract, 64.7% propylene glycol, and 34.5% water was evaluated in the neutral red uptake phototoxicity test (3T3 NRU test), using the SIRC fibroblast cell line.[46] The trade name mixture was diluted to the following test concentrations: 52.1 µg/ml, 104.2 µg/ml, 208 .3 µg/ml, 416.6 µg/ml, 833.3 µg/ml, 1666.6 µg/ml, 3333.3 µg/ml, and 6666.6 µg/ml. Fibroblasts were exposed for 50 min to test concentrations in the presence of ultraviolet (UV) light (1.7 mW/cm^2 long-wave UV (UVA) (~5 J/cm^2)). *Para*-aminobenzoic acid and chlorpromazine served as negative and positive controls, respectively. Cytotoxicity was not observed over the range of concentrations tested, and the trade name mixture had no phototoxic potential after UVA irradiation. Results for the positive and negative controls met expectations.

OCULAR IRRITATION STUDIES

In Vitro

Vanilla Tahitensis Fruit Extract

The ocular irritation potential of a trade name mixture containing 0.80% Vanilla Tahitensis Fruit Extract, 64.7% propylene glycol, and 34.5% water (tested at 10%; effective concentration of extract = 0.08%) was evaluated in the in vitro hen's egg chorioallantoic membrane test (HET-CAM).[46] Details relating to the test protocol are not included. Sodium chloride (0.9%) and lauryl sulfobetaine (3.2%) served as negative and positive controls, respectively. The test material was considered slightly irritating at the concentration tested. Results for the positive and negative controls met expectations.

CLINICAL STUDIES

Provocative Studies

Vanilla planifolia or Vanilla tahitensis fruit

The skin irritation potential of *Vanilla planifolia*- or *Vanilla tahitensis*-fruit was evaluated using 31 eczema patients.[49] Two were sensitive to wood tar, and one was sensitive to turpentine. Patch tests were performed using pieces (5 mm in length) of vanilla pods. The pieces were split, and the pulp side applied to the skin. For all patients, results were negative at 48 h, 96 h, and 120 h. In one case, a delayed reaction (undefined) was observed on day 9.

The skin sensitization potential of vanilla fruit (*Vanilla planifolia* and *Vanilla tahitensis*) was evaluated using 73 patients who were sensitive to balsam of Peru.[49] Patch tests (concentration not stated) were performed using pieces (5 mm in length) of vanilla fruit. The pieces were split, and the pulp side applied to the skin. The duration of patch application was not stated. Thirty-four patients (46% of patients tested) had positive reactions to both vanilla plant species. The authors noted that 58 of the 73 patients were described as consecutive, and 24 of the 58 had positive reactions. A consecutive case series is a clinical study that includes all eligible patients identified by the researchers during the study registration period. The patients are treated in the order in which they are identified. Ten of the remaining 15 patients had positive reactions, which may be ascribed to a selection of the patients examined. The authors also noted that these study results indicate that balsam of Peru cross-sensitizes to vanilla fruit.

Nine eczema patients from the preceding sensitization study were patch tested (protocol not stated) with a 10% w/w vanilla extract (alcohol extract) and 10% w/w vanilla extract (acetone extract).[49] The plant source of both extracts was either

Vanilla planifolia or *Vanilla tahitensis*. Seven of 9 patients had positive reactions to 10% w/w vanilla extract (alcohol extract), and 1 of 9 patients had a positive reaction to 10% w/w vanilla extract (acetone extract).

Case Reports

Vanilla Extract and Vanilla Fruit

Mostly positive patch test reactions have been reported in various case reports on a vanilla extract (12 report tests) and vanilla fruit (1 test). A summary of these reports appears below and the details relating to each report are presented in Table 10.

In a case report involving a tinea pedis patient, positive patch test reaction (+++) to a 10% w/w vanilla extract (alcohol extract) was observed on day 18.[49] A negative reaction to a 10% w/w vanilla extract (acetone extract) was reported on the same day. In the same patient, a positive (+++) patch test reaction to vanilla extract (concentration not stated) was reported. Four other case reports involved employees of a cookie/bread factory or bakery. Patch testing with vanilla extract (concentration not stated) yielded positive reactions (++ or +++) in all 4 reports.[49] In another case report, patch testing with vanilla extract yielded a ++ reaction; whether natural or synthetic vanilla was tested is unknown.[50] Additional case reports involved a patient with lip dermatitis who had positive (++) patch test reactions to 10% vanilla extract in petrolatum and a lip salve containing vanilla extract , and a photodermatitis patient with positive (++) patch test and photopatch test reactions to vanilla extract (concentration not stated) and vanilla fruit.[51,52] Negative results were reported for an eczema patient patch tested, for cross reactivity from balsam of Peru, with vanilla extract at concentrations of 10% and 25% in petrolatum.[53] Whether natural or synthetic vanilla was tested in this study is unknown.

SUMMARY

The safety of 9 vanilla-derived ingredients as used in cosmetics is reviewed in this CIR safety assessment. According to the *Dictionary*, 6 of the ingredients are reported to function as skin conditioning agents in cosmetic products, 2 are reported to function only as abrasives, and one as an antioxidant and skin protectant in cosmetics.

A method of manufacture of a Vanilla Tahitensis Fruit Extract trade name mixture consisting of 64.7% propylene glycol, 34.5% water, and 0.8% Vanilla Tahitensis Fruit Extract was submitted. Pods of *Vanilla tahitensis* are extracted using a mixture of propylene glycol and water. This process is followed by filtration, yielding the Vanilla Tahitensis Fruit Extract trade name mixture. A similar production method for another Vanilla Tahitensis Fruit Extract trade name mixture consisting of 68.7% butylene glycol, 30% water, and 1.3% Vanilla Tahitensis Fruit Extract was also submitted. The method is the same, except for the extraction of *Vanilla tahitensis* pods with a mixture of butylene glycol and water.

Most of the composition data in this safety assessment are on Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract, which contain numerous volatile components (one of which is vanillin). The amount of vanillin in vanilla extracts obtained from various regions of the world is approximately 2%. Furthermore, most commercial grade batches of vanilla beans (i.e., *Vanilla planifolia* fruit) from Madagascar, where reportedly the majority of vanilla is produced, contain 1.2 % to 2.2 % vanillin. The composition of a Vanilla Planifolia Fruit Extract trade name mixture is as follows: water (49% to 49.5%), propylene glycol (49% to 49.5%), and Vanilla Planifolia Fruit Extract (1% to 2%).

Various elements (e.g., magnesium, copper, zinc, and strontium) have been detected in *Vanilla planifolia* fruit from regions (Indonesia and Papua New Guinea) in two different continents.

The impurities content of a Vanilla Planifolia Fruit Extract trade name mixture has been described as less than the quantification limit of 0.01 mg/kg (for pesticide levels) and ≤ 10 ppm (for heavy metals content). Residues of the pesticide quintozene have been detected in *Vanilla planifolia* fruit. It has been reported that *Cymbidium mosaic* virus and the *Cucumber mosaic* virus have been detected in *Vanilla planifolia* plants growing in India.

According to 2020 VCRP data, Vanilla Planifolia Fruit Extract is reported to be used in 383 cosmetic products (240 leave-on products, 136 rinse-off products, and 7 products that are diluted for (bath) use). Of the vanilla-derived ingredients reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey conducted by the Council in 2017 indicate that Vanilla Planifolia Fruit Extract is used at maximum use concentrations up to 0.33% in leave-on products (face and neck products (not spray)) and up to 0.25% in rinse-off products (skin cleansing products). These are the highest use concentrations in leave-on and rinse-off products reported for the vanilla-derived ingredients reviewed in this safety assessment. According to VCRP and Council survey data, the following 2 ingredients are not currently in use in cosmetic products: Vanilla Planifolia Seed and Vanilla Tahitensis Seed.

Vanilla Planifolia Seed, Vanilla Planifolia Seed Powder, and Vanilla Tahitensis Seed are, according to the US FDA, GRAS for use as spices and other natural seasonings and flavorings in food. Additionally, Vanilla Planifolia Fruit Extract, Vanilla Tahitensis Fruit Extract, Vanilla Planifolia Fruit Oil, Vanilla Planifolia Fruit Water, Vanilla Planifolia Seed, Vanilla Planifolia Seed Powder, and Vanilla Tahitensis Seed are, according to the US FDA, GRAS in animal feed.

After 2 subjects ingested vanilla extract (ethanol extract), conjugated 3-methoxy-4-hydroxybenzylamine was detected in the urine 24 h later. No other toxicokinetics data were found in the literature or submitted.

In an acute dermal toxicity study on vanilla extract (ethanol extract) involving rats (number and strain not stated), the LD_{50} was determined to be > 2 g/kg. An acute oral LD_{50} of > 5 g/kg was reported in a study on vanilla extract (ethanol extract) involving rats (number and strain not stated).

The genotoxicity of a trade name mixture containing 1.3% Vanilla Tahitensis Fruit Extract was evaluated in the Ames test using *S. typhimurium* strains TA98, TA100, TA 102, TA1535, and TA1537. At doses of the test material up to 5 µL per plate (highest dose tested), with and without metabolic activation, the test material was found to be non-mutagenic and non-promutagenic.

The skin irritation potential of a trade name mixture containing 0.80% Vanilla Tahitensis Fruit Extract (tested at 10%; effective concentration of the extract = 0.08%) was evaluated for skin irritation potential in vitro using the PREDISKIN™ method (human skin samples). The test material did not cause any morphological alterations of human skin samples at the concentration tested, and was considered non-irritating. Moderate skin irritation was observed in rabbits (number not stated) after application of undiluted vanilla extract (ethanol extract) for 24 h. In a 48-h, single occlusive patch test involving 22 subjects, of a trade name mixture containing 0.80% Vanilla Tahitensis Fruit Extract (tested at 10%; effective concentration of the extract = 0.08%), the test material was classified as a non-irritant.

In a 48-h, occlusive patch test involving 5 male subjects, a vanilla extract (ethanol extract, 10% in petrolatum) did not induce skin irritation. The same material (10% in petrolatum) did not induce contact sensitization in a maximization test involving 25 male subjects. In an HRIPT involving 108 subjects, a leave-on product containing 0.02% Vanilla Planifolia Fruit Extract was a non-irritant and a non-sensitizer. However, a low-level reaction was observed in one subject during induction and in one subject during the challenge phase. A trade name mixture containing 0.80% Vanilla Tahitensis Fruit Extract (tested at 5%; effective concentration of the extract = 0.04%) was evaluated for skin sensitization potential in an HRIPT (occlusive patches) involving 55 subjects. The test material was classified as non-irritating and non-sensitizing.

The phototoxicity of a trade name mixture containing 0.80% Vanilla Tahitensis Fruit Extract was evaluated in vitro (3T3 NRU test, using the SIRC fibroblast cell line). The fibroblasts were exposed to the trade name mixture, diluted to test concentrations up to 6.7 µg/ml, in the presence of UVA light. No phototoxicity was observed.

Ocular irritation potential of a trade name mixture containing 0.80% Vanilla Tahitensis Fruit Extract (tested at 10%; effective concentration of the extract = 0.08%) was evaluated in the in vitro HET-CAM test. The test material was considered slightly irritating at the concentration tested.

In provocative studies, the skin irritation potential of *Vanilla planifolia* or *Vanilla tahitensis* fruit was evaluated using 31 eczema patients patch tested with vanilla fruit. Results were negative at 48 h, 96 h, and 120 h. In one patient, a delayed reaction (undefined) was observed on day 9.

The skin sensitization potential of *Vanilla planifolia* and *Vanilla tahitensis* fruit was evaluated using 73 patients (sensitive to balsam of Peru) patch tested with vanilla pods. Thirty-four patients (46% of patients tested) had positive reactions to pods from both vanilla plant species. Nine patients from the preceding study were patch tested with a 10% w/w vanilla extract (alcohol extract) and a 10% w/w vanilla extract (acetone extract). Seven of 9 patients had positive reactions to 10% w/w vanilla extract (alcohol extract), and 1 of 9 patients had a positive reaction to 10% w/w vanilla extract (acetone extract).

In a case report involving a tinea pedis patient, positive and negative patch test reactions to 10% w/w a vanilla extract (alcohol extract) and 10% w/w natural vanilla extract (acetone extract), respectively, were reported. A positive patch test reaction to vanilla extract (concentration not stated) in this patient was also reported. Additional case reports involved a patient with lip dermatitis who had positive patch test reactions to 10% vanilla extract in petrolatum and a lip salve containing a vanilla extract, and a photodermatitis patient with positive patch test and photopatch test reactions to a vanilla extract (concentration not stated) and vanilla fruit. The patch testing of individuals employed in the baking industry with a vanilla extract (concentration not stated) yielded positive reactions in 4 case reports. For another employee in the baking industry, a positive patch test reaction to a vanilla extract (whether natural or synthetic unknown; concentration not stated) was reported. Negative results were reported for an eczema patient patch tested with a vanilla extract (whether natural or synthetic unknown) at concentrations of 10% and 25% in petrolatum.

DISCUSSION

This report assesses the safety of cosmetic ingredients derived from the plants *Vanilla planifolia* and *Vanilla tahitensis*. Because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For vanilla-derived ingredients, the Panel was concerned about the presence of the following constituents, which are known sensitizers, in cosmetics: benzyl alcohol, benzaldehyde, linalool oxide, and limonene. Concern over cross-reactivity of cinnamyl alcohol, cinnamaldehyde, and methyl cinnamate with balsam of Peru was also expressed. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

The Panel discussed the positive (++) test reactions to vanilla extract observed in a photopatch test in a photodermatitis patient. However, because the strength of the reactions at photoirradiated and non-irradiated sites were the same, it was agreed that these test results do not warrant concern over photosensitization potential.

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

The following vanilla-derived ingredients are reported as used in products that are sprayed: Vanilla Planifolia Fruit Extract (concentrations up to 0.003% in hair spray and 0.013% in body and hand spray) and Vanilla Tahitensis (concentrations up to 0.002% in deodorant spray). Thus, the Panel discussed the issue of incidental inhalation exposure from formulations that may be aerosolized. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

Finally, the Panel determined that the available data are insufficient to arrive at a conclusion on the safety of Vanilla Planifolia Flower Extract and Vanilla Planifolia Leaf Cell Extract. The data requests on these two ingredients include:

- Method of manufacture and impurities
- Composition
- Concentration of use
- 28-day dermal toxicity
    - Depending on the results, other toxicological endpoints may be needed (e.g., genotoxicity and DART)

CONCLUSION

The CIR Expert Panel concluded that the following 7 vanilla-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing.

Vanilla Planifolia Fruit Extract
Vanilla Planifolia Fruit Oil
Vanilla Planifolia Fruit Water
Vanilla Planifolia Seed*
Vanilla Planifolia Seed Powder
Vanilla Tahitensis Fruit Extract
Vanilla Tahitensis Seed*

**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.*

The Panel further concluded that the available data are insufficient to support a conclusion of safety for Vanilla Planifolia Flower Extract and Vanilla Planifolia Leaf Cell Extract under intended conditions of use in cosmetic formulations.

TABLES

Table 1. Definitions and functions of the ingredients in this safety assessment.[1]

Ingredient CAS No.	Definition	Function(s)
Vanilla Planifolia Flower Extract 8024-06-4 84650-63-5	Vanilla Planifolia Flower Extract is the extract of the flowers of *Vanilla planifolia*.	Skin-Conditioning Agents - Miscellaneous
Vanilla Planifolia Fruit Extract 8024-06-4 84650-63-5	Vanilla Planifolia Fruit Extract is the extract of the fruit (bean) of *Vanilla planifolia*.	Skin-Conditioning Agents - Miscellaneous
Vanilla Planifolia Fruit Oil 8024-06-4 84650-63-5	Vanilla Planifolia Fruit Oil is the oil expressed from the fruit of *Vanilla planifolia*.	Skin-Conditioning Agents - Emollient
Vanilla Planifolia Fruit Water 8024-06-4 84650-63-5	Vanilla Planifolia Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Vanilla planifolia*.	Skin-Conditioning Agents - Miscellaneous
Vanilla Planifolia Leaf Cell Extract 8024-06-4 84650-63-5	Vanilla Planifolia Leaf Cell Extract is the extract of a culture of the leaf cells of *Vanilla planifolia*.	Antioxidants; Skin Protectants
Vanilla Planifolia Seed 8024-06-4 84650-63-5	Vanilla Planifolia Seed is the seed of *Vanilla planifolia*.	Skin-Conditioning Agents - Miscellaneous
Vanilla Planifolia Seed Powder 8024-06-4 84650-63-5	Vanilla Planifolia Seed Powder is the powder obtained from the dried, ground seeds of *Vanilla planifolia*.	Abrasives
Vanilla Tahitensis Fruit Extract 94167-14-3	Vanilla Tahitensis Fruit Extract is the extract of the fruit (bean) of *Vanilla tahitensis*.	Skin-Conditioning Agents - Miscellaneous
Vanilla Tahitensis Seed	Vanilla Tahitensis Seed is the seed of *Vanilla tahitensis*.	Abrasives

Table 2. Properties of a Vanilla Planifolia Fruit Extract Trade Name Mixture.[7]

Physical State	Liquid*
Color	Amber yellow to amber
Odor	Characteristic
pH	4.1 to 8.1
Relative density	1.0-1 to 1.08
Solubility	Soluble in water and in ethanol

*Trade name mixture consists of water, propylene glycol, and the fruit extract

Table 3. Volatile Components (expressed in mg/kg) of Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract (both dichloromethane extracts).[6]

Components	Vanilla Tahitensis Fruit Extract (fruit from Polynesian Cultivar: Tahiti)	Vanilla Tahitensis Fruit Extract (fruit from Polynesian Cultivar: Haapape)	Vanilla Tahitensis Fruit Extract (fruit commercial sample from Papua New Guinea)	Vanilla Planifolia Fruit Extract (fruit commercial sample from Madagascar)
Aldehydes				
Hexanal	52 ± 7	28 ± 3	43 ± 2	195 ± 42
Heptanal	11	8	---	7
Octanal	33 ± 1	23 ± 5	13	12 ± 4
Nonanal	84 ± 19	69 ± 2	23 ± 2	56 ± 2
(E)-2-Heptenal	---	8	9	25
(E)-2-Octenal	4 ± 1	4 ± 1	5 ± 1	---
(E)-2-Nonenal	12	11 ± 41	19 ± 8	46 ± 3
(E)-2-Decenal	13 ± 1	10 ± 3	7	22 ± 1
(E,E)-2,4-Decadienal	117	78	118	133
(E,Z)-2,4-Decadienal	---	46	75	111
3-Methylpentanal	30	48	28 ± 9	23 ± 0.1
Ketones				
2,3-Butanedione	203 ± 60	216 ± 60	65 ± 36	137 ± 44
2,3-Pentanedione	94 ± 20	85 ± 1	15	---
3-Hydroxy-2-butanone	145 ± 28	288 ± 185	49 ± 17	335 ± 23
Cyclohexanone	282 ± 64	132 ± 2	---	33
Acids				
Octanoic acid	384	252	322	409
Nonanoic acid	1116	642	310	862
Lauric acid	277	266	891	397
Myristic acid	209	261	479	224
Esters				
Methyl nicotinate	24	7	9	---
γ-Nonalactone	64	52	40	65
Methyl octanoate	---	---	12	---
Methyl nonanoate	---	---	15	---
Methyl decanoate	---	---	20	77
Methyl laurate	---	---	39	---
Methyl myristate	---	---	---	38
Methyl palmitate	---	---	24	---
Methyl stearate	---	---	346	110
Methyl oleate	---	---	25	---
Methyl linoleate	---	---	250	---
Methyl linolenate	---	---	101	49
Miscellaneous Chemicals				
3-Octanol	---	---	348 ± 6	493 ± 1
1-Octanol	76 ± 18	41 ± 0.1	35 ± 23	---
Furfural	973 ± 149	1325 ± 95	2097 ± 264	1615 ± 100
5-Methyl furfural	48 ± 23	43 ± 2	281 ±4	122 ± 12
Limonene	59	30	10	43
(E)-Linalool oxide	13	10	28	---

Table 3. Volatile Components (expressed in mg/kg) of Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract (both dichloromethane extracts).[6]

Components	Vanilla Tahitensis Fruit Extract (fruit from Polynesian Cultivar: Tahiti)	Vanilla Tahitensis Fruit Extract (fruit from Polynesian Cultivar: Haapape)	Vanilla Tahitensis Fruit Extract (fruit commercial sample from Papua New Guinea)	Vanilla Planifolia Fruit Extract (fruit commercial sample from Madagascar)
Anisyl Chemicals				
Anisyl alcohol	13,512 ± 3209	6420 ± 72	8876 ± 511	185 ± 99
Anisaldehyde	8906 ± 1225	7827 ± 3403	10,502 ± 4580	891 ± 37
Anisylmethylether	250	223	1510	---
Methyl anisate	6338 ± 177	5425 ± 1772	3902 ± 962	668 ± 30
Anisyl formate	171 ± 22	164 ± 6	317 ± 1	---
Anisyl acetate	4468 ± 354	2582 ± 318	3195 ± 465	215 ± 23
Anisic acid	104	146	182	---
p-Vinyl anisole	8	7 ± 4	9 ± 6	---
Cinnamyl Chemicals				
(E)-Cinnamyl alcohol	---	---	---	46 ± 4
(E)-Cinnamaldehyde	15	4	4	121
(Z)-Methyl cinnamate	207 ± 11	164 ± 32	183 ± 73	140 ± 86
(E)-Methyl cinnamate	1076 ± 186	898 ± 71	661 ± 29	574 ± 1
Phenolic Chemicals				
Benzyl alcohol	302 ± 56	232 ± 44	454 ± 108	341 ± 66
Benzaldehyde	30	28 ± 1	42 ± 2	50 ± 7
Benzyl acetate	9	8	26	9
Phenylethanol	41 ± 21	27 ± 6	96 ± 9	109 ± 27
Phenylacetaldehyde	54 ± 1	50 ± 11	48 ± 13	163 ± 53
Benzophenone	39 ± 13	38 ± 8	25	18
Acetophenone	3	5 ± 2	6 ± 1	---
4-Phenoxymethylbenzoate	515 ± 101	506 ± 35	292 ± 8	---
Phenol	183 ± 41	232 ± 4	509 ± 39	1225 ± 134
p-Vinylphenol	39	51	106 ± 12	104 ± 26
Guaiacol	653 ± 180	298 ± 44	614 ± 24	9099 ± 4291
p-Vinylguaiacol	2530 ± 599	1121 ± 60	2293 ± 118	1177 ± 56
p-Cresol	84 ± 18	167 ± 35	462 ± 65	199 ± 122
Creosol	88 ± 18	66 ± 1	303 ± 24	480 ± 17
p-Cresol methyl ether	46 ± 8	61 ± 8	45 ± 16	---
Vanillyl Chemicals				
Vanillin	4425 ± 911	1743 ± 81	4532 ± 673	8292 ±1585
Isovanillin	74	49	161	---

Table 4. Components* of Vanilla Planifolia and Vanilla Tahitensis Fruit Extracts (aqueous ethanol extract) From Plants in Different Geographic Regions.[16]

Region/Species	Vanillic acid	Vanillin	*p*-hydroxybenzoic acid	*p*-hydroxybenzaldehyde
Madagascar (*Vanilla planifolia*)	15.0	164.0	5.6	13.7
Indonesia (*Vanilla planifolia*)	7.7	117.0	3.4	9.3
Mexico (*Vanilla planifolia*)	13.0	90.0	4.0	7.0
Costa Rica (*Vanilla planifolia*)	12.0	135.0	5.2	14.0
Jamaica (*Vanilla planifolia*)	4.2	216.0	Not detected	8.4
Tonga (*Vanilla planifolia*)	7.6	197.0	2.1	10.0
Tahiti (*Vanilla tahitensis*)	4.4	103.0	32.8	13.0

*expressed as mg/100 ml of extract

Table 5. Concentrations* of 2- or 4- Methoxylated Constituents in Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract (aqueous pentane/diethyl ether extract).[17]

Constituents	Vanilla Planifolia Fruit Extract (from Madagascar)	Vanilla Planifolia Fruit Extract (from Comoro)	Vanilla Tahitensis Fruit Extract (from Tahiti)
2-Methoxylated Constituents			
2-Methoxy-4-Methylphenol	2	6	0.5
Eugenol	0.6	0.7	Not detected
2-Methoxy-4-Vinylphenol	Not detected	1	0.1
Vanillin	6201	8053	1501
Acetovanillone	4	5	1.0
Vanillyl alcohol	4	Not detected	1.0
4-Methoxylated Constituents			
Anisaldehyde	0.3	0.3	19
Anysyl acetate	Not detected	0.3	14
Anisyl alcohol	8	6	1175
Isovanillin	Not detected	Not detected	34
Methyl anisate	Not detected	0.5	3
Anisyl formate	Not detected	Not detected	0.9
Anisic acid	Not detected	Not detected	238

*expressed as µg/g

Table 6. Components of Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract

Extractants	Vanilla Tahitensis Fruit Extract	Vanilla Planifolia Fruit Extract
Enzyme mixture + ethanol		**Major Components** (μg/mL extract): 4-Hydroxy-3-methoxy benzyl alcohol (185 ± 0.13) , Vanillin (259 ± 0.17), 4-Hydroxy benzyl alcohol (64 ± 0.22), Vanillic acid (43 ± 0.04), 4-Hydroxy-and benzaldehyde (26 ± 0.04).[12]
TLEE + ethanol		**Major Components** (μg/mL extract): 4-Hydroxy-3-methoxy benzyl alcohol (222 ± 0.14), Vanillin (421 ± 0.24), 4-Hydroxy benzyl alcohol (105 ± 0.26), Vanillic acid (70 ± 0.02), and 4-Hydroxy-benzaldehyde (42 ± 0.05).[12]
Acetate buffer		**Glucoside Components** (amounts not stated): β-D-glucopyranoside of *p*-nitrophenol, β-D-glucopyranoside of vanillin, β-D-glucopyranoside of vanillic acid, β-D-glucopyranoside of *p*-hydroxybenzaldehyde, β-D-glucopyranoside of ferulic acid, β-D-glucopyranoside of *p*-cresol, β-D-glucopyranoside of 2-phenylethanol, β-D-glucopyranoside of guaiacol, β-D-glucopyranoside of creosol, β-D-glucopyranoside of vanillyl alcohol, β-D-glucopyranoside of glucoside A, and β-D-glucopyranoside of glucoside B.[18]
Headspace solid-phase microextraction		**Components** (%): 2-Hydroxy-propanamide (0.8), Acetic acid (4.21), (3-Methyl-oxiran-2-yl)-methanol (0.38), 3-Methyl-1-butanol (0.53), 2,4,5-Trimethyl-1,3-diboxolane (0.52), 2,3-Butanediol (5.61), Furfural (1.45), 3h-1,2,4-Triazole-3-thione, 1,2-dihydro- (1.21), 4-Ethyl-4-heptanol (2.54), α-Pinene (0.68), Benzaldehyde (0.48), 4,5-Dimethyl-2-cyclohexyl-1,3-dioxolane (1.23), 1-Octen-3-ol (0.74), 2-Pentyl-furan (0.85), 2-Pentadecyl-1,3-dioxepane (7.37), 2-Pyrrolidinethione (0.52), Acetoxyacetic acid tridec-2-ynyl ester (0.50), Benzyl alcohol (0.85), 1-Octanol (0.68), Guaiacol (15.54), Ethyl hydrogen succinate (0.52), Methyl salicylate (0.50), Methyl nonanoate (0.50), 1-(4-Methoxyphenyl)-1,3 – butanedione (0.38), 1-Methoxy-4-(1-propenyl)-benzene (0.41), Nonanoic acid (0.56), Vanillin (48.28), and Butylated hydroxytoluene (0.33).[19]
Not stated		**Amino Acid Components** (amount not stated): Alanine, α-Alanine, ß-Alanine, γ-Aminobutyric acid, Arginine, Aspartic acid, Cystine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Pipecolic acid, Proline, Serine, Threonine, Tyrosine, and Valine.[20]
Ethanol	**Components** (mg/kg dry matter): Isobutanal; 2,3-Butanedione (160-189); Isovaleraldehyde, 2,3-pentanedione (80-84); Valeraldehyde; 3-methyl-2-buten-1-ol; Hexanal (30-76); 3-methyl-2-butene-1-thiol; Isovaleric acid; 2-methylbutyric acid; 2-methylfuran-3-thiol; Methional; 2-acetylpyrroline; Dimethyltri-sulfide; 1-octen-3-one; (Z)–1,5-octadien-3-ol; 2,4-heptadienal; Octanal (26-46); p-Cresol methyl ether (21-67); Phenylacetaldehyde (55-104); p-Cresol (20-191); Guaiacol (267-526); (Z) 6-nonenal; Nonanal (70-141); Phenylethanol (23-35); (E,Z) 2,6-nonadienal; (E) 2-nonenal (8-30); Creosol (19-75); p-Menthenal; Anisaldehyde (6,337-10,233); (E) 2-decenal (8-58); Anisyl alcohol (2.0-5.7); (E,Z) 2,4-decadienal (59-117); (E,E) 2,4-decadienal (46); p-Vinylguaiacol (1,163-2,106); Methyl anisate (6,463-10,677); (E) methyl cinnamate (580-948); and Anisyl acetate (1076-4218).[9]	

Table 6. Components of Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract

Extractants	Vanilla Tahitensis Fruit Extract	Vanilla Planifolia Fruit Extract
Ethanol	**Key constituents in aroma chemistry of vanilla. Aromatic constituents**: Vanillin, Vanillyl alcohol, Vanillic acid, Isovanillin, Anisyl alcohol, Anisaldehyde, Methyl anisate, Anisyl formate, Anisyl acetate, Guaiacol, *p*-Vinylguaiacol, Creosol, Phenol, *p*-Vinylphenol, *p*-Cresol, Proto-catechuic acid, *p*-Hydroxybenzyl alcohol, *p*-Hydroxybenzaldehyde, *p*-Hydroxybenzoic acid, and Methyl *p*-hydroxybenzoate. **Aliphatic constituents**: 2,3-Butanedione, 2,3-Pentanedione, Hexanal, Octanal, Nonanal, (E)-2-Nonenal, (E)-2-Docenal, (E,E)-2,4-Decadienal, and (E,Z)-2,4-Decadienal.[5]	
Formic acid in 80% methanol	**Components** (amount no stated). **Flavonoids**: Cyanidin 3-O-(6″-p-coumaroyl-glucoside); Cyanidin; Kaempferol; Malvidin 3-O-arabinoside; Pelargonidin; Pelargonidin 3-O-arabinoside; Peonidin; Petunidin 3-O-galactoside; Petunidin 3-O-rutinoside; Xanthohumol; Phloretin; Phloretin 2′-O-xylosyl-glucoside; Dihydroquercetin; (+)-Catechin; (+)-Catechin 3-O-glucose; (-)-Epigallocatechin; Eriodictyol; 6-Geranylnaringenin; Hesperetin; Naringenin 7-O-glucoside; Pinocembrin; Sakuranetin; Apigenin 6,8-di-C-glucoside; Chrysoeriol 7-O-glucoside; Cirsilineol; Cirsimaritin; 7,4′-Dihydroxy-flavone; 5,6-Dihydroxy-7,8,3′,4′-tetramethoxyflavone; 6-Hydroxyluteolin 7-O-rhamnoside; Naringenin 7-O-glucoside; Naringin 6′-malonate; Nobiletin; Tetramethylscutellarein; 7,3′,4′-Trihydroxyflavone; 3,7-Dimethylquercetin; (-)-Epigallocatechin; Isorhamnetin; Isorhamnetin 3-O-galactoside; Isorhamnetin 3-O-glucuronide; Isorhamnetin 3-O-glucoside 7-O-rhamnoside; Myricetin; Kaempferide; Kaempferol; Quercetin 3-O-(6″-acetyl-galactoside) 7-O-rhamnoside; Quercetin 3-O-acetyl-rhamnoside; Spinacetin 3-O-glucosyl-(1-6)-glucoside; Dihydroquercetin 3-O-rhamnoside; Formononetin; 6″-O-Acetylgenistin; Genistin; 6″-O-Acetylglycitin; and 6″-O-Malonyldaidzin. **Lignins**: 1-Acetoxypinoresinol; Arctigenin; Cyclolariciresinol; and Dimethylmatairesinol. **Polyphenols**: Coumestrol; 3,4-Dihydroxyphenylglycol; Phlorin; Pyrogallol; 4-Vinylsyringol; 5-Heneicosylresorcinol; 5-Pentadecylresorcinol; Bisdemethoxycurcumin; Xanthotoxin; 2,3-Dihydroxy-1-guaiacylpropanone; 3,4-dihydroxyphenyl-2-oxypropanoic acid; 3-Methoxyacetophenone; Sinapaldehyde; Esculin; Acetyl eugenol; Juglone; Carnosol; Rosmanol; and p-HPEA-EDA. **Phenolic Acids**: Ellagic acid arabinoside; Gallic acid ethyl ester; Avenanthramide 2c; Avenanthramide 2f; Caffeoyl tartaric acid; Cinnamic acid; m-Coumaric acid; p-Coumaric acid ethyl ester; 3-p-Coumaroylquinic acid; p-Coumaroyl tartaric acid; Feruloyl glucose; 3-Feruloyl-quinic acid; Hydroxycaffeic acid; Rosmarinic acid; Sinapic acid; 3-Sinapoylquinic acid; Sinapal-dehyde; 3,4-Dihydroxyphenyl-acetic acid; Homoveratric acid; Dihydrocaffeic acid; Dihydro-p-coumaric acid; and 3,4-dihydroxyphenyl-2-oxypropanoic acid. **Stilbenes**: Resveratrol; Resveratrol 3-O-glucoside; Piceatannol; Pinosylvin; Pterostilbene; and d-Viniferin.[3]	
Ethanol/water and dichloromethane	**Components** (ppt): Anisyl alcohol (225); Anisic acid (87.4); Anisaldehyde (25); Dianisyl ether (3.1); Anisyl ethyl ether (15); Anisyl methyl ether (0.8); Anisyl anisate (6.6); Anisyl trans-cinnamate (0.5); Caffeine (0.1); Theobromine (0.1); α-Ionone (0.4); β-Ionone (0.4); Dihydroactinidiolide (0.2); Vitispirane (0.3); Anisyl 4-hydroxybenzoate (7.4); and Anisyl cis-cinnamate (0.2).[21]	
Ethanol and methanol	**Components** (g/100 g): p-Hydroxybenzoic acid (0.477-0.589); Vanillic acid (0.028-0.056); p-Hydroxybenzaldehyde (0.089-0.150); Vanillin (0.450-0.607); Anisyl alcohol (0.508-0.681); Ethylvanillin (negative, < 0.001); Piperonal (negative, < 0.001); Coumarin (negative, < 0.001); Anisic acid (0.429-0.560); *m*-Anisaldehyde (trace); *p*-Anisaldehyde (0.016-0.023); and Water (5.5-31.1).[22]	

Table 6. Components of Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract

Extractants	Vanilla Tahitensis Fruit Extract	Vanilla Planifolia Fruit Extract
Pentane	**Components** (%): Neutral lipid content in beans (9.3 ± 0.5); Unsaponifiable matter in neutral lipid fraction (19.5 ± 0.5); Hydrocarbon content in unsaponifiable matter (47.5); Hydrocarbon content in neutral lipid (9.2); and Hydrocarbon content in beans (0.6).[23]	
Pentane	**β-dicarbonyl compound Components** (~28% of the neutral lipids); following 5 identified (amount not stated): 16-Pentacosene-2,4-dione; 18-Heptacosene-2,4-dione; 20-Nonacosene-2,4-dione; 22-Hentriacontene-2,4-dione; and 24-Tritriacontene-2,4-dione.[24]	
Pentane and methylene chloride	**4-Demethylsterol Components** (%): Cholesterol (trace); Brassicasterol (0.02); Ergosta-5,25-dien-3β-ol— (2.4); Campesterol1.32 (not detected); 24-Methylene cholesterol1.36 (5.1); Stigmasterol1.44 (26.7); Stigmasten-22-ol (not detected); Stigmasta-5,22,25-trien-3β-ol (not detected); Ergosta-7,24(28)-dien-3β-ol (not detected); Stigmasta-5,23-dien-3β-ol (not detected); β-Sitosterol (57.5); Fucosterol (not detected); Δ5-Avenasterol (8.1); and Δ7-Avenasterol (trace).[25]	
Column Chromatography	**Hydrocarbon Components** (%). **Alkanes**: *n*-decane (0.6 ± 0.5); *n*-dodecane (0.6 ± 0.5); *n*-tetra-decane (0.4 ± 0.5); *n*-pentadecane (0.2 ± 0.5); *n*-hexadecane (2.4 ± 0.5); *n*-heptadecane (0.4 ± 0.5); *n*-octadecane (2.9 ± 0.5); *n*-nona-decane (7.9 ± 0.5); *n*-eicosane (2.2 ± 0.5); *n*-heneicosane (1.8 ± 0.5); *n*-docosane (4.6 ± 0.5); *n*-tricosane (7.8 ± 0.5); *n*-tetra-cosane (4.0 ± 0.5); *n*-pentacosane (9.0 ± 0.5); *n*-hexacosane (2.3 ± 0.5); *n*-heptacosane (7.5 ± 0.5); *n*-octacosane (2.7 ± 0.5); *n*-nona-cosane (12.8 ± 0.5); *n*-triacontane (10.8 ± 0.5); *n*-hentriacontane (6.0 ± 0.5); *n*-dotriacontane (1.7 ± 0.5); *n*-tritriacontane (0.7 ± 0.5); *n*-tetratriacontane (3.1 ± 0.5); *n*-pentatriacontane (1.9 ± 0.5); *n*-hexatriacontane (4.9 ± 0.5). **3-Methylalkanes**: 3-Methylpenta-decane (0.3); 3-Methylhepta-decane (0.4); 3-Methylnona-decane (0.5); 3-Methyleicosane (0.6); 3-Methyldocosane (11.4); 3-Methyltetracosane (26.4); 3-Methylhexacosane (54.2); 3-Methylhentriacontane (5.0); and 3-Methyltritriacontane (1.2). **Ethylalkanes**: 5-Ethyltetradecane (0.4); 5-Ethylhexadecane (0.8); 5-Ethyloctadecane (1.0); 5-Ethyl-pentacosane (10.0); 5-Ethylhepta-cosane (18.4); 5-Ethylnonacosane (41.5); 5-Ethylhentriacontane (25.9); 5-Ethyltritriacontane (2.0). **Alkenes**: 1-Tetradecene (not detected); 1-Hexadecene (0.2); 1-Octadecene (0.1); 1-Eicosene (0.9); 1-Docosene (0.8); 1-Trico-sene (1.0); 1-Pentacosene (2.0); 1-Heptacosene (21.1); 1-Nonaco-sene (23.2); 1-Hentriacontene (38.5); 1-Dotriacontene (0.4); and 1-Tritriacontene (11.8).[23]	

Table 7. Elements detected in *Vanilla planifolia* Fruit From Regions In Two Different Continents.[27]

Impurities (mg/kg) ± SD	Indonesia	Papua New Guinea
Sodium	86	86
Magnesium	1469 ± 179	1142 ± 74
Aluminum	79 ± 35	141 ± 84
Sulfur	976 ± 365	804 ± 301
Phosphorus	1201 ± 81	790 ± 60
Chlorine	2709 ± 427	527 ± 40
Potassium	20,786 ± 2532	10,715 ± 358
Calcium	3552 ± 698	1160 ± 389
Manganese	69 ± 16	23 ± 2
Iron	69 ± 28	102 ± 1
Copper	6 ± 1	13 ± 2
Zinc	21 ± 9	16 ± 4
Bromine	7 ± 16	0
Rubidium	63 ± 12	16
Strontium	67 ± 10	19 ± 7
Barium	44 ± 12	5 ± 3

Table 8. Components of *Vanilla planifolia* leaf.[30]

Components	Sun Leaf	Shade Leaf
Chlorophyll (Chl) a + b (µmol m^{-2})	309 ± 33	309 ± 13
Carotenoids (mmol mol Chl a + b^{-1})		
Neoxanthin	43.7 ± 1.7	45.7 ± 1.5
Sum of violaxanthin, antheraxanthin, and zeaxanthin	85 ± 3.9	29 ± 2.6
Lutein	249.2 ± 7.6	201.3 ± 5.4
Lutein epoxide	2.2 ± 1.2	not detectable
α-Carotene	3.1 ± 0.5	not detectable
β-Carotene	69.7 ± 8.2	63 ± 7.9

Table 9. Frequency (2020) and Concentration (2017) of Use According to Duration and Type of Exposure.[34,35]

	# of Uses	*Max Conc. of Use (%)*	*# of Uses*	*Max Conc. of Use (%)*	*# of Uses*	*Max Conc. of Use (%)*
	Vanilla Planifolia Fruit Extract		**Vanilla Planifolia Flower Extract**		**Vanilla Planifolia Fruit Oil**	
Totals*	**383**	**0.00005-0.33**	**61**	**NR**	**95**	**NR**
Duration of Use						
Leave-On	*240*	*0.00055-0.33*	*46*	*NR*	*56*	*NR*
Rinse off	*136*	*0.00005-0.25*	*5*	*NR*	*28*	*NR*
Diluted for (bath) Use	*7*	*0.0026-0.04*	*10*	*NR*	*11*	*NR*
Exposure Type						
Eye Area	3	0.036	1	NR	1	NR
Incidental Ingestion	14	0.007-0.055	NR	NR	3	NR
Incidental Inhalation- Sprays	16;99[a];79[b]	0.0005-0.013;0.14[a]	4;37[a]	NR	9;24[a];9[b]	NR
Incidental Inhalation- Powders	79[b]; 2[c]	0.00055-0.33[c]	NR	NR	9[b];3[c]	NR
Dermal Contact	346	0.00005-0.33	61	NR	87	NR
Deodorant (underarm)	4[a]	0.0004	NR	NR	4[a]	NR
Hair - Non-Coloring	22	0.0001-0.14	NR	NR	5	NR
Hair-Coloring	1	0.011	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	114	0.001-0.055	15	NR	33	NR
Baby Products	4	0.001	NR	NR	3	NR
	Vanilla Planifolia Fruit Water		**Vanilla Planifolia Leaf Cell Extract**		**Vanilla Planifolia Seed Powder**	
Totals*	**8**	**NR**	**5**	**NR**	**10**	**NR**
Duration of Use						
Leave-On	*8*	*NR*	*5*	*NR*	*4*	*NR*
Rinse off	*NR*	*NR*	*NR*	*NR*	*4*	*NR*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*	*2*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	2	NR	NR	NR
Incidental Inhalation- Sprays	2[a];3 [b]	NR	2[a]	NR	2[a];2[b]	NR
Incidental Inhalation- Powders	3[b]	NR	NR	NR	2[b]	NR
Dermal Contact	8	NR	3	NR	8	NR
Deodorant (underarm)	1[a]	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	2	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	2	NR	6	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Vanilla Tahitensis Fruit Extract					
	# of Uses	Conc. (%)				
Totals*	**20**	**0.00005-0.007**				
Duration of Use						
Leave-On	*17*	*0.00005-0.0008*				
Rinse off	*2*	*0.00005-0.007*				
Diluted for (bath) Use	*1*	*NR*				
Exposure Type						
Eye Area	NR	NR				
Incidental Ingestion	3	NR				
Incidental Inhalation- Sprays	2; 8[a]	0.002				
Incidental Inhalation- Powders	NR	0.0008[c]				
Dermal Contact	14	0.00005-0.002				
Deodorant (underarm)	NR	0.00005 (not spray) 0.002 (aerosol)				
Hair - Non-Coloring	3	0.00005-0.007				
Hair-Coloring	NR	NR				
Nail	NR	NR				
Mucous Membrane	4	0.00055				
Baby Products	NR	NR				

NR = Not Reported

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses

[a]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays

[b]Not specified these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories

[c]It is possible that these products may be powders, but it is not specified whether the reported uses are powders

Table 10. Case Reports on Vanilla Extract

Test Substance	Patients	Test Protocol	Results
10% w/w vanilla extract (alcohol extract) and 10% w/w vanilla extract (acetone extract)	Female tinea pedis patient with no history of occupational contact to vanilla	Patch test protocol details not included	A positive reaction (+++) to 10% w/w vanilla extract (alcohol extract) was observed on day 18. A negative reaction to 10% w/w vanilla extract (acetone extract) was reported on the same day.[49]
Vanilla extract (concentration not stated)	Female tinea pedis patient with no history of occupational contact with vanilla extract	Patch test protocol details not included	A positive reaction (+++) was observed on days 9, 11, 13, and 15. When the patch test was repeated, a positive reaction (+++) was observed on days 11, 13, and 15. [49]
Vanilla extract (concentration not stated)	Baker at a bread factory who presented with hand eczema. He did not recall any irritation reactions to vanilla extract or after the use of balsam of Peru for burns.	Patch test protocol details not stated	Positive (++) patch test reaction after 48 h and 96 h. [49]
Vanilla extract (concentration not stated)	Female bakery employee. Work included cleaning the bakery and washing the baker's work clothes. Patient presented with nummular eczema	Patch test protocol not stated	Patch test results were positive (+++).[49]
Vanilla extract (concentration not stated)	Assistant at a bakery presented with hand eczema	Patch test protocol not stated	Patch test results were positive (+++).[49]
Vanilla extracts (10% and 25% in petrolatum; whether or not this is natural or synthetic vanilla is unknown)	Female eczema patient	Patches were removed at day 2 and reactions were scored at days 2 and 4.	Negative results for both test concentrations.[53]
10% vanilla extract (from *Vanilla planifolia*) in petrolatum and a lip salve product containing vanilla extract (from *Vanilla planifolia*)	Girl with history of recurrent dermatitis lip dermatitis. She had used a variety of lip salves regularly over a 2-year period.	Patch test protocol not stated	Positive (++) patch test reactions to 10% vanilla extract in petrolatum and the lip salve.[52]
Vanilla extract (concentration not stated; whether or not this is natural or synthetic vanilla is unknown)	Female employee of a cookie factory presented with a 2-week history of eczema over both palms	48-h patch test (details not included)	Positive (2+) patch test reaction.[50]
Vanilla extract (concentration not stated) and vanilla fruit	Woman with photodermatitis after treatment of wounds with a gel containing ketoprofen and sunbathing days later. Whether or not vanilla extract or fruit were components of gel not stated. Acute exudative eczema observed at treated sites. This patient also received an oral dose of a medication (contained vanillin extract) for pharyngitis. Erythema and swelling (on face, neck, chest, forearms, and hands) were observed on the following day.	Patch and photopatch tests (protocols not stated) performed 2 months later	Patch test results for ketoprofen negative on days 2 and 4, but photopatch test results were positive (++ reaction). Patch test results for vanilla extract and vanilla fruit positive (++ reaction) on days 2 and 4, and photopatch test results were also positive (++ reaction).[51]

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2020 FDA VCRP Data

Vanilla Planifolia Fruit Extract

1A-Baby Shampoos	1
1B-Baby Lotions, Oils, Powders, and Creams	2
1C-Other Baby Products	1
2A-Bath Oils, Tablets, and Salts	2
2B-Bubble Baths	3
2D-Other Bath Preparations	2
3D-Eye Lotion	3
4A-Cologne and Toilet waters	5
4E-Other Fragrance Preparation	11
5A-Hair Conditioner	7
5F-Shampoos (non-coloring)	9
5G-Tonics, Dressings, and Other Hair Grooming Aids	4
5I-Other Hair Preparations	1
6C-Hair Rinses (coloring)	1
7C-Foundations	1
7E-Lipstick	14
7F-Makeup Bases	1
7I-Other Makeup Preparations	1
10A-Bath Soaps and Detergents	50
10B-Deodorants (underarm)	4
10E-Other Personal Cleanliness Products	43
11E-Shaving Cream	2
12A-Cleansing	22
12B-Depilatories	1
12C-Face and Neck (exc shave)	33
12D-Body and Hand (exc shave)	46
12F-Moisturizing	90
12G-Night	2
12I-Skin Fresheners	1
12J-Other Skin Care Preps	18
13C-Other Suntan Preparations	2
Total	**383**

Vanilla Planifolia Fruit

2A-Bath Oils, Tablets, and Salts	3
2B-Bubble Baths	1
7E-Lipstick	2
10A-Bath Soaps and Detergents	10
10E-Other Personal Cleanliness Products	4
12A-Cleansing	2
12C-Face and Neck (exc shave)	2
12D-Body and Hand (exc shave)	1
12F-Moisturizing	13
12G-Night	1
12J-Other Skin Care Preps	1

Total	**40**

Vanilla Planifolia Flower Extract

2A-Bath Oils, Tablets, and Salts	8
2B-Bubble Baths	2
3D-Eye Lotion	1
4B-Perfumes	1
4E-Other Fragrance Preparation	3
10A-Bath Soaps and Detergents	5
12F-Moisturizing	37
12J-Other Skin Care Preps	4
Total	**61**

Vanilla Planifolia Fruit Oil

1B-Baby Lotions, Oils, Powders, and Creams	3
2A-Bath Oils, Tablets, and Salts	9
2B-Bubble Baths	1
2D-Other Bath Preparations	1
3D-Eye Lotion	1
4B-Perfumes	3
4E-Other Fragrance Preparation	6
5A-Hair Conditioner	1
5E-Shampoos (non-coloring)	2
5G-Tonics, Dressings, and Other Hair Grooming Aids	2
7E-Lipstick	2
9A-Dentifrices	1
10A-Bath Soaps and Detergents	13
10B-Deodorants (underarm)	4
10E-Other Personal Cleanliness Products	6
12A-Cleansing	5
12C-Face and Neck (exc shave)	2
12D-Body and Hand (exc shave)	7
12F-Moisturizing	21
12G-Night	1
12J-Other Skin Care Preps	4
Total	**95**

Vanilla Planifolia Fruit Water

7C-Foundations	1
10B-Deodorants (underarm)	1
12C-Face and Neck (exc shave)	3
12F-Moisturizing	2
12J-Other Skin Care Preps	1
Total	**8**

Vanilla Planifolia Leaf Cell Extract

7E-Lipstick	2

12F-Moisturizing	2
12J-Other Skin Care Preps	1
Total	**5**

Vanilla Planifolia Seed - No FDA Data

Vanilla Planifolia Seed Powder

2A-Bath Oils, Tablets, and Salts	1
2B-Bubble Baths	1
5G-Tonics, Dressings, and Other Hair Grooming Aids	2
10A-Bath Soaps and Detergents	4
12C-Face and Neck (exc shave)	1
12D-Body and Hand (exc shave)	1
Total	**10**

Vanilla Tahitensis Fruit - No FDA Data

Vanilla Tahitensis Fruit Extract

2A-Bath Oils, Tablets, and Salts	1
4B-Perfumes	1
5B-Hair Spray (aerosol fixatives)	1
5F-Shampoos (non-coloring)	1
5G-Tonics, Dressings, and Other Hair Grooming Aids	1
7A-Blushers (all types)	1
7C-Foundations	2
7E-Lipstick	3
12F-Moisturizing	5
12H-Paste Masks (mud packs)	1
12J-Other Skin Care Preps	1
13B-Indoor Tanning Preparations	2
Total	**20**

Vanilla Tahitensis Seed - No FDA Data

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: December 3, 2019

SUBJECT: Draft Tentative Report: Safety Assessment of Vanilla-Derived Ingredients as Used in Cosmetics (draft prepared for the December 2019 CIR Expert Panel meeting)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Safety Assessment of Vanilla-Derived Ingredients as Used in Cosmetics.

Key Issue

On June 26, 2019 Dr. Anne Marie Api, RIFM, sent Wilbur Johnson an e-mail (copy attached) to clarify the human maximization test provided by RIFM. The material tested in the Kligman 1972 report was a vanilla tincture tested at 10% in petrolatum. The study was labeled 71-10-87, with 10 representing the concentration tested. This concentration still needs to be added to the Sensitization and Summary sections of the CIR report.

Additional Considerations

Method of Manufacture, Vanilla Planifolia Fruit Extract - Please delete "Vanilla extract" at the end of the first paragraph (or add a sentence with the subject Vanilla extract).

Dermal Irritation, Vanilla extract; Summary - The 48-hour patch tests in humans cited to reference 44 and reference 2 are the same study. Please check the reference section in reference 2 (RIFM monograph), the 48-hour patch test is cited to Kligman 1972, the same as reference 44 in the CIR report.

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Carol Eisenmann

From: Anne Marie Api <amapi@rifm.org>
Sent: Wednesday, June 26, 2019 3:36 PM
To: Wilbur Johnson
Cc: Carol Eisenmann
Subject: CIR review of vanilla ingredients

Dear Wilbur,

I learned that CIR is in the process of reviewing the safety of vanilla-derived ingredients. We provided data on vanilla (CAS 8024-06-4) and I wanted to clarify the data we provided on the human maximization test.

The study conducted by Kligman dated June 1, 1972 was on a sample of vanilla tincture labeled as 71-10-87. The first number "71 designates the year we received the sample and the "10" designates the concentration. As such it was tested at a concentration of 10% in petrolatum. The data have been reported in the monograph we published in 1982. The vanilla tested was a vanilla tincture which is an alcoholic extract of vanilla.

I hope this helps. Please let me know if I can help any further.

Sincerely,
Anne Marie
Note: my email is now amapi@rifm.org

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Visit our new Resource Center: http://fragrancematerialsafetyresource.elsevier.com/

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: January 14, 2020

SUBJECT: Tentative Report: Safety Assessment of Vanilla-Derived Ingredients as Used in Cosmetics (release date: December 16, 2019)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Vanilla-Derived Ingredients as Used in Cosmetics.

Abstract; Conclusion - It is not clear what is meant by "intended conditions of use in cosmetic formulations" for the insufficient data ingredients, especially for those ingredients with no uses or use concentrations reported.

Introduction - As it is not known if RIFM will review the materials with the INCI names Vanilla Planifolia Fruit and Vanilla Tahitensis Fruit, it would be better not to speculate that it is "probable" that these ingredients will be reviewed by RIFM. The fragrance industry does not use the same naming conventions as used for INCI names. It should be made clear that the "vanilla tincture" previously reviewed by RIFM is an ethanol extract.

Composition, *Vanilla planifolia* fruit - Please look at table 3 of reference 26. Although the units for vanillin content are not stated in the text of this reference, they are stated in table 3: "1.72 to 2.18", "1.38 to 2.45" and "1.37 to 2.45" should all be associated with units of g/100 g (not "units not stated").

Discussion - What are the "chemical and biological properties" of these ingredients that support safety? Much of the information in tables in this report concerns composition. Perhaps it should be stated that the composition was considered to support the safety of these ingredients.

Table 1 - As it is not clearly stated elsewhere in the report, it would be helpful to state that Vanilla Planifolia Fruit Oil is an essential oil. As this essential oil is produced by expression from the fruit, a method of manufacture frequently used for fixed oils, it is not clear from the definition that it is an essential oil.

Table 2 - It would be helpful to add a footnote to Table 2 to indicate the extraction solvent.