PART B | COSMETIC PRODUCT SAFETY ASSESSMENT

1. Assessment conclusion

A detailed assessment was performed for the available information on the cosmetic product Macadeia Men Deodorant Body Spray - Wild.

This product is safe for human health when used under normal or reasonably foreseeable conditions.

The information provided in this report was assembled from reliable sources and based on current scientific knowledge. It is believed to be accurate at the date of this report's preparation.

For some ingredients, it was not possible to provide toxicological values or safety reference values, due to the inexistence of scientific studies. However, even without this information, based on the available information nowadays, it is unlikely that the ingredients of this specific formula, would exhibit toxicity or pose a risk for consumer's health. The specific ingredients that have been chosen for the manufacturing of this product have been used for years, for same products, without any known toxicity problems, under reasonable and foreseeable conditions of use. According to the available scientific information, all the ingredients are safe at the concentrations used in the formulation. The interaction between the ingredients in the cosmetic product and between these and the packaging material is not expected.

This assessment is valid until:

- Update or amendment to the current regulatory requirements concerning cosmetic products;

- Alteration of the cosmetic product's qualitative and quantitative formula;

- Alteration of the manufacturing method;

- Alteration of the packaging material and/or labelling;

- Safety Assessor has not timely access to information that may impact the risk-benefit ratio of the cosmetic product, such as information on serious adverse effects.

2. Labelled warnings and instructions of use

In accordance with the provisions of subparagraph d) of paragraph 1 of Article 19 of Regulation (EC) No 1223/2009 of November 30, 2009, it is not necessary to include any warning or instructions of use on the product's label, provided that all mandatory aerosol warnings and pictograms are displayed as required.

3. Reasoning

The product's safety assessment was based on the evaluation of the individual safety profile of each ingredient present in the formulation:

ALCOHOL DENAT.

FDA includes Alcohol (ethanol) on its list of direct food substances considered Generally Recognized as Safe (GRAS).[37] The safety of Alcohol and related ingredients has been assessed by the Cosmetic Ingredient Review Expert Panel. The CIR Expert Panel was not concerned with the safety of Alcohol as used in cosmetics and personal care products because, in comparison with the intake of Alcohol in alcoholic beverages, dermal application or inhalation of cosmetic products containing Alcohol would not produce significant systemic exposure to Alcohol.[18] This ingredient is considered acceptable for use in the cosmetic product under assessment.

BUTANE

The Cosmetic Ingredient Review (CIR) Expert Panel has already assessed the safety of Butane; Also, the European Chemicals Agency (ECHA) has a registration dossier for this ingredient. Butane is a low molecular weight alkane. The alkanes are characterized by singly bonded carbon atoms and have a low specific density, are nonpolar and cannot form hydrogen bonds; They are practically insoluble in water but are generally soluble in such low polarity liquids as benzene, carbon tetrachloride, chloroform, and other alkanes. Alkanes are primarily derived from petroleum and natural gas, and from the hydrogenation of alkenes. Butane is a by-product of petroleum refining or gasoline manufacturing and is used in organic syntheses and in the manufacture of ethylene, rubber, and high octane liquid fuels; It is also used as a household and industrial fuel, a solvent, a refrigerant, a standby and enricher gas, a propellant in aerosols, a Generally Recognised as Safe (GRAS) food additive, and an instrument calibration fluid. The human skin studies on the alkanes are few and incomplete, but such studies are not considered particularly important; As aerosols, Isobutane, Propane, Isopentane, and Butane are so greatly diluted in the air when discharged that the amount coming into contact with the skin is much less than the stated amounts used in the clinical tests; Since alkanes are highly volatile and have low water solubility, it is estimated that, as propellants, they would remain on the skin no longer than 10 seconds; Even the alkanes in foam products would not remain in contact with the skin longer than 10 sec; Such a short period of contact makes the absence of sensitization, phototoxicity, and photosensitization studies relatively unimportant. Many studies have been conducted on the anaesthetic effects of these ingredients on laboratory animals; Mice, rabbits, dogs, and monkeys that inhaled 25-35% concentrations of the ingredients in the air became anaesthetised to varying degrees; at somewhat greater concentrations, the animals died; The range of concentrations between those producing anaesthesia and death is narrow; A consistent effect of inhalation in all animals tested was sensitisation of the myocardium to epinephrine; It is believed, however, that these observations have little relevance to the advisability of the use of these ingredients in cosmetic formulations, because of the brief and low-level exposures involved in their use. Butane was mild to moderately irritating to the skin of rabbits.[3] Mutagenicity was assessed in an Ames Test performed in accordance with the OECD Guideline 471 (Bacterial Reverse Mutation Assay) using Salmonella typhimurium strains TA1535, TA100, TA97 and TA98, in the presence and absence of metabolic activation; Under the conditions of this study, Butane

was not mutagenic. There are no carcinogenicity studies available for any of the C1-C4 alkane gases which comprise the Petroleum Gases category; However, the weight of evidence from subchronic tests (up to 90 days), a consideration of their simple chemical structures, which have no reactive groups and carry no alerts for likely genotoxic carcinogenic activity from established Structure-Activity Relationship analysis, together with the conclusion that C1-C4 alkanes are not genotoxic, provide a strong case for concluding that none will show any significant carcinogenic activity; Taking these data into account, together with the general lack of toxicity across other endpoints, it is considered that there is no justification for conducting further animal carcinogenicity studies; This reasoning leads to the conclusion that Petroleum Gases category can be considered to have low concern for human carcinogenicity. There is also adequate information available from which to assess the potential of Petroleum Gases to induce reproductive or developmental effects and to conclude that classification is not warranted. No effects on offspring survival (to post-natal day 4), pup body weight, or macroscopic postmortem evaluations were observed in a 6-week study performed in accordance with OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)in which 0, 900, 3000, or 9000 ppm butane was administered to male and female rats by inhalation; The experimentally defined NOAEC is 9000 ppm (21394 mg/m3). Butane may contain very small amounts of 1,3-butadiene, which is produced during the refining of butane. Butane containing a concentration of butadiene equal or superior to 0,1 % is included in Annex II (List of substances prohibited in cosmetic products) to Regulation (EC) No 12223/2009 since it is classified as a carcinogenic (1A) and a mutagenic (1B) substance. The classification as a carcinogen or mutagen does not apply if it can be shown that the ingredient contains less than 0,1 % w/w 1,3- butadiene. In this situation, Butane is allowed in cosmetic products.[38] The CIR Expert Panel concluded that Butane is safe as a cosmetic ingredient in the described practices of use and concentration. In 2005, as part of the scheduled re-evaluation of ingredients, the Panel considered available new data on this ingredient and reaffirmed the above conclusion.[3] Taking into account the available toxicological data and having regard to the fulfilment of the maximum content of 1,3-butadiene, the ingredient Butane is considered acceptable for use in the cosmetic product under assessment.

PROPANE

The Cosmetic Ingredient Review (CIR) Expert Panel has already assessed the safety of Propane; Also, the European Chemicals Agency (ECHA) has a registration dossier for this ingredient. Propane is a low molecular weight alkane. The alkanes are characterized by singly bonded carbon atoms and have a low specific density, are nonpolar and cannot form hydrogen bonds; They are practically insoluble in water but are generally soluble in such low polarity liquids as benzene, carbon tetrachloride, chloroform, and other alkanes. Alkanes are primarily derived from petroleum and natural gas, and from the hydrogenation of alkenes. Propane is a by-product of petroleum refining or gasoline manufacturing is used in organic syntheses and in the manufacture of ethylene. It is also a household and industrial fuel, a solvent, refrigerant, gas enricher, aerosol propellant, extractant, and is a Generally Recognised as

Safe (GRAS) food additive. The human skin studies on the alkanes are few and incomplete, but such studies are not considered particularly important; As aerosols, Propane is so greatly diluted in the air when discharged that the amount coming into contact with the skin is much less than the stated amounts used in the clinical tests; Since alkanes are highly volatile and have low water solubility, it is estimated that, as propellants, they would remain on the skin no longer than 10 seconds; Even the alkanes in foam products would not remain in contact with the skin longer than 10 sec; Such a short period of contact makes the absence of sensitization, phototoxicity, and photosensitization studies relatively unimportant. Many studies have been conducted on the anaesthetic effects of these ingredients on laboratory animals; Mice, rabbits, dogs, and monkeys that inhaled 25-35% concentrations of the ingredients in the air became anaesthetised to varying degrees; at somewhat greater concentrations, the animals died; The range of concentrations between those producing anaesthesia and death is narrow; A consistent effect of inhalation in all animals tested was sensitisation of the myocardium to epinephrine; It is believed, however, that these observations have little relevance to the advisability of the use of these ingredients in cosmetic formulations, because of the brief and low-level exposures involved in their use. Propane was mild to moderately irritating to the skin of rabbits.[3] Mutagenicity was assessed in an Ames Test performed in accordance with the OECD Guideline 471 (Bacterial Reverse Mutation Assay) using Salmonella typhimurium strains TA1535, TA100, TA97 and TA98, in the presence and absence of metabolic activation; Under the conditions of this study, Propane was not mutagenic. There are no carcinogenicity studies available for any of the C1-C4 alkane gases which comprise the Petroleum Gases category; However, the weight of evidence from subchronic tests (up to 90 days), a consideration of their simple chemical structures, which have no reactive groups and carry no alerts for likely genotoxic carcinogenic activity from established Structure-Activity Relationship analysis, together with the conclusion that C1-C4 alkanes are not genotoxic, provide a strong case for concluding that none will show any significant carcinogenic activity; Taking these data into account, together with the general lack of toxicity across other endpoints, it is considered that there is no justification for conducting further animal carcinogenicity studies; This reasoning leads to the conclusion that Petroleum Gases category can be considered to have low concern for human carcinogenicity. There is also adequate information available from which to assess the potential of Petroleum Gases to induce reproductive or developmental effects and to conclude that classification is not warranted. No effects on offspring survival (to post-natal day 4), pup body weight, or macroscopic postmortem evaluations were observed in a 6-week study performed in accordance with OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)in which 0, 900, 3000, or 9000 ppm Butane was administered to male and female rats by inhalation; The experimentally defined NOAEC is 9000 ppm (21394 mg/m3). Due to the similar structure and and close relation of Butane and Propane, this value can be assumed to be valid for Propane as well. The CIR Expert Panel concluded that Propane is safe as a cosmetic ingredient in the described practices of use and concentration. In 2005, as part of the scheduled re-evaluation of ingredients, the Panel considered available new data on this ingredient and reaffirmed the above conclusion.[3] Taking into account the available toxicological

data[2] the ingredient Propane is considered acceptable for use in the cosmetic product under assessment.

ISOPROPYL PALMITATE

The safety of alkyl esters currently described as cosmetic ingredients has been assessed by the CIR Expert Panel[21] . These ingredients are the product of the reaction between fatty acids and alcohols. Although there are data gaps for individual ingredients, there are adequate data on many of the ingredients, and the relatedness of molecular structures, physicochemical properties, and functions and concentrations in cosmetics noted above allowed grouping these ingredients together and extending the available toxicological data to support the safety of the entire group. Earlier safety assessments had determined that dermal penetration of long-chain alcohols is predicted to be low, so the Panel extended that information to suggest that dermal penetration for alkyl esters is likely to be even lower. However, the Panel recognized that some of the alkyl esters can enhance the penetration of other ingredients through the skin. The ingredient Isopropyl Palmitate is reported to be used in topical formulations as a lipid layer penetration enhancer. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern. As some of the alkyl esters may be formed from plant-derived or animal-derived acid or alcohol constituents, the Panel thus expressed concern regarding pesticide residues and heavy metal that may be present in botanical ingredients. The Panel was also concerned that the potential exists for dermal irritation with the use of products formulated using some of the alkyl esters. The Panel specified that products must be formulated to be non-irritating. The Panel also noted that although no carcinogenicity data were available, the negative genotoxicity data coupled with the fact that dermal penetration is expected to be low led the Panel to conclude that carcinogenicity would not be a concern with cosmetic use. The Panel discussed the issue of incidental inhalation exposure to alkyl esters from powders and products that may be aerosolized. There were no repeated dose inhalation toxicity data available for the alkyl esters; however, the actual exposure in the breathing zone is small and given the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. Moreover, these ingredients are large molecules and most are quite insoluble in water, which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract. The Panel also considered the data available to characterize the potential for alkyl esters to cause systemic toxicity, irritation, sensitization, or other effects and concluded that ingredients of this family tend not to not to produce significant systemic toxicity in oral repeated-dose studies. The CIR Expert Panel concluded that Isopropyl Palmitate is safe in the practices of use and concentration described in the published safety assessment and when formulated to be non-irritating. Taking into account the available toxicological data, Isopropyl Palmitate is considered acceptable for use in the cosmetic product under assessment.

PARFUM

The parfum used in this formulation has been evaluated in accordance with the International Fragrance Association (IFRA) standards. This IFRA assessment, which encompasses both the active fragrance components and their associated allergens, confirms that the use levels are within the established safety limits. Consequently, the risk analysis for the fragrance and its allergens is considered fully addressed by the IFRA evaluation, and no additional separate margin of safety calculations have been performed in this CPSR.

GLYCERIN

The Cosmetic Ingredient Review (CIR) Expert Panel has already assessed the safety of this ingredient; Also, the European Chemicals Agency (ECHA) has a registration dossier for this ingredient. Glycerin is naturally occurring in all animals and plant matter in combined form as glycerides in fats and oils or in intracellular spaces as lipids. The US Pharmacopeia-National Formulary standards state that the amount of any individual impurity in glycerin cannot exceed 0.1% and that the total for all impurities, including diethylene glycol and ethylene glycol, must not exceed 1%; The US Food and Drug Administration (FDA) notes that glycerin is a byproduct of biodiesel fuel produced from the Jatropha species of plant; There is a possibility that toxic impurities, including phorbol esters, may be present in glycerin produced this way; Conventional impurity tests may not detect these toxins, and glycerin from this source should therefore not be used in human and animal food, medical products, cosmetics, and other FDA-regulated products; The FDA advises industry to be aware of the potential for a substitution or use of oils, glycerin, and proteins derived from the Jatropha plant. Glycerin was not dermally irritating in rabbits at concentrations up to 100% when administered to 30% of the body surface 8 h/d, 5 d/wk for 45 weeks, but was a mild dermal irritant at 100% in guinea pigs. Glycerin (50% in water) was not irritating to human subjects with dermatitis (n=420) when administered for 20-24 h under occlusion; Glycerin (10%; 0.05 mL) was slightly irritating in a 48-hour occlusive patch test; In a patch test, glycerin (25%; 0.2mL) was not an irritant when administered to subjects (n=33) for 24h.[24] Glycerin was not irritating to the eyes of rabbits at concentrations up to 100%; Glycerin (100%) was reported to be non-irritating when administered to the eyes of human patients; There was a strong burning and stinging sensation, with tear production, but no injury was observed. Concerning the sensitization potential, human subjects (n=15) who worked in a foam rubber factory and were regularly exposed to Glycerin, were not sensitized to Glycerin when patched tested at 100% for 48 h; A moisturizer containing glycerin (65.9%) was not sensitizing in a modified Draize test (n=48); There were no reactions during either the induction phase or the challenge phase; The test substance was administered 10 times under occlusion for 48 or 72 hours, The challenge patch was in place for 48 hours; The test site was observed at removal and 48 hours after removal. Glycerin was not genotoxic in multiple Ames tests using multiple strains of Salmonella typhimurium, with and without metabolic activation; Negative results were also obtained in a bone marrow chromosomal aberration assay. Glycerin administered in the feed of rats at doses up to 20% in the feed for 1 year or up to 10 g/kg for 2 years did not increase the incidence of tumours.[23] [24]

Glycerin was administered by oral gavage to groups of male and female rats through two generations; There was no effect noted on growth, fertility and reproductive performance through two generations at 2000 mg/kg/day. Also, a developmental toxicity study was conducted in rats, mice and rabbits; There was no effect on the developmental toxicity of offspring of female rats dosed with Glycerin at doses as high as 1310 mg/kg/day; There was no effect on the developmental toxicity of offspring of female mice dosed with Glycerin at doses as high as 1280 mg/kg/day; There was no effect on the developmental toxicity of offspring of female rabbits dosed with Glycerin at doses as high as 1180 mg/kg/day.[15] Glycerin is considered to be Generally Recognised as Safe (GRAS) by the FDA for food packaging and as a multiple-purpose food substance. When considering the safety of Glycerin, the CIR Panel noted that it is naturally occurring and abundant in animal and human tissues, including the skin and blood; The available data demonstrated low systemic oral and dermal toxicity for multiple animal species and humans, in both acute and long-term studies; Glycerin was not genotoxic in multiple in vitro tests and it was not carcinogenetic to rats in a long-term feeding study; This ingredient was not a dermal or ocular irritant and was non-sensitizing to guinea pigs and humans; The Panel also noted the high frequency of use that is reported for Glycerin and the low instances of reports of toxicity, irritation, or sensitization in the literature and the fact that Glycerin is GRAS. The source materials and intermediate forms of Glycerin (eg, epichlorohydrin) should be completely consumed and/or eliminated in the manufacturing process; The Panel noted the FDA's warning that companies should monitor and audit their naturally derived ingredients because of the potential presence of phorbol esters if the source material is the Jatropha plant. The Panel also assessed the issue of incidental inhalation exposure from hair sprays, deodorants, body and hand sprays, face and neck products and suntan products; The Panel noted that 95%–99% of droplets/particles would not be respirable to any appreciable amount; Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredient is used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The CIR Expert Panel concluded that Glycerin is safe in the present practices of use and concentration.[24] Taking into account the available toxicological information, the ingredient Glycerin is acceptable for use in cosmetic products under assessment.

PANTHENOL

The Food and Drug Administration (FDA) includes Panthenol on its list of nutrients (in this case a vitamin) and/or dietary supplements Generally Recognized as Safe (GRAS). The CIR Expert Panel reviewed studies that found that products containing Panthenol did not induce significant skin irritation or sensitization. Significant skin irritation was also not observed with 100% Panthenol. Based on ultraviolet light absorption data, the CIR Expert Panel did not considered Panthenol to be photoirritant or photosensitizer. The ingredient was non-toxic in developmental and reproductive toxicity studies. Although no carcinogenicity studies were located in the literature, many in vitro studies evaluating genotoxicity were available. The low concentrations of use of this ingredient in cosmetics and personal

care products and the requirement of vitamin B5 for normal metabolism suggested that the dietary exposure levels of

this ingredient would greatly exceed the amount that could be absorbed from cosmetic use[25] . Based on this information Panthenol is considered acceptable for use in the cosmetic product under assessment.

AQUA

The quality of water used in the production of cosmetics and personal care products, called process water, is monitored according to Good Manufacturing Practices outlined in FDA's Guidance on Cosmetic Manufacturing Practice Guidelines, and in international guidelines on Good Manufacturing Practices known as ISO 22716. Some companies may also comply with the U.S. Pharmacopeia (USP) standards for the purity of the water used in drugs, devices and diagnostics published in the Purified Water monograph. USP Purified Water is prepared from water complying with the regulations of the U.S. Environmental Protection Agency (EPA) with respect to drinking water. It contains no intentionally added substances.

LIMONENE

The Cosmetic Ingredient Review (CIR) Expert Panel hasn't already assessed the safety of this ingredient; However, the European Chemicals Agency (ECHA) has a registration dossier for d-Limonene; In addition, the Research Institute for Fragrance Materials (RIFM) has a fragrance ingredient safety assessment on dl-limonene (racemic). Limonene exists as two optical isomers, d- and l-limonene, and the racemic mixture dipentene. Limonene (d-limonene, l-limonene and dl-limonene) is considered to have fairly low toxicity.[26] Dermal irritation was investigated in a primary dermal irritation study performed in accordance with OECD Guideline 404 (Acute Dermal Irritation / Corrosion) where 3 rabbits were exposed to d-Limonene under semiocclusive conditions for 4 hours; Animals were then observed for 7 days; Irritation was scored at 1, 24, 48 and 72 hours and 7 days; Signs of erythema and oedema, as well as desquamation from the skin surface, were observed in all animals on day 7; In this study, d-limonene was found to be skin irritant when applied topically to the rabbit.[16] In a study in which the sensitivity of four patch testing systems was evaluated in human volunteers, d-Limonene (perfume-grade) reacted strongly in all types of patches within 10-15 minutes of exposure; Skin irritation was assessed before application, as well as immediately and 1, 24, 48, and 72 hours after removal of the patch, using a scoring system based broadly on that used for rabbit irritation studies, but modified to account for the nature of reactions on human skin; There was evidence of sensory effects and urticarial responses on the removal of the patches; Significant irritation persisted for 24 hours, and these reactions persisted for 48 and 72 hours in many volunteers.[26] The ocular irritation potential was evaluated in a study conducted according to OECD Guideline 405 (Acute Eye Irritation / Corrosion); Undiluted d-Limonene was instilled in the eyes of 3 rabbits; The other eye served as control; The eyes were examined for irritation scores at 1 hour and 1, 2, 3, 4 and 7 days after dosing; Instillation of d-Limonene resulted in slight to moderate redness of conjunctivae associated with moderate chemosis in all treated

animals after 1 hour of instillation; The irritation completely resolved within 7 days; Limonene was classified as mildly irritating. Although testing of d-limonene in rabbits demonstrated some moderate irritating effects on the skin and slight irritating effects on the eyes, these irritating effects were not sufficiently severe for classification of the substance as skin or eye irritant according to CLP criteria. The sensitisation potential was assessed in a study performed in accordance with OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay); d-Limonene was applied to groups of mice (4 females/dose) at concentrations of 0 (vehicle control), 10, 25, 50, 75 or 100% v/v in ethanol/diethyl phthalate (3: 1 v/v) for three consecutive days; Limonene was classified as sensitising.[16] When Limonene was tested in four different sensitisation assays with guinea pigs (Open Epicutaneous Test, Maximization Test, Draize's Test, and a test with Freund's Complete Adjuvant), it was sensitising in all but Draize's Test. Although d-limonene was once considered the main allergen in citrus fruits, data from studies in animals have revealed air-oxidized d-limonene, rather than unoxidized d-limonene, to be the sensitising agent; Hydroperoxides and other oxidation products of d-Limonene formed on exposure to the air have proved to be potent contact allergens when tested with Freund's Complete Adjuvant in guinea-pigs, whereas unoxidized d-Limonene did not cause any sensitisation.[26] Several several studies have been performed using Limonene where the oxidation state is not given, but intended to be low; In one study, 0.6% positive reactions to limonene (3% pet.) were observed in 1606 consecutive patients; In another study yielded 0.1% (95% CI: 0.03 – 0.4%) positive reactions in 2396 patients consecutively Patch Tested with Limonene (2% pet.); In another study, 0.28% (95% CI: 0 – 0.57%; percentages standardised for age and sex) of 1241 patients Patch tested with dipentene reacted to the compound; In a further study, no positive reactions to this allergen, tested at 2% pet., were observed in 320 patients. Limonene is a monocyclic monoterpene existing in two enantiomers: (R)-(+)-limonene and (S)-(–)-Limonene; The allergenicity of Limonene is closely related to oxidation; It has been demonstrated that both enantiomers, R-(+)- and S-(-)-limonene spontaneously autoxidize and that the primary oxidation products formed, the hydroperoxides, are strong and clinically relevant contact allergens; Among 2411 consecutive patients in a multi-centre European study, 63 (2.6 % [95%CI: 2.0-3.3]) reacted to oxidised (R)-(+)-and/or (S)-(–)-limonene (3.0% pet.); In other multi-studies also, a considerable proportion of patients showed positive patch test reactions to oxidised R-(+)- limonene, e.g., between 0.3% and 5.1% of subgroups of 2800 patients depending on test concentration, oxidation state and department and between 0.3% and 6.5% in 4 different departments in altogether 2273 patients.[39] Mutagenicity was investigated in an Ames test performed according to OECD Guideline 471 (Bacterial Reverse Mutation Assay), using Salmonella typhimurium strains TA 1535, TA 1537, TA 98, TA 100 and TA 102, in the presence and absence of metabolic activation; The test substance did not show any mutagenic activity and it is not considered as mutagenic. Mutagenicity was also investigated in an in vitro Mammalian Cell Gene Mutation Test, performed in accordance with OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test) and d-Limonene was not considered as mutagenic; In an in vitro DNA damage and/or repair study conducted according to OECD Guideline 479 (Genetic Toxicology: In Vitro Sister Chromatid Exchange Assay in Mammalian Cells), and also in an in vitro cytogenicity/chromosome aberration study in mammalian cells

performed in accordance to OECD Guideline 473 (In Vitro Mammalian Chromosome Aberration Test), d-Limonene is not considered as cytogenetic in CHO cells. d-Limonene has been studied in carcinogenicity studies in rats and mice (2-year study by gavage); Increased incidences of renal tubular cell hyperplasia, adenomas, and adenocarcinomas of the kidney have been observed in male rats; No increased incidences of tumours have been reported in female rats and in mice; The mechanism of nephrocarcinogenicity has been proven as being male-rat specific and not relevant for humans.[16] There is no evidence that Limonene has teratogenic or embryotoxic effects in the absence of maternal toxicity.[26] No effects were observed on reproductive organs in a 90-day repeated dose toxicity study conducted in rats and mice (gross pathology and histopathology examination of prostate/testes or ovaries/uterus); Therefore no effects on reproductive performance are anticipated.[16] Based on the available UV/Vis absorbance spectra, dl-limonene (racemic) would not be expected to present a concern for phototoxicity or photoallergenicity. The Expert Panel for Fragrance Safety concludes that this ingredient is safe as described in the safety assessment.[27] Taking into account the available toxicological information, the ingredient Limonene is acceptable for use in cosmetic products under assessment.

LINALOOL

The Cosmetic Ingredient Review (CIR) Expert Panel hasn't already assessed the safety of this ingredient; However, the European Chemicals Agency (ECHA) has a registration dossier for this ingredient; In addition, the Research Institute for Fragrance Materials (RIFM) has a fragrance ingredient safety assessment on this ingredient. Two in vitro studies similar to OECD Guideline 428 (Skin Absorption: In Vitro Method) were performed to determine dermal absorption of Linalool; In the first study, occlusion of the test system resulted in a higher absorption rate after 24 hours (3.0% after open application versus 12.7% after occlusion) after incubation with 201 µg/cm² of Linalool; In the second study, Linalool was applied at 500 mg/0.65 cm² to human skin and the amount of Linalool in the stratum corneum and epidermis and dermis was determined after 1, 2, and 4 h; Under the conditions of this in vitro penetration study in human skin, 0.17% of the applied dose could be recovered in epidermis and dermis. The dermal irritation potential was investigated in a primary dermal irritation study performed in accordance with OECD Guideline 404 (Acute Dermal Irritation/Corrosion); A single 4-hour-exposure of Linalool (100% concentration) under semi-occlusive conditions in three independent experiments caused slight irritation on rabbit skin; Marked and slight desquamation from skin surface appeared at day 1, 2, 3, and 7 days; The skin responses (erythema and/or oedema) did not disappear in all animals after 7 days; Based on these data it can be assumed that Linalool is irritating to the rabbit skin. The ocular irritation potential was evaluated in a study conducted according to OECD Guideline 405 (Acute Eye Irritation/Corrosion); The test substance in its natural state, or of the oil-based solution was applied in the tear duct of the left eye of each of 6 rabbits; Concentrations used were 100% (product in its natural state), and 30%, 10% and 3% (product in solution using groundnut oil); Observation period was 7 days; The undiluted product was a moderate irritant to the eye; Effects were fully reversible within 7 days; As

an oil-based solution the product produced no irritant effect at concentrations up to 30% in the eye; Based on these results, Linalool is considered to be moderately irritating. The sensitization potential of Linalool was evaluated in a Local Lymph Node Assay (LLNA) where three groups of mice (5 per group) were treated with different concentrations of Linalool (25, 50 and 100%) by topical application at the dorsum of each ear once daily on three consecutive days; Five days after the first application, the mice were intravenously injected into a tail vein with radiolabelled thymidine, then sacrificed and the lymph nodes were pooled per animal; Linalool was found to be a skin sensitiser.[17] Several studies have been performed on contact allergy to Linalool, with oxidation state not given, but intended to be low; In a study, none of the 218 patients with known contact allergy to fragrance ingredients had a positive reaction to Linalool 5% pet.; In another study, yielded 0.3% (95% CI: 0.1-0.6%) positive reactions in 2401 patients consecutively tested with stabilised Linalool (10% pet.); In another study, 1 patient had a weak, and another a ++ reaction among the n=985 patients tested with 10% Linalool (stabilised) in pet; In the 2009 study, 0.6% (95% CI: 0.1-2.2%) had positive reactions to this allergen; In addition, in another study with 1825 consecutively tested patients yielded 3 positive reactions to Linalool. The allergenicity of Linalool is closely related to oxidation and the primary oxidation products, the hydroperoxides, are the main allergens; In a clinical study performed in 6 European centres including 1511 consecutive patients, 1.3% showed a positive reaction to oxidised Linalool (2.0% pet.) and 1.1% to the hydroperoxide fraction; A recent dose-response study in Sweden including 3400 patients in two test centres showed a positive reaction in 5.3% of the 1725 patients tested with oxidised Linalool 6% pet.[28] Linalool is not predicted to be directly reactive to skin proteins; However, the autoxidation products of Linalool are protein reactive based on in vivo skin sensitization data.[29] Mutagenicity was investigated in an Ames test performed according to OECD Guideline 471 (Bacterial Reverse Mutation Assay), using Salmonella typhimurium strains TA 1535, TA 1537, TA 98, TA 100, and TA 1538, in the presence and absence of metabolic activation; The test substance did not show any mutagenic activity and it is not considered as mutagenic in this bacterial system. The results for Linalool in two other in vitro assays, a Chromosomal aberration test and an in vitro Mammalian cell gene mutation assay were both negative; These results were also confirmed by an in vivo Micronucleus test in mice; Therefore, it can be concluded that Linalool is not mutagenic. There is an experimental result indicating that Linalool elicited a weak tumour-promoting response; However, the publication provides very limited information on the design and result of the experiment; Therefore, the result is regarded to be of doubtful relevance due to major reporting limitations; Another study described that oral administration of Linalool for 20 weeks did not increase the number of tumours in rats; These results and the results from (in vivo) genotoxicity tests (negative) and repeated dose toxicity studies (no pre-neoplastic effects found) indicate that Linalool is not a potential carcinogenic substance. Linalool was also not teratogenic in a developmental toxicity study in rats. Based on the result that all NOAELs for developmental toxicity are identical to or exceed the NOAELs for maternal toxicity, reproduction and developmental toxicity are not expected.[17] In human and guinea pig studies, no reactions indicative of phototoxic responses were observed. Based on the lack of absorbance and study data, linalool does not present a concern for phototoxicity. Based on the

lack of absorbance, Linalool does not present a concern for photoallergenicity. The Expert Panel for Fragrance Safety concludes that this ingredient is safe as described in the safety assessment.[29] Taking into account the available toxicological information, the ingredient Linalool is acceptable for use in cosmetic products under assessment.

ALOE BARBADENSIS LEAF EXTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel[30] has evaluated the safety of the ingredients derived from the Aloe barbadensis species. These ingredients were not toxic in acute oral studies in mice and rats. The Panel noted that aloe-derived ingredients may contain anthraquinones, which can be of concern if present at high levels. However, the data available for review by the CIR Expert Panel supported the conclusion that the manufacturing process is well-established and that current controls followed during production are adequate to ensure that anthraquinones remain below the level of concern. Although the phototoxicity of anthraquinone components of aloe plants has been demonstrated, several clinical studies of preparations derived from Aloe barbadensis demonstrated no phototoxicity, confirming that the concentrations of anthraquinones in such preparations are too low to induce phototoxicity. In aloe-derived ingredients used in cosmetics, regardless of species, anthraquinone levels should not exceed 50 ppm. Regarding inhalation exposure to these ingredients, the Panel expects that aerosolized formulations in which these ingredients are found would not contain aerosolized particles of a respirable size. Aloe Barbadensis Leaf Extract was considered safe for use in cosmetics. IARC has issued a monograph on the carcinogenicity potential of whole leaf extract of Aloe vera[31] . The Working Group considered there was sufficient evidence in experimental animals for the carcinogenicity of whole leaf extract of Aloe vera and classified it as possibly carcinogenic to humans (Group 2B). This conclusion has been disputed, however, as the studies were apparently performed with non-purified Aloe material (unlike those used in cosmetic formulations). No alterations were detected upon histopathological examination in rats given drinking-water containing Aloe vera decolorized whole leaf juice. Taking into account the available information, the ingredient is considered acceptable for use in the cosmetic product under assessment.

CITRIC ACID

The safety of Citric Acid and its salts and esters has been assessed by the Cosmetic Ingredient Review (CIR) Expert Panel.[32] Citric Acid is a normal component of the human body. Therefore, the Panel focused on the potential for Citric Acid and its salts and esters to cause adverse effects when applied on the skin. At concentrations used in cosmetics and personal care products, Citric Acid and its salts and esters were not eye irritants, nor did they result in skin irritation or sensitization. The CIR Expert Panel noted that although Citric Acid could be considered an alpha-hydroxy acid, it is also a beta-hydroxy acid. This makes it distinct from the alpha-hydroxy acids previously reviewed by the CIR Expert Panel. The Panel concluded that the concern about increased sun sensitivity resulting from the use of alpha-hydroxy acid containing products was not relevant to products containing Citric Acid and its salts and esters. Based on the available data, the CIR Expert Panel concluded that Citric Acid and its salts

and esters were safe for use in cosmetics. Furthermore, the safety of Citric Acid has been assessed by the Joint FAO/WHO Expert Committee on Food Additives. The most recent review concluded that it was not necessary to limit the dietary intake of Citric Acid and its salts. Citric Acid and its salts can be found on FDA's list of direct food substances affirmed as Generally Recognized as Safe (GRAS)[40] . Citric Acid is considered acceptable for use in the cosmetic product under assessment.

4. Assessor's credentials and approval of part B

This report was prepared with information provided by the company Tukkunet Oy, as well as available scientific information about the ingredients used in this formulation.

The author of this report has the qualifications required according to the defined in paragraph 2 of Article 10 of Regulation (EC) 1223/2009.

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