
Safety Assessment of Vanilla-Derived Ingredients as Used in Cosmetics

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All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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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1620 L STREET, NW, SUITE 1200 ♦ WASHINGTON, DC 20036-4702 ♦ PH 202.331.0651 ♦ FAX 202.331.0088 ♦ CIRINFO@CIR-SAFETY.ORG

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*), most of these ingredients function as skin conditioning agents in cosmetic products.¹ Vanilla Planifolia Fruit and Vanilla Tahitensis Fruit are only reported to function as fragrance ingredients in cosmetics, and it is very likely that the safety of vanilla will be reviewed by the Research Institute for Fragrance Materials (RIFM). Thus, the safety of Vanilla Planifolia Fruit and Vanilla Tahitensis Fruit in cosmetics will not be reviewed by CIR. However, because Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract are extracts of Vanilla Planifolia Fruit and Vanilla Tahitensis Fruit, respectively, data therein are included in this report for use in the safety evaluation of these other fruit-derived ingredients (which have do not function as a fragrance). Regarding the vanilla-derived ingredients that are being reviewed in this safety assessment, most are reported to function as skin conditioning agents, but 2 are reported to function only as abrasives (See Table 1)

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 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*.² 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 the primary component of the extract of the vanilla bean.³ 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.⁴ *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.⁵

Method of Manufacture

Vanilla planifolia fruit and *Vanilla tahitensis* fruit

The curing method for *Vanilla planifolia* and *Vanilla tahitensis* 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.⁵

Vanilla Tahitensis Fruit Extract

According to one study, vanilla pods are harvested at full maturity in a shadehouse.⁶ 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).⁷ To the first portion, 1% v/v of a mixture of arabinases, cellulases, hemicellulases, xylanases, and pectinases from *Aspergillus* was added. Tea leaf enzyme extract (TLEE, 2% v/v) was added to the second portion. Addition of the enzyme mixture/enzyme extract was followed by incubation at 50 °C for 12 h. Ethyl alcohol (equal volume w/w) was added to the reaction mixture for extraction of vanilla constituents. The entire mixture was passed through the improvised filter paper to obtain Vanilla Planifolia Fruit Extract.

Vanilla extract

Vanilla extract is generally prepared via either the percolation method or the oleoresin method.⁸ The percolation method consists of circulating a solvent, an ethanol/water solution (in the range 35 - 50:65:50 (v/v)), over and through the beans under vacuum. The oleoresin method consists of pulverizing whole beans and then circulating ethanol over the beans under vacuum at ~ 45°C. The excess alcohol is removed by evaporation.

Composition

Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract

A *Vanilla planifolia* fruit extract consists mostly of vanillin (80% of the total quantified).⁴ Anisyl constituents represent 7% of the volatile content. Of the anisyl constituents identified, the major ones 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*.

A *Vanilla tahitensis* fruit extract contains *p*-hydroxybenzyl or vanillyl derivatives, but also consists predominantly of anisyl derivatives.⁴ Data on the concentrations of a *Vanilla tahitensis* fruit extract components are as follows: vanillin (25 - 30%), anisyl alcohol (30%), anisic acid (15%), *p*-hydroxybenzyl constituents (20%), and protocatechyl derivatives (5%), for a total content of 47,000 ppm. In a *Vanilla tahitensis* fruit extract, anisyl constituents represent 70% of the volatile content. Like *Vanilla planifolia*, the major *Vanilla tahitensis* fruit extract anisyl constituents identified are: anisyl alcohol, anisaldehyde, methyl anisate, and anisyl acetate. The vanillin content of *Vanilla tahitensis* fruit extract ranges from 5 - 10%. *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 2.⁵ 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 3.⁹ 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 4.¹⁰ Table 5 contains composition data on Vanilla Tahitensis Fruit Extract and Vanilla Planifolia Fruit Extract resulting from the use of various extractants.^{2,4,6,7,11-18}

Vanilla planifolia Fruit

In commercial practice, size, shape and color serve as quality criteria for vanilla beans from Madagascar.¹⁹ The commercial grades are described as follows: The black beans are the highest grade and are usually used in the retail market. The second quality is 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 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% (Reunion), 1.75% (Mexico), 1.75% (Caribbean), 1.70% (Tahiti), 1.75% (Indonesia), 1.5% (Sri Lanka), and 1.5% (India).⁸ According to another source, vanilla extract (specific gravity of 0.984; lead number of 0.66) contains alcohol (36%) and vanillin (0.199).²⁰

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.²¹ 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 6.²² 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.²³ 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 7.²⁴ Residues of the pesticide, quintozone, have been detected in Vanilla Planifolia fruit.²⁵

Vanilla planifolia

The *Cymbidium mosaic* virus has been detected in *Vanilla planifolia* plants grown in 2 states in India.²⁶

Vanilla planifolia leaf

The *Cucumber mosaic* virus has been detected in the leaves of *Vanilla planifolia* plants grown in southern India.²⁷

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.²⁸ 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.²⁹

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).²⁸ Of the vanilla-derived ingredients reviewed in this safety assessment, this is the greatest reported use frequency. 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).²⁹ These are the highest use concentrations in leave-on and rinse-off products reported for the vanilla-derived ingredients that 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.

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% and 0.00055%, respectively). Additionally, Vanilla Planifolia Fruit Extract could be incidentally ingested (at 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.^{30,31,32,33} 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.^{30,31}

According to 2019 VCRP data, some of the vanilla-derived ingredients are used in baby products, including baby lotions, oils, powders, and creams.²⁸ 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.²⁹ 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.^{34,35,36}

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.²⁹

Non-Cosmetic

Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract

In the US, 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 generally recognized as safe (GRAS) direct food additives, within the meaning of section 409 of the Federal Food, Drug, and Cosmetic Act [21 CFR 182.20; 21 CFR 582.20] (this regulation pertains to use in animal drugs, feed, and related products). Vanilla Planifolia Seed, Vanilla Planifolia Seed Powder, and Vanilla Tahitensis Seed are 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; 21 CFR 582.10].

TOXICOKINETIC STUDIES

Dermal Penetration

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

Absorption, Distribution, Metabolism, and Excretion

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

TOXICOLOGICAL STUDIES

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

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

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

GENOTOXICITY STUDIES

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

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 SENSITIZATION STUDIES

Irritation

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.³⁷ 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.

Sensitization

Vanilla extract

The skin sensitization potential of a vanilla extract (concentration not stated) was evaluated in the maximization test using 25 male subjects.³⁷ Initially, the volar forearm was pretreated for 24 h with 5% aqueous SLS (under occlusion). The test material was then applied to 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.

OCULAR IRRITATION STUDIES

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

CLINICAL STUDIES

Irritation

Vanilla planifolia or *Vanilla tahitensis* fruit

The skin irritation potential of *Vanilla planifolia*- or *Vanilla tahitensis*-fruit was evaluated using 31 eczema patients.³⁸ 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.

Sensitization

Vanilla Extract and *Vanilla planifolia* or *Vanilla tahitensis* fruit

The skin sensitization potential of vanilla fruit (*Vanilla planifolia* and *Vanilla tahitensis*) was evaluated using 73 patients who were sensitive to balsam of Peru.³⁸ 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. 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).³⁸ 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 18.³⁸ 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.³⁸ In another case report, patch testing with vanilla extract yielded a ++ reaction; whether natural or synthetic vanilla was tested is unknown.³⁹ 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 vanillaextract, and a photodermatitis patient with positive (++) patch test and photopatch test reactions to vanilla extract (concentration not stated) and vanilla fruit.^{40,41} 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.⁴² 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*, the following ingredients function as skin conditioning agents in cosmetic products, accounting for most of the ingredients reviewed in this safety assessment: Vanilla Planifolia Fruit Extract, Vanilla Planifolia Flower Extract, Vanilla Planifolia Fruit Oil, Vanilla Planifolia Fruit Water, Vanilla Planifolia Seed, and Vanilla Tahitensis Fruit Extract. Vanilla Planifolia Seed Powder and Vanilla Tahitensis Seed function as abrasives. Vanilla Planifolia Leaf Cell Extract is the only ingredient reported to function as an antioxidant and skin protectant in cosmetics.

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.

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 g vanillin/100 g.

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 quintozone 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.

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 direct food additives in animal feed. Additionally, 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.

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 test involving the same 25 male subjects.

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.

Nine patients from the following sensitization study were patch tested with a 10% w/w vanilla extract (alcohol extract) and another 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). 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

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 total. 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.

INFORMATION SOUGHT

The following data are requested for the vanilla-derived cosmetic ingredients reviewed in this safety assessment:

- 1) Method of manufacture data
- 2) Chemical characterization data
- 3) Impurities data
- 4) Dermal toxicity data
- 5) Genotoxicity data
- 6) Human skin irritation and sensitization data at maximum reported concentrations of use
- 7) Any additional data that would inform this safety assessment

TABLES

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

Ingredient CAS No.	Definition & Structures	Function(s)
Vanilla Planifolia Flower Extract 8024-06-4 84650-63-5	Vanilla Planifolia Flower Extract is the extract of the flowers of <i>Vanilla planifolia</i> .	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 <i>Vanilla planifolia</i> .	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 <i>Vanilla planifolia</i> .	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 <i>Vanilla planifolia</i> .	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 <i>Vanilla planifolia</i> .	Antioxidants; Skin Protectants
Vanilla Planifolia Seed 8024-06-4 84650-63-5	Vanilla Planifolia Seed is the seed of <i>Vanilla planifolia</i> .	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 <i>Vanilla planifolia</i> .	Abrasives
Vanilla Tahitensis Fruit Extract 94167-14-3	Vanilla Tahitensis Fruit Extract is the extract of the fruit (bean) of <i>Vanilla tahitensis</i> .	Skin-Conditioning Agents - Miscellaneous
Vanilla Tahitensis Seed	Vanilla Tahitensis Seed is the seed of <i>Vanilla tahitensis</i> .	Abrasives

Table 2. Volatile Components (expressed in mg/kg) of Vanilla Planifolia Fruit Extract and Vanilla Tahitensis Fruit Extract (both dichloromethane extracts).⁵

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)
<u>Aldehydes</u>				
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
<u>Ketones</u>				
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
<u>Acids</u>				
Octanoic acid	384	252	322	409
Nonanoic acid	1116	642	310	862
Lauric acid	277	266	891	397
Myristic acid	209	261	479	224
<u>Esters</u>				
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
<u>Miscellaneous Chemicals</u>				
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).⁵

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)
<u>Anisyl Chemicals</u>				
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	---
<i>p</i> -Vinyl anisole	8	7 ± 4	9 ± 6	---
<u>Cinnamyl Chemicals</u>				
(<i>E</i>)-Cinnamyl alcohol	---	---	---	46 ± 4
(<i>E</i>)-Cinnamaldehyde	15	4	4	121
(<i>Z</i>)-Methyl cinnamate	207 ± 11	164 ± 32	183 ± 73	140 ± 86
(<i>E</i>)-Methyl cinnamate	1076 ± 186	898 ± 71	661 ± 29	574 ± 1
<u>Phenolic Chemicals</u>				
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-Phenoxyethylbenzoate	515 ± 101	506 ± 35	292 ± 8	---
Phenol	183 ± 41	232 ± 4	509 ± 39	1225 ± 134
<i>p</i> -Vinylphenol	39	51	106 ± 12	104 ± 26
Guaiacol	653 ± 180	298 ± 44	614 ± 24	9099 ± 4291
<i>p</i> -Vinylguaiacol	2530 ± 599	1121 ± 60	2293 ± 118	1177 ± 56
<i>p</i> -Cresol	84 ± 18	167 ± 35	462 ± 65	199 ± 122
Creosol	88 ± 18	66 ± 1	303 ± 24	480 ± 17
<i>p</i> -Cresol methyl ether	46 ± 8	61 ± 8	45 ± 16	---
<u>Vanillyl Chemicals</u>				
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.⁹

Region/Species	Vanillic acid	Vanillin	<i>p</i> -hydroxybenzoic acid	<i>p</i> -hydroxybenzaldehyde
Madagascar (<i>Vanilla planifolia</i>)	15.0	164.0	5.6	13.7
Indonesia (<i>Vanilla planifolia</i>)	7.7	117.0	3.4	9.3
Mexico (<i>Vanilla planifolia</i>)	13.0	90.0	4.0	7.0
Costa Rica (<i>Vanilla planifolia</i>)	12.0	135.0	5.2	14.0
Jamaica (<i>Vanilla planifolia</i>)	4.2	216.0	Not detected	8.4
Tonga (<i>Vanilla planifolia</i>)	7.6	197.0	2.1	10.0
Tahiti (<i>Vanilla tahitensis</i>)	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).¹⁰

Constituents	Vanilla Planifolia Fruit Extract (from Madagascar)	Vanilla Planifolia Fruit Extract (from Comoro)	Vanilla Tahitensis Fruit Extract (from Tahiti)
<u>2-Methoxylated Constituents</u>			
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
<u>4-Methoxylated Constituents</u>			
Anisaldehyde	0.3	0.3	19
Anisyl 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 ($\mu\text{g/mL}$ 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). ⁷
TLEE + ethanol		Major Components ($\mu\text{g/mL}$ 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). ⁷
Acetate buffer		Glucoside Components (amounts not stated): β -D-glucopyranoside of <i>p</i> -nitrophenol, β -D-glucopyranoside of vanillin, β -D-glucopyranoside of vanillic acid, β -D-glucopyranoside of <i>p</i> -hydroxybenzaldehyde, β -D-glucopyranoside of ferulic acid, β -D-glucopyranoside of <i>p</i> -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. ¹¹
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-dioxolane (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). ¹²
Not stated		Amino Acid Components (amount not stated): Alanine, α -Alanine, β -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. ¹³
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); <i>p</i> -Cresol methyl ether (21-67); Phenylacetaldehyde (55-104); <i>p</i> -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); <i>p</i> -Menthonal; 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); <i>p</i> -Vinylguaiacol (1,163-2,106); Methyl anisate (6,463-10,677); (E) methyl cinnamate (580-948); and Anisyl acetate (1076-4218). ⁶	
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, <i>p</i> -Vinylguaiacol, Creosol, Phenol, <i>p</i> -Vinylphenol, <i>p</i> -Cresol, Proto-catechuic acid, <i>p</i> -Hydroxybenzyl alcohol, <i>p</i> -Hydroxybenzaldehyde, <i>p</i> -Hydroxybenzoic acid, and Methyl <i>p</i> -hydroxybenzoate. Aliphatic constituents: 2,3-Butanedione, 2,3-Pentanedione, Hexanal, Octanal, Nonanal, (E)-2-Nonenal, (E)-2-Decenal, (E,E)-2,4-Decadienal, and (E,Z)-2,4-Decadienal. ⁴	

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	<p>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-Geranylningenin; Hesperetin; Naringenin 7-O-glucoside; Pinoembrin; 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.</p> <p>Lignins: 1-Acetoxy-pinorensinol; Arctigenin; Cyclolariciresinol; and Dimethylmatairesinol.</p> <p>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; Sinapaldehyde; 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.²</p>	
Ethanol/water and dichloromethane	<p>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).¹⁴</p>	
Ethanol and methanol	<p>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).¹⁵</p>	
Pentane	<p>Components (%): Neutral lipid content in beans (9.3 \pm 0.5); Unsaponifiable matter in neutral lipid fraction (19.5 \pm 0.5); Hydrocarbon content in unsaponifiable matter (47.5); Hydrocarbon content in neutral lipid (9.2); and Hydrocarbon content in beans (0.6).¹⁶</p>	
Pentane	<p>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.¹⁷</p>	

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

Extractants	<i>Vanilla Tahitensis</i> Fruit Extract	<i>Vanilla Planifolia</i> Fruit Extract
Pentane and methylene chloride	4-Demethylsterol Components (%): Cholesterol (trace); Brassicasterol (0.02); Ergosta-5,25-dien-3 β -ol— (2.4); Campesterol 1.32 (not detected); 24-Methylene cholesterol 1.36 (5.1); Stigmasterol 1.44 (26.7); Stigmasten-22-ol (not detected); Stigmasta-5,22,25-trien-3 β -ol (not detected); Ergosta-7,24(28)-dien-3 β -ol (not detected); Stigmasta-5,23-dien-3 β -ol (not detected); β -Sitosterol (57.5); Fucosterol (not detected); Δ 5-Avenasterol (8.1); and Δ 7-Avenasterol (trace). ¹⁸	
Column Chromatography	Hydrocarbon Components (%). Alkanes: <i>n</i> -decane (0.6 \pm 0.5); <i>n</i> -dodecane (0.6 \pm 0.5); <i>n</i> -tetra-decane (0.4 \pm 0.5); <i>n</i> -pentadecane (0.2 \pm 0.5); <i>n</i> -hexadecane (2.4 \pm 0.5); <i>n</i> -heptadecane (0.4 \pm 0.5); <i>n</i> -octadecane (2.9 \pm 0.5); <i>n</i> -nonadecane (7.9 \pm 0.5); <i>n</i> -eicosane (2.2 \pm 0.5); <i>n</i> -heneicosane (1.8 \pm 0.5); <i>n</i> -docosane (4.6 \pm 0.5); <i>n</i> -tricosane (7.8 \pm 0.5); <i>n</i> -tetra-cosane (4.0 \pm 0.5); <i>n</i> -pentacosane (9.0 \pm 0.5); <i>n</i> -hexacosane (2.3 \pm 0.5); <i>n</i> -heptacosane (7.5 \pm 0.5); <i>n</i> -octacosane (2.7 \pm 0.5); <i>n</i> -nona-cosane (12.8 \pm 0.5); <i>n</i> -triacontane (10.8 \pm 0.5); <i>n</i> -hentriacontane (6.0 \pm 0.5); <i>n</i> -dotriacontane (1.7 \pm 0.5); <i>n</i> -tritriacontane (0.7 \pm 0.5); <i>n</i> -tetratriacontane (3.1 \pm 0.5); <i>n</i> -pentatriacontane (1.9 \pm 0.5); <i>n</i> -hexatriacontane (4.9 \pm 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-Ethyl-octadecane (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). ¹⁶	

Table 6. Components of *Vanilla Planifolia* leaf.²²

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

Table 7. Elements detected in *Vanilla Planifolia* Fruit From Regions In Two Different Continents.²⁴

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.^{28,29}

	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						
<i>Leave-On</i>	232	0.00055-0.33	46	NR	52	NR
<i>Rinse off</i>	133	0.00005-0.25	5	NR	25	NR
<i>Diluted for (bath) Use</i>	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 Leaf Cell Extract		Vanilla Planifolia Seed Powder	
Totals/Conc. Range	7	NR	5	NR	10	NR
Duration of Use						
<i>Leave-On</i>	7	NR	5	NR	4	NR
<i>Rinse off</i>	NR	NR	NR	NR	4	NR
<i>Diluted for (bath) Use</i>	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						
<i>Leave-On</i>	16	0.00005-0.0008				
<i>Rinse off</i>	2	0.00005-0.007				
<i>Diluted for (bath) Use</i>	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

^aIt is possible that these products may be sprays, but it is not specified whether the reported uses are sprays

^bNot 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

^cIt 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. ³⁸
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. ³⁸
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. ³⁸
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 (+++). ³⁸
Vanilla extract (concentration not stated)	Assistant at a bakery presented with hand eczema	Patch test protocol not stated	Patch test results were positive (+++). ³⁸
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. ⁴²
10% vanilla extract (from <i>Vanilla planifolia</i>) in petrolatum and a lip salve product containing vanilla extract (from <i>Vanilla planifolia</i>)	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. ⁴¹
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. ³⁹
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). ⁴⁰

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