Safety Assessment of Vanilla-Derived Ingredients as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: May 10, 2019
Panel Date: June 6-7, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by 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: May 10, 2019

Subject: Draft Report on *Vanilla*-derived Ingredients

Enclosed is a draft report on 9 *Vanilla*-derived ingredients. This ingredient family comprises cosmetic ingredients that are derived from two vanilla species, *Vanilla planifolia* and *Vanilla tahitensis.* A Scientific Literature Review (SLR) was announced on March 28, 2019.

The attached report (*vanill062019rep*) includes the following unpublished data that were received from the Council:

(1) Use concentration data from a Council survey (*vanill062019data1*and *vanill062019data2)*
(2) Method of manufacture and composition data on 2 Vanilla Tahitensis Fruit Extract trade name mixtures (one containing 0.80% and the other containing 1.3% Vanilla Tahitensis Fruit Extract) (*vanill062019data3)*
(3) Safety test data on a trade name mixture containing 0.80% Vanilla Tahitensis Fruit Extract: ocular irritation (in vitro), skin irritation (in vitro, human skin samples), skin irritation (human), skin sensitization (human), and phototoxicity (in vitro) (*vanill062019data3)*
(4) Genotoxicity data (in vitro) on a trade name mixture containing 1.3% Vanilla Tahitensis Fruit Extract (*vanill062019data3)*

Also included in this package for your review are the CIR report history (*vanill062019hist*), flow chart (*vanill062019flow*), literature search strategy (*vanill062019strat*), ingredient data profile (*vanill062019prof*), 2019 FDA VCRP data (*vanill062019fda*), and comments that were received from the Council (*vanill062019pcpc*) on the SLR. The Council's comments have been addressed.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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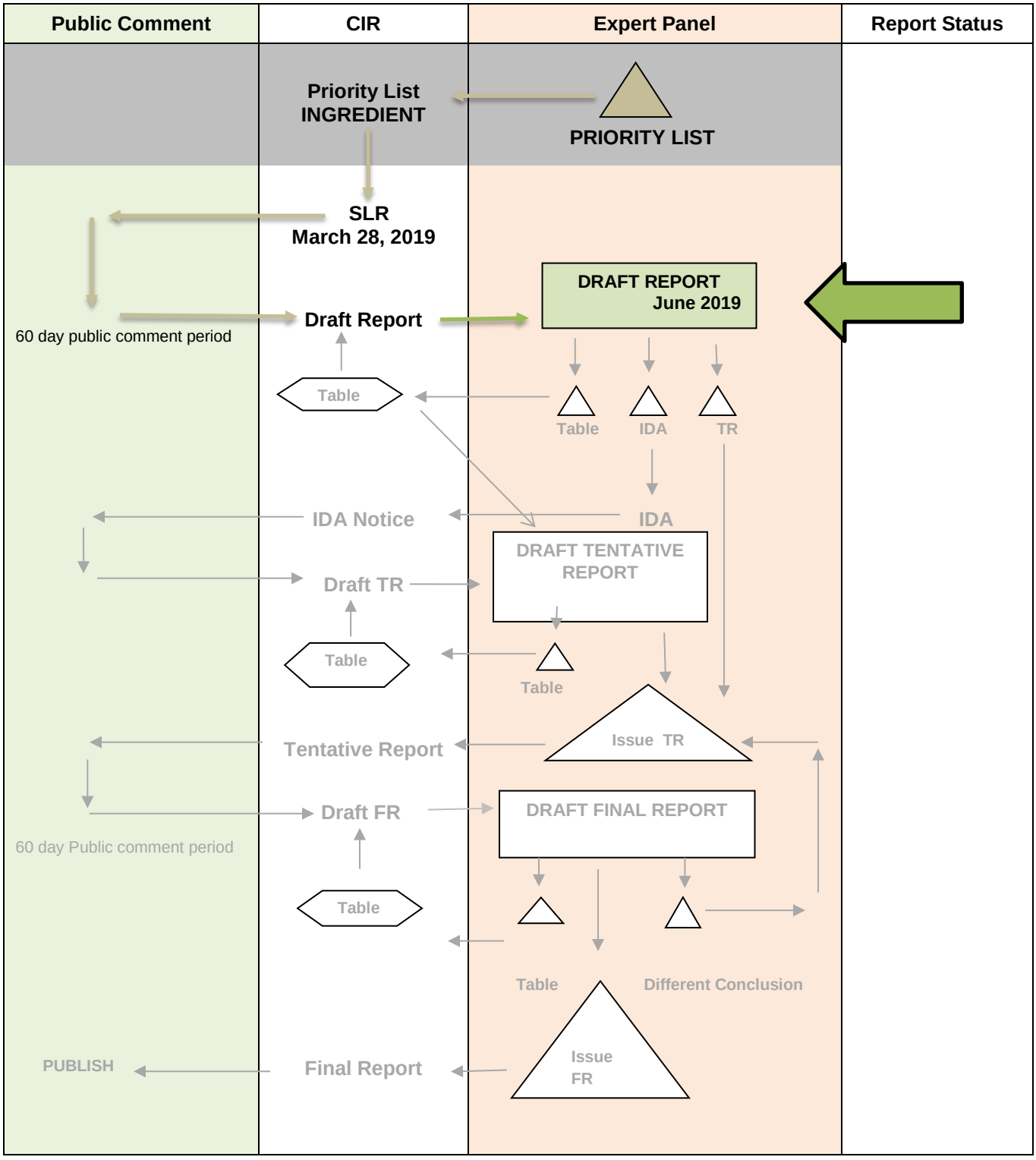
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Vanilla-derived Ingredients

MEETING June 2019



CIR History of:

Vanilla-derived Ingredients

A Scientific Literature Review (SLR) on Vanilla-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

Vanilla-derived Ingredients Data Profile* – June 6-7, 2019 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																												
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]

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

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

[*identify total # of hits /# hits that were useful or examined for usefulness*]

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	

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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 very likely that the safety of these will be reviewed by the Research Institute for Fragrance Materials (RIFM). (RIFM previously issued a monograph on "vanilla tincture."[2]) 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).

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]

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]

Vanilla Tahitensis Fruit Extract

According to one study, vanilla pods are harvested at full maturity in a shadehouse.[7] The vanilla pods are then cured according to the traditional Polynesian curing method in order to obtain ~ 50% moisture vanilla pods. Vanilla samples composed of cured vanilla pods are used for extraction (e.g., ethanolic extraction).

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 min. After cooling to ambient temperature, the beans are pureed in a laboratory grinder and separated into 2 equal portions (100 g each).[8] 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.

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.[9] 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.[10] 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 extract

Vanilla extract is generally prepared via either the percolation method or the oleoresin method.[11] 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.

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. These 2 islands were the locations of most of the vanilla production in French Polynesia at that time. These samples were analyzed by high performance liquid chromatography, together with 22 samples of *Vanilla planifolia* and 9 samples from Papua New Guinea.

Composition

Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract

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. These 2 islands were the locations of most of the vanilla production in French Polynesia at that time. These samples were analyzed by high performance liquid chromatography, together with 22 samples of *Vanilla planifolia* and 9 samples 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).[5] 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*.

According to the same study, 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 - 30%), 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). In a *Vanilla tahitensis* fruit extract, anisyl constituents represent 70% of the volatile content (~3.3% of the total extract composition). 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/Papua New Guinea), and in Vanilla Planifolia Fruit Extract from Madagascar (dichloromethane extract), are presented in Table 2.[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 3.[12] 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 4.[13] Table 5 contains composition data on Vanilla Tahitensis Fruit Extract and Vanilla Planifolia Fruit Extract, resulting from the use of various extractants.[3,5,7,8,14-21]

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%).[22] Another Vanilla Tahitensis Fruit Extract trade name mixture consists of: butylene glycol (68.7%), water (30%), and Vanilla Tahitensis Fruit Extract (1.30%).[23]

***Vanilla planifolia* fruit**

In commercial practice, size, shape and color serve as quality criteria for vanilla beans from Madagascar.[24] 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 (black beans), 1.38 to 2.45 (red non-split), and 1.37 to 2.18 (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.

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).[11] According to another source, vanilla extract contains alcohol (36%) and vanillin (0.199%).[25]

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.[26] 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 in Table 6.[27] 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.[28] 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**

Data on the elemental composition of *Vanilla planifolia* fruit harvested in Indonesia and in Papua New Guinea are presented in Table 7.[29] Residues of the pesticide, quintozene, have been detected in *Vanilla planifolia* fruit.[30]

***Vanilla planifolia* plant**

The *Cymbidium mosaic* virus has been detected in *Vanilla planifolia* plants grown in 2 states in India.[31]

***Vanilla planifolia* leaf**

The *Cucumber mosaic* virus has been detected in the leaves of *Vanilla planifolia* plants grown in southern India.[32]

USE

Cosmetic

The safety of 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.[33] 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.[34]

According to 2019 VCRP data, Vanilla Planifolia Fruit Extract is reported as being used in 370 cosmetic products (232 leave-on products, 133 rinse-off products, 5 products that are diluted for (bath) use).[33] Of the vanilla-derived ingredients reviewed in this safety assessment, this is the greatest reported use frequency of use. The 2019 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).[34] 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 8.

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.[35,36,37,38] 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.[35,36] 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.[36] 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.[33] 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.[34] 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.[39,40,41]

The vanilla-derived ingredients reviewed in this safety assessment are not included on the European Union's list of substances that are restricted or list of substances that are prohibited in cosmetic products.[34]

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

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.

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.)

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity 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.[42] 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).[43] 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.[43] 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 (concentration not stated) was applied, under occlusion, for 24 h to the back.[44] Because skin irritation was not observed, the decision to pretreat the skin with sodium lauryl sulfate (SLS) prior to patch application in the maximization test was made.

When tested at a concentration of 10% (in petrolatum) in a 48-h closed patch test involving human subjects, vanilla extract (ethanol) did not cause primary skin irritation.[2] The number of subjects tested and details relating to the test protocol were not stated.

Sensitization

Human

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 a human repeated insult patch test (HRIPT) involving 55 subjects.[43] 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, concentration not stated) was evaluated in a maximization test using 25 male subjects.[44] 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 Balb/c 3T3 (mouse strain) neutral red uptake phototoxicity test (3T3 NRU test), using the SIRC fibroblast cell line.[43] 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 hens's egg chorioallantoic membrane test (HET-CAM).[43] 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.[45] 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.[45] 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).[45] 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 details relating to each report are presented in Table 9.

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.[45] 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.[45] In another case report, patch testing with vanilla extract yielded a ++ reaction; whether natural or synthetic vanilla was tested is unknown.[46] 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.[47,48] 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.[49] 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.

Various elemental impurities (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. Residues of the pesticide quintozene have also 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 2019 VCRP data, Vanilla Planifolia Fruit Extract is reported to be used in 370 cosmetic products (232 leave-on products, 133 rinse-off products, and 5 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 *Salmonella 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. When tested at a concentration of 10% in a 48-h patch test involving human subjects (number not stated), primary skin irritation was not observed. In another 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 24-h, occlusive patch test involving 25 male subjects, a vanilla extract (concentration not stated) did not induce skin irritation. The same material (concentration not stated) did not induce contact sensitization in a maximization text involving the same 25 male subjects. 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

To be developed.

CONCLUSION]

To be determined.

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. 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)-Linalol oxide	13	10	28	---

Table 2. 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 3. Components* of Vanilla Planifolia and Vanilla Tahitensis Fruit Extracts (aqueous ethanol extract) From Plants in Different Geographic Regions.[12]

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 4. Concentrations* of 2- or 4- Methoxylated Constituents in Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract (aqueous pentane/diethyl ether extract).[13]

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 5. 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).[8]
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).[8]
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.[14]
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).[15]
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.[16]
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).[7]	
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]	

Table 5. Components of Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract

Extractants	Vanilla Tahitensis Fruit Extract	Vanilla Planifolia Fruit Extract
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).[17]	
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).[18]	
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).[19]	
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.[20]	

Table 5. Components of Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract

Extractants	Vanilla Tahitensis Fruit Extract	Vanilla Planifolia Fruit Extract
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).[21]	
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).[19]	

Table 6. Components of *Vanilla planifolia* leaf.[27]

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 7. Elements detected in *Vanilla planifolia* Fruit From Regions In Two Different Continents.[29]

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. Frequency (2019) and Concentration (2017) of Use According to Duration and Type of Exposure.[33,34]

	Vanilla Planifolia Fruit Extract		Vanilla Planifolia Flower Extract		Vanilla Planifolia Fruit Oil	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	**370**	**0.00005-0.33**	**58**	**NR**	**88**	**NR**
Duration of Use						
Leave-On	*232*	*0.00055-0.33*	*46*	*NR*	*52*	*NR*
Rinse off	*133*	*0.00005-0.25*	*5*	*NR*	*25*	*NR*
Diluted for (bath) Use	*5*	*0.0026-0.04*	*7*	*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;95[a];79[b]	0.0005-0.013;0.14[a]	4;37[a]	NR	9;20[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	334	0.00005-0.33	58	NR	80	NR
Deodorant (underarm)	NR;1[a]	0.0004	NR	NR	NR;4[a]	NR
Hair - Non-Coloring	21	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	111	0.001-0.055	12	NR	32	NR
Baby Products	4	0.001	NR	NR	3	NR

	Vanilla Planifolia Fruit Water		Vanilla Planifolia Leaf Cell Extract		Vanilla Planifolia Seed Powder	
Totals/Conc. Range	**7**	**NR**	**5**	**NR**	**10**	**NR**
Duration of Use						
Leave-On	*7*	*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];2[b]	NR	2[a]	NR	2[a];2[b]	NR
Incidental Inhalation- Powders	2[b]	NR	NR	NR	2[b]	NR
Dermal Contact	7	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/Conc. Range	**19**	**0.00005-0.007**
Duration of Use		
Leave-On	*16*	*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	13	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

Totals = Rinse-off + Leave-on + Diluted for Use Product 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 9. 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.[45]
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. [45]
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. [45]
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 (+++).[45]
Vanilla extract (concentration not stated)	Assistant at a bakery presented with hand eczema	Patch test protocol not stated	Patch test results were positive (+++).[45]
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.[49]
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.[48]
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.[46]
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).[47]

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2019 FDA VCRP Data

Vanilla Planifolia Fruit Extract

01A - Baby Shampoos	1
01B - Baby Lotions, Oils, Powders, and Creams	2
01C - Other Baby Products	1
02A - Bath Oils, Tablets, and Salts	1
02B - Bubble Baths	2
02D - Other Bath Preparations	2
03D - Eye Lotion	3
04A - Cologne and Toilet waters	5
04E - Other Fragrance Preparation	11
05A - Hair Conditioner	7
05F - Shampoos (non-coloring)	8
05G - Tonics, Dressings, and Other Hair Grooming Aids	4
05I - Other Hair Preparations	1
06C - Hair Rinses (coloring)	1
07C - Foundations	1
07E - Lipstick	14
07F - Makeup Bases	1
07I - Other Makeup Preparations	1
10A - Bath Soaps and Detergents	49
10B - Deodorants (underarm)	1
10E - Other Personal Cleanliness Products	43
11E - Shaving Cream	2
12A - Cleansing	21
12B - Depilatories	1
12C - Face and Neck (exc shave)	33
12D - Body and Hand (exc shave)	46
12F - Moisturizing	86
12G - Night	2
12I - Skin Fresheners	1
12J - Other Skin Care Preps	17
13C - Other Suntan Preparations	2
Total	**370**

Vanilla Planifolia Fruit

02A - Bath Oils, Tablets, and Salts	3
07E - Lipstick	2
10A - Bath Soaps and Detergents	10
10E - Other Personal Cleanliness Products	4
12A - Cleansing	1
12C - Face and Neck (exc shave)	2
12D - Body and Hand (exc shave)	1
12F - Moisturizing	12
12G - Night	1
12J - Other Skin Care Preps	1
Total	**37**

Vanilla Planifolia Flower Extract

02A - Bath Oils, Tablets, and Salts	6
02B - Bubble Baths	1
03D - Eye Lotion	1
04B - Perfumes	1
04E - Other Fragrance Preparation	3
10A - Bath Soaps and Detergents	5
12F - Moisturizing	37
12J - Other Skin Care Preps	4
Total	**58**

Vanilla Planifolia Fruit Oil

01B - Baby Lotions, Oils, Powders, and Creams	3
02A - Bath Oils, Tablets, and Salts	9
02B - Bubble Baths	1
02D - Other Bath Preparations	1
03D - Eye Lotion	1
04B - Perfumes	3
04E - Other Fragrance Preparation	6
05A - Hair Conditioner	1
05F - Shampoos (non-coloring)	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
07E - Lipstick	2
09A - Dentifrices	1
10A - Bath Soaps and Detergents	12
10B - Deodorants (underarm)	4
10E - Other Personal Cleanliness Products	6
12A - Cleansing	3
12C - Face and Neck (exc shave)	2
12D - Body and Hand (exc shave)	7
12F - Moisturizing	17
12G - Night	1
12J - Other Skin Care Preps	4
Total	**88**

Vanilla Planifolia Fruit Water

07C - Foundations	1
10B - Deodorants (underarm)	1
12C - Face and Neck (exc shave)	2
12F - Moisturizing	2
12J - Other Skin Care Preps	1
Total	**7**

Vanilla Planifolia Leaf Cell Extract

07E - Lipstick	2
12F - Moisturizing	2

12J - Other Skin Care Preps	1
Total	**5**

Vanilla Planifolia Seed - No FDA Data

Vanilla Planifolia Seed Powder

02A - Bath Oils, Tablets, and Salts	1
02B - Bubble Baths	1
05G - 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

02A - Bath Oils, Tablets, and Salts	1
04B - Perfumes	1
05B - Hair Spray (aerosol fixatives)	1
05F - Shampoos (non-coloring)	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
07A - Blushers (all types)	1
07C - Foundations	2
07E - Lipstick	3
12F - Moisturizing	5
12H - Paste Masks (mud packs)	1
13B - Indoor Tanning Preparations	2
Total	**19**

Vanilla Tahitensis Seed - No FDA Data

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Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: December 13, 2017

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

Concentration of Use by FDA Product Category – Vanilla-Derived Ingredients*

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
Vanilla Tahitensis Fruit Extract
Vanilla Tahitensis Seed

Ingredient	Product Category	Maximum Concentration of Use
Vanilla Planifolia Fruit Extract	Baby lotions, oils and creams Not powder	 0.001%
Vanilla Planifolia Fruit Extract	Bubble baths	0.0026-0.04%
Vanilla Planifolia Fruit Extract	Other bath preparations	0.0013%
Vanilla Planifolia Fruit Extract	Eyebrow pencils	0.036%
Vanilla Planifolia Fruit Extract	Colognes and toilet waters	0.0005%
Vanilla Planifolia Fruit Extract	Other fragrance preparations	0.001%
Vanilla Planifolia Fruit Extract	Hair conditioners	0.0001-0.011%
Vanilla Planifolia Fruit Extract	Hair sprays Aerosol	 0.003%
Vanilla Planifolia Fruit Extract	Shampoos (noncoloring)	0.0001-0.012%
Vanilla Planifolia Fruit Extract	Tonics, dressings and other hair grooming aids	0.14%
Vanilla Planifolia Fruit Extract	Other hair preparations (noncoloring)	0.006%
Vanilla Planifolia Fruit Extract	Hair dyes and colors	0.011%
Vanilla Planifolia Fruit Extract	Foundations	0.036%
Vanilla Planifolia Fruit Extract	Lipstick	0.007-0.055%
Vanilla Planifolia Fruit Extract	Bath soaps and detergents	0.001-0.04%
Vanilla Planifolia Fruit Extract	Deodorants Not spray	 0.0004%
Vanilla Planifolia Fruit Extract	Shaving cream	0.00043%
Vanilla Planifolia Fruit Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00005-0.25%
Vanilla Planifolia Fruit Extract	Face and neck products Not spray	 0.00055-0.33%
Vanilla Planifolia Fruit Extract	Body and hand products Not spray Spray	 0.005-0.18% 0.001-0.013%
Vanilla Planifolia Fruit Extract	Pastes masks and mud packs	0.0001%
Vanilla Planifolia Fruit Extract	Other skin care preparations	0.0009-0.0023%
Vanilla Tahitensis Fruit Extract	Hair conditioners	0.00005-0.007%
Vanilla Tahitensis Fruit Extract	Shampoos (noncoloring)	0.00005-0.007%
Vanilla Tahitensis Fruit Extract	Bath soaps and detergents	0.00055%
Vanilla Tahitensis Fruit Extract	Deodorants Not spray	 0.00005%

	Aerosol	0.002%
Vanilla Tahitensis Fruit Extract	Body and hand products Not spray	 0.0008%

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

Information collected in 2017
Table prepared December 13, 2017

Personal Care Products Council
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Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: March 5, 2019

SUBJECT: Vanilla Tahitensis Fruit Extract

CEP-Solabia Group. 2009. Manufacturing process Vanirea UP (Propylene Glycol, Water and Vanilla Tahitensis Fruit Extract).

CEP-Solabia Group. 2009. Ingredient breakdown Vanirea UP (Propylene Glycol, Water and Vanilla Tahitensis Fruit Extract).

CEP-Solabia Group. 2019. Summary of safety studies Vanirea UP (Propylene Glycol, Water and Vanilla Tahitensis Fruit Extract).

CEP-Solabia Group. 2009. Manufacturing process Vanirea BG UP (Butylene Glycol, Water and Vanilla Tahitensis Fruit Extract).

CEP-Solabia Group. 2009. Ingredient breakdown Vanirea BG UP (Butylene Glycol, Water and Vanilla Tahitensis Fruit Extract).

CEP-Solabia Group. 2019. Summary of Ames Assay Vanirea BG UP (Butylene Glycol, Water and Vanilla Tahitensis Fruit Extract).

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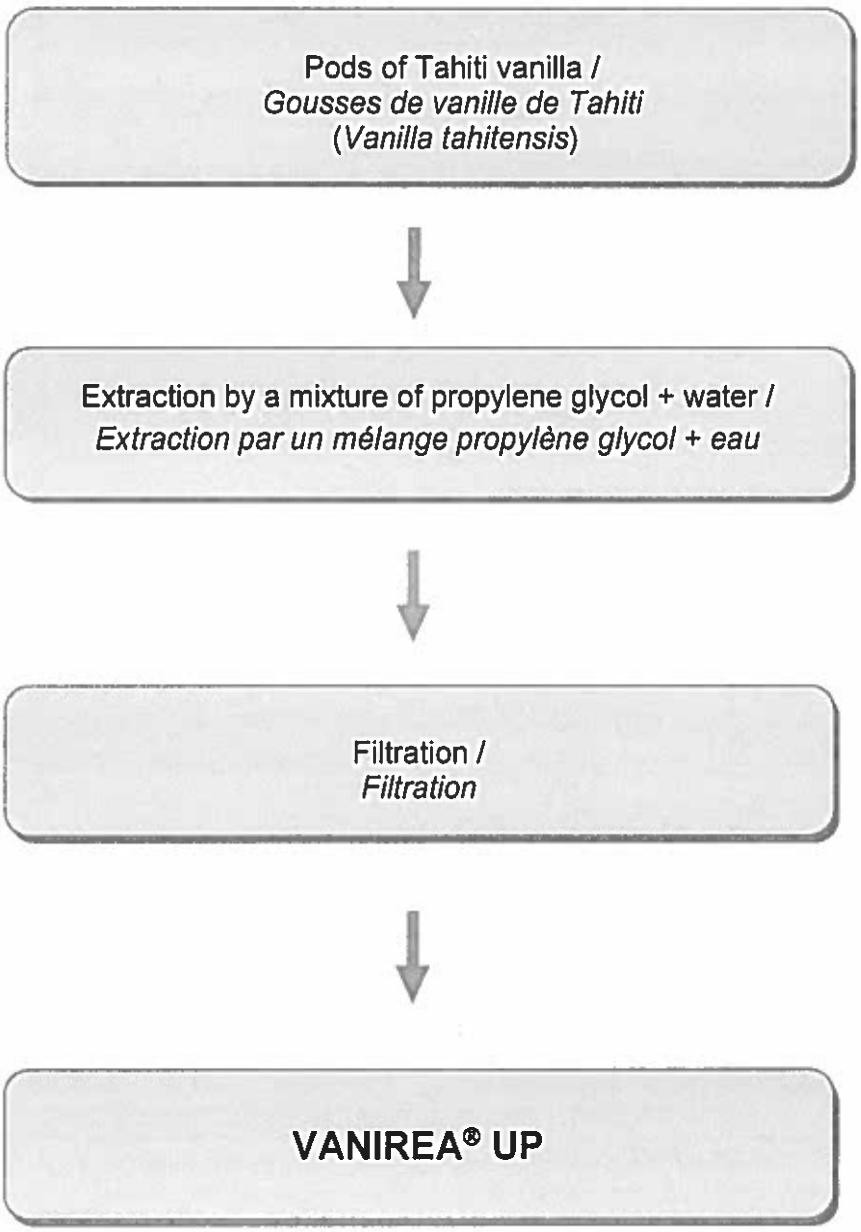
MANUFACTURING PROCESS
PROCEDE DE FABRICATION

VANIREA® UP

Ref. FA513



Produced & Commercialized by CEP - SOLABIA Group
29 Rue Delizy - 93698 Pantin Cedex France
Tel 33 (0)1 48 10 19 40 - Fax 33 (0)1 48 91 18 77 - www.solabia.com

INGREDIENT BREAKDOWN
COMPOSITION CENTESIMALE

VANIREA® UP

Ref. FA513

Propylene glycol	**64.70 %**
Water	**34.50 %**
Vanilla tahitensis fruit extract *expressed as dry extract, 12 hours at 105°C.*	**0.80 %**

Notes - *Remarques :*

- Because of the natural origin of the raw material, the centesimal composition is susceptible to slight variations.

  En raison de l'origine naturelle des matières premières, la composition centésimale est susceptible de subir une légère variation.

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CEP-SOLABIA Group 2019
Summary of Safety Studies
Vanirea UP (64.7% Propylene Glycol, 34.5% Water, 0.8% Vanilla Tahitensis Fruit Extract)

HET-CAM
Study completed in 2002
Sodium chloride (0.9%) was used as the negative control; lauryl sulfobetaine (3.2%) was used as the positive control
The test product (Vanirea UP) was tested at 10%
The controls showed the expected results
Results: The test product was considered slightly irritating at 10%.

Ex Vivo Cutaneous Tolerance using the PREDISKIN method
Study completed in 2002
Test in human skin collected after plastic surgery; 20 hours exposure; morphology of skin assessed by histological observations
Positive control sodium dodecyl sulphate 20 mg/ml
The test product (Vanirea UP) was tested at 10%
Results: Under the experimental conditions, Vanirea UP did not cause any morphological alterations of human skin samples when applied at 10%. The product can be considered as non-irritating, when applied at 10%.

48-Hour Single Patch Test in Humans
Study completed in 2002
The test product (Vanirea UP) was tested at 10% under occlusive conditions
Number of subjects: 22
Skin examined 30 minutes and 24 hours after patch removal.
Results: Non-irritant

Human RIPT (Marzulli and Maibach method)
Study completed in 2002
The test product (Vanirea UP) was tested at 5% in distilled water; 0.02 mL applied to disc of filter paper (7 mm diameter) applied to arm skin and kept in contact with the skin under occlusive patch (9 induction patches; 48 or 72 hours); 15 day rest period; Challenge 0.02 ml of the test article in 5% dilution in distilled water was applied to back skin for 48 hours.
Number of subjects: 55
Results: No irritation or sensitization reaction indicating a cutaneous intolerance was noted. The test article at 5% was non-irritating and non-sensitizing.

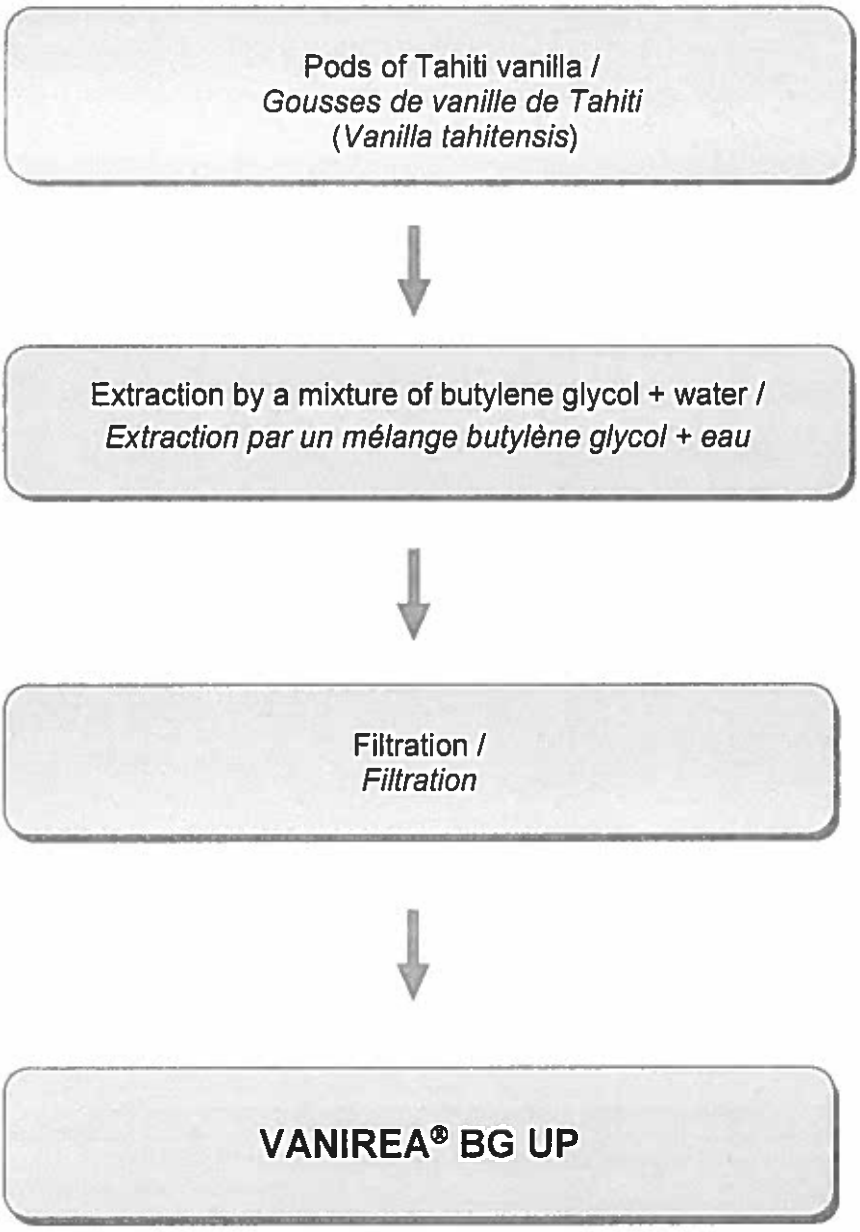
Phototoxicity – 3T3 NRU
Study completed in 2002
PABA was used as a negative control; chlorpromazine served as the positive control
Cell line: SIRC fibroblast cell line

The test product (Vanirea UP) was diluted in Hanks Balance Salt Solution without phenol red completed with calcium chloride and magnesium sulfate. Concentrations tested were 52.1, 104.2, 208.3, 416.6, 833.3, 1666.6, 3333.3 and 6666.6 µg/ml
UV exposure was 50 min with 1.7 mW/cm^2 UVA (~ 5 J/cm^2)
Controls gave the expected results
Results: The test product did not show any cytotoxicity up to the highest test concentration.
The test product had no phototoxic potential after UVA irradiation.

MANUFACTURING PROCESS
PROCEDE DE FABRICATION

VANIREA® BG UP

Ref. FA523



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INGREDIENT BREAKDOWN
COMPOSITION CENTESIMALE

VANIREA® BG UP

Ref. FA523

Butylene glycol	68.70 %
Water	30.00 %
Vanilla tahitensis fruit extract *12 hours at 105°C.*	1.30 %

Notes - *Remarques :*

- Because of the natural origin of the raw material, the centesimal composition is susceptible to slight variations.

  En raison de l'origine naturelle des matières premières, la composition centésimale est susceptible de subir une légère variation.

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CEP-SOLABIA Group - 2019
Summary of Ames Assay
Vanirea BG UP (68.7% Butylene Glycol, 30% water, 1.3% Vanilla Tahitenisis Fruit Extract)

Assay completed in 2007

Method: OECD Guideline 471

Salmonella typhimurium strains: TA98, TA100, TA102, TA1535 and TA1537

Doses: 0.05, 0.167, 0.5, 1.67 or 5 µL undiluted Vanirea BG UP/plate; solvent control (negative control) and standard mutagens used a positive control

Tested in the presence and absence of an exogenous metabolic activation system.

Results: The test item was found to be non-mutagenic and non-promutagenic under the test conditions.

Personal Care Products Council
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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: April 23, 2019

SUBJECT: Scientific Literature Review: Safety Assessment of Vanilla-Derived Ingredients as Used in Cosmetics (release date March 28, 2019)

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

Key Issues

In the Introduction, it would be helpful to note that RIFM published a monograph on "Vanilla Tincture" (an ethanol extract) (the monograph can be found in *Food and Chemical Toxicology* Volume 20 Supplement, 1982 p. 849-850). Was RIFM contacted to see if there are plans to complete a review of Vanilla Planifolia Fruit and Vanilla Tahitensis Fruit?

The 1982 RIFM monograph includes an oral LD_{50} of >5 g/kg for vanilla tincture in rats and a dermal LD_{50} of >2 g/kg in rabbits. This information should be added to the CIR report. Additional information in the RIFM monograph that should be added to the CIR report includes a rabbit dermal irritation test (moderately irritating; undiluted) and the concentration tested in the human maximization test (10% in petrolatum).

Additional Considerations

Method of Manufacture, Vanilla Tahitensis Fruit Extract - It is not clear why the method of manufacture for a Vanilla Planifolia Fruit Extract is presented under the Vanilla Tahitensis Fruit Extract subheading.

Composition - When describing the components of a *Vanilla tahitensis* fruit extract, it is not clear why the individual components are given as percentages while the total is given as ppm (components listed appear to account for 100% of the content).

Composition, Vanilla extract - Please explain what is meant by "lead number". According to the 2nd edition (2019) of the *Handbook of Vanilla Science & Technology* (some pages available on the internet), lead number for vanilla represents the organic acid content of

vanilla extracts and there is an AOAC method for its determination. Please add the units for vanillin composition.

Non-Cosmetic Use; Summary - It should be made clear that vanilla extracts are considered GRAS for human consumption (21CFR 182.20) and animal consumption (21CFR 582.20). The CIR report seems to imply that vanilla extracts only have GRAS status for animal products. This is not correct.

Reference 37 - This reference does not appear to be complete as it says "In: 1972: 1-3". Does CIR have unpublished report 1804 from RIFM, or did the information cited to this reference come from a secondary source?

Reference 42 - Is this (Scheman A, Gupta S. Photoallergic contact dermatitis from diallyl disulfide. Contact Dermatitis. 2001;45(3):179.) the correct reference for the case of an eczema patient patch tested for cross reactivity from balsam of Peru with vanilla extract?