Innovant RESEARCH

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SAFETY ASSESSMENT

Product Name: Roc project New Night
Formula: # 538-088 (PR 002279)

The following Safety Assessment is carried out according to the Council Directive 76/768/EEC, on the Safety of Cosmetic Products and as amended by Commission Directives 2003/15/EC (7th Amendment), 2003/83/EC (30th Amendment), and 2003/80/EC (31st Amendment).
The Assessment is conducted in accordance with the principles of Good Laboratory Practice referred to in Article 1 of Council Directive 2004/10/EC on the applications of the principles of good laboratory practice and the verification of their application for tests on chemical substances.
This assessment takes account of:

a) the general toxicological profile of each ingredient used:
b) the chemical structure of each ingredient:
c) the level of exposure of each ingredient;
d) the specific exposure characteristics of the areas on which the cosmetic product will be applied;
e) the specific exposure characteristics of the class of individuals for whom the cosmetic product is intended.

Review of Ingredients.

All of the ingredients have a history of use in cosmetic and toiletry products. Ingredients that are:

- Prohibited under the Cosmetics Directive
- Restricted when used beyond the allowed authorised conditions
- With toxicological data incompatible with the intended concentration and use

- Which have insufficient toxicological data nor safety in use experience
- Which are not properly characterised with regard to purity and analytical composition

Are excluded.

ASSESSMENT

Assessment is based on ingredient safety review and information on the final formulation.

Ingredient Safety Review

Ingredients are listed below. Detailed information on the safety and toxicology of ingredients is provided below.

Aqua
Dimethicone
Glycerin
Isodecyl Neopentanoate
Ethylhexyl Hydroxystearate
Tetrahydroxypropyl Ethylenediamine
Stearyl Alcohol
Cetearyl Alcohol
Glyceryl Stearate
PEG-100 Stearate
Ceteareth-20
Steareth-10
Retinol
Zinc Gluconate
Magnesium Aspartate
Copper Gluconate
Butyrospermum Parkii (Shea Butter)
Caprylyl Glycol
Methyl Methacrylate Crosspolymer
Squalane
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer
Aluminum Starch Octenylsuccinate
Xanthan Gum
Polysorbate 20
Polysorbate 60
Disodium EDTA
Glycolic acid
Citric Acid
BHT
Ascorbic Acid

BHA
Phenoxyethanol
Methylparaben
Propylparaben
Parfum ref: Misty MOD 4-144713

The above ingredients have been reviewed for potential to be skin irritants, sensitisers or photo-sensitisers.
In addition in some instances data is available for systemic and sub-chronic toxicity.
A review of the literature and of the structural chemistry has been made for each ingredient to estimate the likely potential for genotoxicity, reproductive effects and carcinogenicity.
The fragrance is formulated to IFRA Guidelines for safety.
Taking the above into account and taking the safety data on file, it is considered that this formulation is safe for marketing.

FINISHED PRODUCT SAFETY

The above formulation is based on known ingredients with history of safe use in cosmetic products.

SUMMARY

In reviewing the safety and toxicity profile of the ingredients used and their history of safe use, it is concluded that there are no likely safety hazards from normal use of this product and when used as directed or from foreseeable conditions of misuse.
The product is considered safe for sale in all EU countries.

Dated: March 25th 2007

John Hopkins

Dr. JOHN HOPKINS BSc. PhD. MI Biol. C Biol.

Safety Assessor.

DIMETHICONE

The acute oral toxicity of dimethicone is very low at 29g/kg.
The acute dermal toxicity is also low with LD 50 > 32g/kg in the rabbit.
Skin irritation toxicity is rated as non-irritating. Eye irritation in the rabbit is rated as mild/ slight irritating in a Draize test.
A guinea pig Sensitisation test and a human RIPT study gave no sensitising potential.
Mice and rats were dosed with up to 10% for up to 90 days without adverse effects.
Dimethicone was considered to be not mutagenic in all genotoxicity assays.
There was no evidence of dermal absorption in a test in adult human volunteers. Evidence from reproductive toxicity studies in rabbits and rats indicates no reproductive toxicity hazard. No data is available for carcinogenicity, but based on a review of the chemical structure, dimethicone is unlikely to be a carcinogen.

REFERENCES

1. IJT 22(S2):11-35, 2003.
2. Data on file, Innovant Research.
3. CIR Compendium 2004.

GLYCERIN

The full toxicity status of glycerin has been reviewed in a BIBRA profile (1).
Oral exposure in rats, mice, guinea pigs and rabbits gave LD50 values of 7.75 – 38.1 gm/kg. The intravenous LD50 for rat and mouse is 4.25 – 6.3 gm/kg. Skin contact with 2.52 gm of neat liquid (12.9gm/kg) for 20 minutes resulted in excretion of haemoglobin in male rats indicating red blood cell damage.
Oral exposure in humans gave only evidence of headache, nausea and increased urine output at high dose levels ie greater than 700mg /kg bodyweight.
Skin irritancy testing in humans showed no evidence of irritancy with a 50% solution in several thousand dermatitis patients.
Formulations containing glycerin have been tested in human volunteers and shown not to have sensitisation, photo-sensitisation nor photo-toxic potential.
There is no evidence of reproductive effects in rats treated orally or dermally. Tests for mutagenicity have generally given negative results
Carcinogenicity studies in a 2 year rat study indicated no increase in tumors compared to control when rats were dosed at 5 or 10 mg / kg for 2 years.

Chronic studies in animals at high doses indicate a very low order of toxicity with possible target organs of stomach and kidneys.
In man repeat topical application is a rare cause of sensitisation, but with a low irritation potential to eyes and skin.
In summary, glycerin is considered to be safe as used in the current formulation.

REFERENCE

1. Toxicity Profile, Glycerin. BIBRA 1987.

ISODECYL NEOPENTANOATE

The toxicity profile of isodecyl neopentanoate is essentially similar to that of isostearyl neopentanoate, for which more data is available.
For isodecyl neopentanoate, dermal irritation in man via a 48 hr patch test gave a rating of "non-irritant", while an in-vitro test for eye irritancy potential gave a rating of "slight irritant".
For the similar ester, isostearyl neopentanoate, the acute oral toxicity is low, with an LD50 of >40ml/kg in the rat. In addition, sensitisation studies in Guinea pigs by the Maximisation test and by the Landsteiner and Jacobs test, indicated no sensitising potential.
Similarly there was only a minimal irritancy response in the rabbit eye irritation test.
Tested in a cream at 3% dilution, isostearyl neopentanoate was not phototoxic, nor was it comedogenic at 3% nor 50% dilution.
It is considered that the data for isostearyl neopentanoate is applicable to isodecyl neopentanoate.
Based on a review of the chemical structure it is considered that isodecyl neopentanoate is not likely to be a carcinogen, mutagen, nor a teratogen and is considered safe as used in the current formulation.

REFERENCE

1 Data on file Innovant Research Ltd.

ETHYLHEXYL HYDROXY STEARATE

Ethylhexyl hydroxstearate also termed octyl hydroxystearate is the ester of 2-ethylhexyl alcohol and 12-hydroxystearic acid.
It can be considered to be toxicologically equivalent to ethylhexyl stearate (octyl stearate), which is the subject of a CIR monograph and a review in JACT (1985). It has a low order of toxicity orally and also to the skin and eyes. The oral LD50 in mice is >10g/kg.
The acute dermal toxicity has been investigated in the very-similar ingredient octyl palmitate, where this was applied to intact and abraded skin of rabbits at 9.4ml/kg without adverse effects.

In dermal irritation studies in rabbits to intact and abraded skin, octyl stearate gave signs of mild irritation under conditions of 24 hr occlusion.
In repeat skin application studies to hairless mice there were no adverse effects. An eye irritation study in rabbits showed only slight transient irritation.
A guinea pig sensitisation study showed no potential for sensitisation.
In a sub-chronic toxicity test in which groups of rats were fed at 1000mg/kg/day for 90 days there were no adverse systemic effects; organs, tissues and biochemical parameters were also unaffected.
In an Ames type test for genotoxicity, no genotoxic effects were seen.
A rat teratogenicity study showed no signs of teratogenic effects, nor effects for maternal toxicity at doses up to the maximum administered, 100mg/kg.
Based on the above results and considering the chemical structure it is not considered that ethylhexyl hydroxystearate is likely to be a carcinogen.
In summary this ingredient can be considered safe as used in this formulation.

REFERENCES

1. Cosmetic Ingredient Review (2004)
2. JACT (1985) 4(5) 107-146.

TETRAHYDROXYPROPYL ETHYLENE DIAMINE

Acute oral toxicity studies in rats show a low order of toxicity with an LD 50 of 3280 mg /kg.
Testing for skin irritation in rabbits gave a rating of non-irritant, similarly eye irritation was also rated as non-irritant.
A Guinea pig maximisation test gave no evidence of sensitisation potential. In a sub-chronic feeding study in the rat over 90 days at 0.1, 0.3, 1, 3 and 5% in the diet there were no signs of overt toxicity up to 1% in the diet. There were slight borderline effects at doses of 3% and 5 % but these were rated as of questionable significance.
An Ames type test and a Reverse Mutation assay for genotoxicity showed no signs of mutagenicity.
Based on the above and on the chemical structure it is considered unlikely that this ingredient is a carcinogen or will have reproductive toxicity effects.
In summary this ingredient can be regarded as safe as used in this formulation.

REFERENCE

1 Data on file Innovant Research.

STEARYL ALCOHOL

Stearyl and oleyl alcohols are the subjects of a CIR monograph (2004) and of a review in JACT (1985).
The acute oral toxicity of stearyl alcohol in rats gives an LD50 of 20g/kg.
Skin irritancy studies in rabbits gave a rating of "minimally irritant"
Ocular irritation in rabbits is rated as "minimally irritant".
A Draize repeat topical application in the Guinea pig for sensitisation demonstrated no potential for sensitisation.
Clinical patch testing in humans demonstrated a very low order of irritation or sensitisation.
Products containing stearyl alcohol have been tested for photo-sensitization and photo –toxicity with no adverse results.
The mutagenic potential from results of an Ames test gave no genotoxic effects.
Carcinogenic and reproductive effects have not been reported but from a review of the chemistry this is considered to be unlikely.
In summary stearyl alcohol is considered safe as an ingredient in the current formulation.

REFERENCE

1 JACT 1985,4(5) 1-29

CETEARYL ALCOHOL

Cetearyl alcohol is the subject of a CIR monograph (2004) and of a review in JACT (1988).
This ingredient has a low order of toxicity with an oral LD50 in the rat of >10g/kg. The safety profile is similar to that of cetyl alcohol.
A dermal study in rabbits at 100% active under occlusion gave a rating of "non-irritant". An eye irritation test in the rabbit of 0.1ml of undiluted material gave zero irritation effects.
A Magnussen and Kligman Guinea pig test for sensitisation revealed no evidence of sensitising potential, with application at 5% and challenge at 25%.
Human data also indicate no sensitisation potential.
A sub-chronic toxicity test over 90 days was conducted at up to 1000mg/kg/day in rats dosed orally. The NOAEL was set at 1000mg/kg, based on the results of this study.
A fraction of cetearyl alcohol, (octadecanol) was tested for genotoxicity in an Ames type test and showed no evidence of mutagenic potential.
Similarly an in-vivo chromosome mutagenicity test in mice gave no evidence of mutagenicity with no chromosomal aberrations.
A teratogenicity study on an octadecanol fraction of cetearyl alcohol indicated no teratogenic effects at up to 2000mg/kg bodyweight.

Based on the above data and on the chemical structure and metabolism it is unlikely that cetearyl alcohol has carcinogenic potential.
In summary it is concluded that this ingredient is safe as used in this formulation.

REFERENCES

1 Cosmetic Ingredient Review 2004
2 JACT 7(3) 359-413 (1988)
3 Data on file Innovant Research.

GLYCERYL STEARATE

Glyceryl stearate is the subject of a CIR monograph (2004). It is the subject of a review in JACT (1982). The acute oral toxicity in rats gives an LD50 of >5-10 g/kg.
Skin irritation testing in the rabbit by a Draize test at 2 –100% gives a rating of "mild irritant". Eye irritation testing in the rabbit eye is "non-irritant " at 2-3% and a minimal –slight irritant at up to 50% concentration.
Sensitisation testing of glyceryl stearate in the Guinea pig shows no sensitisation potential.
Sub chronic toxicity testing topically in the rabbit with 4-5% for 4 weeks showed no haematological, clinical or pathological effects versus controls.
Chronic toxicity testing of glyceryl stearate in rabbits at 4-5% topically for 13 weeks showed only slight irritant effects but no systemic pathological effects.
Photo allergy and photo toxicity testing and human repeat application followed by challenge of finished formulations containing glyceryl stearate showed no photo allergic or photo toxic potential, nor potential for sensitisation.
An Ames type mutagenicity test showed no evidence of genotoxic effects.
A carcinogenicity test of glyceryl stearate in mice at 2 dose levels for 2 years showed no adverse effects that were regarded as significant. However a slight trend towards greater brain tumours was seen versus the control group. This is regarded as being of doubtful significance. The CIR review has concluded that glyceryl stearate is safe used at up to 25% in a leave-on formulation.
Glyceryl stearate is considered safe as currently used in the current application.

REFERENCES

1 JACT 1982, 1(4) 169-192
2 Data on file Innovant Research

PEG 100 STEARATE

The class of PEG Stearates from PEG 2 to PEG 150 Stearates has been the subject of a monograph in CIR 2004, and in a review in JACT 1983.
The PEG stearates are non lethal in animal acute toxicity tests up to a dose of 10 g/kg.
There is evidence of only slight skin or eye irritation in animals at 100% concentration.
When tested as part of a formulation at 3% there was no evidence of photo-allergy, photo-toxicity, nor of sensitisation in an HRIPT test.
In long term feeding studies PEG 100 produced no significant changes in growth, mortality, histopathology or haematology in rats.
Multi generation studies for PEG 8 and – 40 were negative for reproductive toxicity effects.
Clinical studies indicate that there is no sensitisation, photo sensitisation or photo toxic potential with PEG –2 and – 8 stearates. It is considered that the higher substitution of PEG 100 stearate will be even less likely to have sensitisation effects.
There is no data on carcinogenic potential, or for mutagenicity. However structural review of the formula indicates that this is unlikely.

REFERENCE

1. JACT 1983 2 (7) 17-60

CETEARETH 20

The Ceteareths including Ceteareth 20 are the subject of a CIR monograph(1).
Ceteareths are PEG ethers of cetearyl alcohol and have extensive cosmetic use with little evidence of toxicity.
Since there is only limited information for Ceteareth 20, data for PEG's and for cetearyl alcohol are considered relevant in the safety assessment of ceteareth 20.
The acute oral and dermal toxicity of PEG's is low ranging from LD50 values of 17g/kg to 76g/kg orally in rabbits.
In dermal irritation studies in rabbits a cream containing 3% cetearyl alcohol was mildly irritating. There was no eye irritation in rabbits with a 3% cream of cetearyl alcohol.
Similarly there was no rabbit eye irritation with PEG's 6 and 75.
In human clinical tests with a cream containing ceteareth-20 at 4% and tested for photo toxicity, photo allergy and repeat application followed by challenge, there was no evidence of adverse effects.
In chronic toxicity studies PEG's 6, 32, and 75 did cause adverse effects in rats dosed for up to 90 days and for a year.

No adverse reproductive effects were seen during 90 day and 2 year oral feeding studies in rats for PEG 6, 32, and 75.
A mutagenicity study for PEG8 was negative in the Chinese hamster ovary cell mutation test and in the Sister chromatid exchange test.
PEG 8 was not carcinogenic when given to mice orally for 30 weeks, or to rats intra-peritoneally for 6 months.
In summary from the evidence available Ceteareth-20 can be considered safe as used in this formulation.

REFERENCE

1 Cosmetic Ingredient Review 2004

STEARETH 10

The Steareth group of compounds is the subject of a CIR monograph (2004) and of a JACT review (1988).
The oral LD 50 in rats is >2g/kg and the dermal LD50 is >0.2g/kg.
Steareth 10 was non-toxic to rats in acute oral toxicity studies. At concentrations of up to 60% in water steareth 10 was, at most only mildly irritating to rabbit's eyes and only mildly irritating when tested at 60 % in cosmetics. Steareth 10 was neither a primary irritant nor a sensitiser when tested to human skin.
A guinea pig maximization test for Sensitization gave no potential for sensitisation.
Structurally similar polyoxy ethylene alkyl ethers were neither mutagenic nor were tumor promoters. The structurally similar Steareth 20 is non- photo toxic.
A review of the chemical structure suggests that this compound is unlikely to have potential for carcinogenic or repro toxic effects.
In summary Steareth 10 is considered to be safe as currently used in skin care products.

REFERENCE

1 JACT 1988 7(6) 881-910.
2 Cosmetic Ingredient Review (2004)
3 Data on file Innovant Research.

RETINOL

Retinol is the naturally occurring form of vitamin A and is an essential dietary requirement. A full toxicology monograph and review has been published (1).
In addition an earlier review of retinol and retinyl palmitate was published in CIR monograph (2004) and a review in JACT (1987)

The safety profile of retinol is related to the concentration of active in the formulation tested. In addition the base and excipients of the formulation can also affect the dermal safety profile of retinol.
Formulations containing 0.1% and 1.0 % of the ester retinyl palmitate were shown to have a "moderate " irritation index in the rabbit dermal patch test over a 4 day repeat application. The safety profile of retinyl palmitate is of relevance to retinol since both share metabolic pathways.
Retinyl palmitate was shown not to have sensitising or to have phototoxicity or photo allergic potential.
The acute oral toxicity of retinol in the rat indicates a low to moderate toxicity with an LD50 in the mouse of 2.57 g/kg.
In sub chronic studies retinol was well tolerated at low/moderate doses with a LOAEL of 25,000-60,000 IU,
(ie 7500 –18,000 micrograms Retinol equivalents) retinol/kg/day.
In longer term chronic studies, no adverse effects were seen in rats or dogs after 10 months treatment with retinyl palmitate up to 0.28mg/kg or 0.15mg/kg respectively.
Vitamin A in high doses orally has been related to teratogenic effects. However doses less than 10,000 IU per day are shown not teratogenic to humans. Even this amount of retinol would not be absorbed by whole body application of this product.
Retinol, retinyl palmitate and retinaldehyde are not mutagenic as shown in several test systems for genotoxic potential. In fact retinol was anti- mutagenic in several test systems, showing inhibition of the mutagenic effects of several chemicals.
Although no carcinogenicity studies are available, based on the above data it is considered that retinol is not likely to be a carcinogen. In the current formulation, retinol is blended with polysorbate –20 and BHT, which are considered safe as used.
In summary it is considered that retinol is safe at up to 0.25% in cosmetic applications is safe.

REFERENCES

1 J. Toxicol. Cut Ocular Toxicol. (1999)
2 Cosmetic Ingredient Review (2004)
3 JACT 6(3) 279-320 (1987)
4 Data on file Innovant Research.

COPPER GLUCONATE, ZINC GLUCONATE MAGNESIUM ASPARTATE

Copper, magnesium and zinc are biologically important metals for complete nutrition and are a part of the diet.
The quantities present in this formulation are well within the normal dietary intake and can be considered as non toxic.

Zinc salts have been used as a topical treatment in several skin conditions with a long history of safe use.
At the amounts present in the formula no dermal irritation or sensitisation is likely.
In summary, copper and zinc gluconates and magnesium aspartate are considered safe as used in this formulation.

REFERENCE

Data on file Innovant Research

BUTYROSPERMUM PARKII

Butyrospermum parkii, also termed Shea butter is the natural oil/fat extract of the Shea nut.
This ingredient has a toxicity profile similar to that of other vegetable oils, with a low order of oral toxicity. The main constituents are palmitic acid (4%), stearic acid (43%), oleic acid(47%) and linoleic acid(6%).
A dose of 2g/kg, orally was not toxic to rats.
Dermal irritation to the rabbit skin after 4 hours was rated as "not irritant" with only a slight erythema noted.
Application to the mucous membrane of the rabbit eye gave no irritant response except for a slight conjunctival reaction that disappeared within 24 hrs.
In a Guinea pig study there was no evidence of sensitisation potential, nor in a Guinea pig test was there evidence of photo-toxicity.
In an Ames type test for genotoxicity there was no evidence of mutagenicity to this ingredient.
Based on the chemical structure it is considered unlikely that this ingredient will have carcinogenic or reproductive toxicity potential.
In summary Butyrospermum parkii is considered safe as used in this formulation.

REFERENCE

1 Data on file Innovant Research.

CAPRYLYL GLYCOL

Caprylyl glycol is a novel glycol with anti microbial properties.
Based on a review of the structural chemistry and relationship to similar glycols such as butylene glycol it can be regarded as safe in skincare.

Results of rabbit eye testing on the ingredient at full strength show only slight irritant effects.
It was non-irritant to both intact and abraded rabbit skin.
A sensitisation test using the Magnussen & Kligman method suggested a very slight sensitisation potential. However final product testing with several formulations via HRIPT has not revealed sensitisation in human subjects.
Similarly there was no evidence of photo-allergy or photo-toxicity in human volunteer tests of a formulation containing 0.5% caprylyl glycol.
Caprylyl glycol was not mutagenic in an Ames test for genotoxicity.

REFERENCE

1. Data on file Innovant Research.

METHYL METHACRYLATE CROSS POLYMER

This is a copolymer of methyl methacrylate cross linked with glycol dimethacrylate. The toxicity profile is expected to be similar to Carbomer since there is a similarity in structure.
The oral acute toxicity in the rat gives an LD 50 >2.5g/kg.
The acute dermal toxicity in rabbits is LD50>3g/kg.
Skin irritancy in rabbits is rated as “negligible irritation potential”
Eye irritation in rabbits gave a rating of “borderline irritant” while in a cell culture Agar overlay method the rating was “non-irritant”.
Human skin patch testing gave a result of “very weak irritant”, and there was no sensitisation potential.
No data is available for genotoxicity, mutagenicity carcinogenicity or reproductive toxicity. However, based on a review of the structural chemistry this type of effect is considered to be unlikely.
In summary this ingredient is considered to be safe in usual use in skin care products and in this formulation.

REFERENCE

1 Data on file Innovant Research

SQUALANE

Squalane is a hydrogenated form of squalene, which is a constituent of shark liver oil, olive oil and is found in human skin (1). In the liver it is a precursor of cholesterol formation.
Squalane has a long history of use in skin creams as a moisturiser (2).
Because of the similarity to squalene in the skin, it is considered that squalane is safe in cosmetic formulations.

Squalane is the subject of a CIR monograph and a review in JACT (3) and IJT (4). There is a poor skin absorption and poor gastric absorption. The acute animal toxicity by oral and dermal routes is low. It is non-irritant to rabbit skin and eye at 100% concentration. There is no evidence that this material is a sensitizer. It is considered to be safe in the current application.

REFERENCES

1. Scientific Tables, Geigy 1970. J R Geigy, Basel Switzerland.
2. Harry's Cosmeticology 7th Edition 1982. Longman Technical publishing. UK
3. JACT 1(2):37-56, 1982
4. IJT 22 (S1): 1-35, 2003

HYDROXYETHYL ACRYLATE/SODIUM ACRYLOYLDIMETHYLTAURATE COPOLYMER

The above is an inert polymer blend with a low degree of toxicity.
A rat oral safety test on the ammonium salt gave an LD50 >2000 mg/kg, indicating a low order of acute toxicity.
A Hetcam test in the Hen's egg for irritation potential gave a classification on "non-irritant".
A human dermal irritation test gave a rating of "non-irritant" when this ingredient was tested at 100% concentration.
There was no evidence of sensitisation in a human volunteers test and no evidence of genotoxicity in an Ames test for mutagenicity.

This ingredient can be regarded as safe in the current application.

REFERENCE

1. Data on File Innovant Research

ALUMINUM STARCH OCTENYLSUCCINATE

This is sold under the Trade name, Dry Flo PC and is the aluminium salt of the reaction product of octenylsuccinic anhydride with starch. It has a long history of safe use in skin care and is considered safe in the current application.

XANTHAN GUM

Xanthan gum is a high molecular weight hetero-polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with

Xanthomonas campestries. This ingredient has a long-established use in cosmetic, medicinal, and food applications.
Data on file indicates that Xanthan gum is non-toxic in three animal species, rat, cat and dog. No adverse effects were observed in long-term feeding studies in rats (up to 1000mg/kg/day). No adverse effects were seen in a 3-generation reproductive study with rats (up to 500 mg/kg/day).
Human patch test data gave no irritant potential.
The acute oral toxicity is low with an LD50 in the rat of>5g/kg.
Animal dermal tests gave no dermal irritancy or sensitisation potential. An eye irritation study in the rabbit was rated as "non-irritating".
In summary, based on available information and on the established, safe food use this ingredient is considered safe as used in this formulation.

REFERENCE

1 Data on file Innovant Research.

POLYSORBATE 20

Polysorbate 20 and related polysorbates is the subject of a monograph in CIR (2004) and of a JACT review (1984) and a BIBRA Toxicity profile (1989).
The toxicity of several similar polysorbates is regarded as applicable and where data is not available information from Polysorbate 80 is also relevant.
In acute toxicity studies there is very little potential for skin or eye irritancy or oral toxicity. At a 30% dilution polysorbate 20 is rated as "non-irritant" to the rabbit eye. The oral LD50 in the rat is >33g/kg which is very low.
The dermal LD50 in the rabbit gives anLD50 of >3g/kg. There fore Polysorbate 20 is regarded as having a low systemic toxicity.
Undiluted product is rated "minimally irritant" when in 24 hr contact with rabbit skin under a patch test.
Studies for sensitisation potential showed no evidence of sensitisation in 100 dermatitis patients given patch tests.
Extensive clinical testing has shown that polysorbates have no potential for photo toxicity.
In a limited Ames test there was no evidence for mutagenicity and reports also indicate that in mammalian cells in culture Polysorbate 20 was not mutagenic.
In carcinogenicity studies there is very slight evidence of an increase in stomach tumours in rats given polysorbate 20 in drinking water and also in one mouse in a skin painting study where one benign tumour appeared. As with other polysorbates there is evidence of

tumour –promoting effects with carcinogens. This may be related to improved penetration of the carcinogen.
In reproductive toxicity studies there was no evidence of adverse effects in a rat study at 1.1g/kg/day given orally and by dermal application of 2.2 g/kg/day.
In summary Polysorbate 20 can be considered as safe as currently used in the current product application.

REFERENCES
1 Cosmetic Ingredient Review 2004
2 JACT 1984 3(5) 1-82
3 BIBRA Toxicity Profile 1989
4 Data on file Innovant Research

POLYSORBATE 60

Polysorbate 60 is a mixture of stearate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 20 moles of ethylene oxide. Polysorbate 60 and related polysorbates is the subject of a CIR monograph (2004) and of a JACT review (1984).
The toxicity of similar substituted polysorbates is similar to Polysorbate 60 and is applicable where specific data on Polysorbate 60 is unavailable.
In acute studies there is very little potential for rabbit and mouse skin irritation and there is only a minimal and transient eye irritation in a Draize rabbit eye test.
The oral LD50 in the rat is 59g/kg. In the mouse, the oral LD50 is >25g/kg.
There is little evidence of skin sensitisation potential, only isolated clinical dermatological reports.
Extensive clinical testing has shown that the Polysorbates have no potential for photo toxicity.
In an Ames test for mutagenicity there was no evidence for mutagenic effects, nor were there chromosomal breakage in mammalian cells treated with the similar Polysorbate 80.
In carcinogenicity studies there is no evidence of carcinogenic potential with Polysorbate 80, although there is evidence for tumour promoting effects with carcinogens.
Similarly Polysorbate 80 is not a reproductive toxic ingredient and it is reasonable to conclude that Polysorbate 60 does not have adverse dermal, systemic, carcinogenic or reprotoxic effects.
In summary Polysorbate 60 can be considered safe as used in skin care products.

REFERENCE

1. CIR Compendium 2004.

2. JACT 1984 3(5) 1-82.

DISODIUM EDTA

Disodium EDTA has a long history of safe use in skin care and is considered safe in the current application.

GLYCOLIC ACID

Glycolic acid has been used in skin care applications for several years in all regions of the world and has a good safety record. The main application is to improve the appearance of skin lines and skin smoothness.
Glycolic acid has moderate inhalation toxicity with an LC 50 of 7.7ml/kg. The acute oral LD 50 in the rat is 4240 mg/kg for a 70% solution, indicating a low order of toxicity.
At 70% active glycolic acid produces burns to the skin, however at 10% it is only a mild skin irritant, and is well tolerated in commercial products at lesser concentrations.
A Guinea pig sensitisation study was negative.
In animal feeding studies there is a higher excretion of oxalate leading to kidney stones. However there were no significant adverse effects.
In an Ames test for genotoxicity there was no evidence of mutagenicity, with and without metabolic activation.
A study in rats for maternal toxicity and for developmental toxicity gave a NOAEL for maternal toxicity and developmental toxicity of 250mg/kg/day.
It is concluded that glycolic acid can be considered safe as used in this formulation.

REFERENCES

1. Cosmetic Ingredient Review 2004
2. IJT,(Suppl 1) 1998, 1-242.
3. Data on file Innovant Research.

CITRIC ACID

Citric acid has a long-established use as a food and flavour additive. It is a constituent of citrus fruits such as oranges and lemons and is regarded as non-toxic in the amounts used as a pH adjuster in cosmetic products.
The acute toxicity in rats is LD 50 11.7gm/kg.
At full strength concentrations it is irritating to the skin and eyes.
Based on structural formula and on long history of use it is considered unlikely that citric acid is a sensitiser, a photo allergen nor is it photo-toxic.

Mutagenicity testing
In the east gene mutation assay at 3.5gm/kg with and without metabolic activation a "negative" result for mutagenic potential was recorded. There was no genotoxicity in an Ames Salmonella assay for mutagenicity.
In a Dominant Lethal assay in rats at 3gm/kg for 5 days no mutagenic potential was determined.
Carcinogenicity In a 2 year carcinogenicity rat study by oral dosing at 2gm/km per day there was no difference between test and control groups.
Reproductive toxicity. No adverse effects on reproduction were detected in a rat fertility study.
Teratogenicity. There was no difference between test and control groups with respect to teratogenicity or developmental toxicity in the rat.
In summary citric acid is considered safe as usually used as a pH modifier or as an active alpha hydroxy acid in skincare products at typical use levels, ie up to 5%

REFERENCES
1 Data on file …Innovant Research Ltd

BHT

Butylated hydroxy toluene is an anti-oxidant with a long history of safe use in both skincare and food products.
The acute oral toxicity in rodents is low, with anLD50 in the rat up to 3.9g/kg and up to 2 g/kg in the mouse.
Skin irritation studies in rabbits gave a rating of "moderate irritant" for the undiluted material, and "slight to moderate irritant" for a 10% dilution
An ocular irritation test in the rabbit using a small dose (0.03%) of 40% BHT in olive oil was rated as "non-irritant".
Guinea pig studies showed no evidence of sensitisation potential.
There was no evidence of genotoxicity or mutagenicity in an Ames test, a Dominant lethal study in rats, Chromosomal damage and translocation studies.
Studies for carcinogenicity and reproductive toxicity also showed no adverse effects.
A human clinical test of a cream containing 0.1% BHT for photo-toxicity, photo-allergy and sensitisation, based on repeat patch test followed by challenge indicated no potential for sensitisation or photo reaction.
There have been isolated reports in the published literature of human sensitisation to BHT, however this is extremely uncommon considering the wide use of this ingredient.
In summary BHT is considered safe as used in this formulation.

REFERENCE.

1 Data on file Innovant Research.

ASCORBIC ACID

Ascorbic acid has a long-established safety record as a food and dietary ingredient.
The WHO recommended Acceptable Daily Intake (ADI) is 15mg/kg in humans. As a dietary supplement doses of up to 1000mg per day are typical.
Ascorbic acid salts and esters are the subject of a review by the Cosmetic Ingredient Review (1). The esters are considered to penetrate the skin, whereas the pure acid and its salt are not likely to penetrate.
There is a low acute oral toxicity in animals. In chronic feeding studies, decreased bodyweight gain and formation of oxalate stones in the bladder were seen in rats fed high doses of ascorbyl palmitate.
In animal tests ascorbic acid was not a sensitiser, while in human clinical studies ascorbyl palmitate caused no dermal irritation or sensitisation.
The stereo isomer of ascorbic acid, erythorbic acid and sodium erythorbate did produce isolated positive genotoxicity results, however sodium erythorbate did not cause foetal nor maternal toxicity or developmental toxicity to rats and mice fed high dose levels.
Ascorbic acid is considered safe as used in the current formulation.

REFERENCE

1 Cosmetic Ingredient Review 2004
2 Data on file Innovant Research.

BHA

Butylated Hydroxyanisole (BHA) is the subject of a CIR monograph (1) and a review in JACT (2).
It has a long history of use as a preservative and anti-oxidant. The acute oral toxicity is low with a range of 2-5g/kg. It is a permitted food antioxidant in the US.
Formulations containing BHA elicited at most, a minimal or moderate skin and eye irritation in rabbits. There have been several chronic and sub-chronic toxicity studies. BHA given orally or parenterally to rats and mice inhibited the carcinogenic effects of a range of agents. BHA inhibited mutagenesis, and was not a mutagen in a range of standard tests.
There was no carcinogenesis in dogs or rats following dietary administration, although there was an increase in fore-stomach papillomas and squamous cell carcinomas in rats fed BHA. Overall it is concluded that BHA is not a carcinogen.

There were no embryo toxic or teratogenic effects in rats, hamsters, or rabbits fed BHA.
Clinical data from human studies indicate that cosmetic formulations containing BHA are non-sensitising, non-photosensitising and only minimally irritating.
The CIR provides for a maximum use of 25% in formulations for topical application.
It is concluded that BHA is safe as used in the current formulation.

REFERENCE

1. CIR Compendium 2004.
2. JACT 3(5) 83-146. (1984)

PHENOXYETHANOL

Phenoxyethanol is the subject of a monograph in CIR and of a review in JACT 1990 and is a EU Cosmetics Directive-approved preservative listed in Annex 6 for use up to 1%.
The acute oral toxicity in the rat gives an LD50 of>2g/kg indicating a low order of toxicity. In dermal studies phenoxyethanol is not irritating, nor a sensitiser in the Guinea pig.
When tested in a formulation at 1% phenoxyethanol was not a photo-allergen nor photo-toxic, nor a sensitiser in a HRIPT test.
In mouse feeding studies phenoxyethanol was not teratogenic, embryo toxic or foetotoxic. It is not mutagenic in the Ames test and in the mouse micronucleus test.
Phenoxyethanol was not phototoxic in human clinical studies. No data exists on carcinogenicity but in reviewing the structure and metabolism it is not regarded as a carcinogen.

REFERENCE

1. JACT 1990 9(2) 259-277.

PARABEN PRESERVATIVES

The parabens, methyl-, ethyl-, propyl-, butyl , isobutyl and isopropyl-paraben are the subject of a CIR monograph and a review in JACT (1984).
The parabens have been shown to be well tolerated with low irritancy and a low potential for sensitisation, photo-sensitisation and photo-toxicity.
Parabens are not mutagenic in several protocols.
Carcinogenicity and teratogenicity studies were also negative.
Parabens are considered safe as used according to the EU Cosmetics Directive and as used in this formulation.

REFERENCES

1. JACT 3(5) 147-209 (1984)
2. J Amer. Coll Toxicol.5, (5) 301-7 (1986)
3. JACT 14(5) 364-372 (1995)
4. Food Chem Toxicol. 39(6) 513-32 (2001)
5. Cosmetic Ingredient Review (2004)
6. Data on file Innovant Research.

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The above fragrance is formulated in accordance with IFRA Guidelines for dermal safety and is considered safe in the current application.