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COSMETIC PRODUCT SAFETY ASSESSMENT

AMMOYA NATURALS TURMERIC & KOJIC ACID SOAP

Customer Reference:

Cosmetic Product Safety Assessment

CONFIDENTIAL

DELIVERED TO:

Ammoya Naturals LLC

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DATE:

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Cosmetic Product Safety Assessment

Ammoya Naturals Turmeric & Kojic Acid Soap

Customer Reference: N/A

Product Information

The product Ammoya Naturals Turmeric & Kojic Acid Soap is a rinse-off skincare product intended to be used on the body and face by adults.

When a range of concentrations for an ingredient has been provided, the highest concentration of the range has been conservatively taken into account. Thus, the formula sums to over 100%.

Formulation

See Appendix One for product formulation data.

Assessment Conclusion

The detailed formula and other supportive documents listed were provided by the supplier and delivered to the risk assessor; it is the supplier's responsibility to ensure the accuracy of these documents.

This cosmetic product is considered as **safe with restrictions** under normal and reasonably foreseeable conditions of use and when recommended instructions of use and warning are followed (cf. "Labelling Warnings and instructions for use" section). The ingredients are legally permitted to be used in cosmetic products in the USA. They must comply with the relevant purity standards for cosmetic ingredients (cf. "Ingredient Toxicity Review" section). It is assumed that these ingredients do not contain any undisclosed impurities/contaminants that would affect the conclusions reached. In order to confirm the overall good tolerance of the product, it is highly recommended to perform clinical testing. The product must be manufactured in accordance with Good Manufacturing Practices.

Restrictions:
- Due to the presence of Goat Milk, an allergen, the finished product should be labeled to inform individuals sensitized to milk. Additional warnings are highly recommended to be added on the label (cf. "Labelling Warnings and instructions for use" section). Post-market surveillance data should be monitored; if the supplier is aware of an abnormally high level of customer complaints the supplier must bring this to the attention of the safety assessor and submit this formulation for reassessment and notify the competent authorities of corrective actions taken.
- In order to confirm the acceptability of the essential oils, an IFRA Certificate confirming that the essential oil has been safety assessed by the manufacturer and meets the requirements of a specific and recent amendment to the IFRA Code of Practice must be provided for Curcuma Longa (Turmeric) Root Oil, Lavandula Angustifolia (Lavender) Oil, Citrus Limon (Lemon) Peel Oil, Daucus Carota Sativa (Carrot) Seed Oil, Boswellia Carterii (Frankincense) Oil, Cananga Odorata (Ylang Ylang) Flower Oil, and Santalum Album (Sandalwood) Oil.

This safety assessment will have to be updated if there is any change in product formulation, its instructions of use or its targeted population. Any undesirable effect reported after the marketing of this product has to be declared to the safety assessor.

Under normal or reasonably foreseeable conditions of use and when recommended instructions of use and warning are followed, a product made to this formulation is unlikely to produce an abnormally high number of adverse reactions. The product will give users the level of safety they can reasonably expect when used as directed and when recommended instructions of use and warning are followed.

The toxicological data available on the individual substances and the end product, including all chemical and/or

biological interactions and human exposure via intended and likely routes have been taken into account in this assessment. Whenever a NO(A)EL value is available for a specific substance, its Margin of Safety (MoS) has been calculated and taken into account. Where applicable, relevant systemic and local toxicity endpoints of the chemical ingredient in this formulation have been considered as part of this risk assessment to evaluate the safety of cosmetic product formulations.

Labelling Warnings and instructions for use

Warnings

No information provided.

Instructions of Use

No information provided.

Given the type of product and application, the following warnings are recommended for this product from a safety point of view: “Only use as directed. In case of contact with eyes, rinse immediately and thoroughly. Keep out of reach of children. Stop use and ask a doctor if skin irritation develops.” In addition, given the presence of Goat Milk in this product, the following warnings are highly recommended for this product, from a safety point of view: “Do not use if you are allergic to goat milk.”

Fragrance Allergen Labelling

Not a regulated compliance consideration for the purposes of this safety assessment.

Reasoning

Product Toxicity Review

The product is expected to be applied the body, hands, and face of adults making dermal contact the predominant route of exposure. Inhalation and ingestion are unlikely routes of exposure in normal and foreseeable conditions of use. Accidental eye contact may occur during normal use.

No existing in vitro or clinical studies on these products were provided at the time of assessment. Clinical testing is highly recommended in order to confirm the overall good tolerance of the product.

Effects of the product as provided on the skin

This formulation as supplied is unlikely to cause skin irritation during normal use. Due to the presence of Goat Milk, type-I allergy reactions may occur in individuals with susceptibility to milk; they should be warned and not use this product. Warnings and instructions of use must be followed.

Effects of the product as provided on the eye

Accidental eye contact may occur during normal use. Warnings and instructions of use must be followed.

Effects following ingestion of the product as provided

Ingestion is an unlikely route of exposure during normal use.

Effects following inhaling of the product as provided

Inhalation is an unlikely route of exposure during normal use.

Ingredient Toxicity Review

Most of the ingredients are widely used and have a history of safe use in humans. No strong irritating or sensitizing ingredients are present in the formulation; or irritation and sensitization are not expected at the concentration of use of the ingredients in this formula. However, this product contains Goat Milk, an ingredient known as food allergen. Type I allergy (IgE-mediated) can occur resulting in systemic, cutaneous, gastrointestinal or respiratory symptoms in some people. The responsible allergens of type I allergy reactions are proteins present in milk. To minimize this risk, it is highly recommended to warn the consumer and label the product as follows: *"Do not use if you are allergic to goat milk*" Post-market surveillance data should be monitored; if the supplier is aware of an abnormally high level of customer complaints, they must bring it to the attention of the safety assessor and submit this formulation for reassessment and notify the competent authorities of corrective actions taken. In order to confirm the overall good tolerance of the product, it is highly recommended to perform clinical testing.

When an ingredient of this formula has been reviewed by the CIR Expert Panel, it has been deemed safe when used in cosmetics at its reported concentration.

All the ingredients are permitted in cosmetics in the United States. Due to the use of Sodium Hydroxide at up to 9.6% in the final formulation, the final product must have a pH lower than 11. Diethylene glycol (DEG) and ethylene glycol must be < 0.1% in glycerin. The raw materials must be of cosmetic grade. All of the above must be ensured by the manufacturer.

As a rinse-off product, the duration of exposure is expected to be short and thus limited exposure is expected even with repeated and long term use. Due to the nature and/or the expected exposure levels of the ingredients, the formulation is expected to be of low systemic toxicity. Therefore, significant systemic toxicity is not expected in the short, medium or long term with repeated exposure to the product under normal and reasonably foreseeable use.

Where adequate data are available, a Margin of Safety (MoS) has been calculated to be > 100, thus supporting the safety of the ingredient as formulated in this product. Where a NOAEL on an ingredient was not available, a weight of evidence approach using its history of safe use, read-across data and/or information such as food consumption or pharmaceutical applications was considered to evaluate its safe use in this formulation.

Overall, taking into account the intended application, frequency of exposure and the toxicological profiles of the individual ingredients as well as the supplier ensuring that the ingredients are of high purity, the product is not expected to cause damage to human health in the short, medium or long term under normal and reasonably foreseeable conditions and when recommended instructions of use and warning are followed; although it cannot be totally discounted that a few susceptible individuals may experience allergic or other idiosyncratic reaction with the product particularly if already sensitized to one of the ingredients, particularly Goat Milk.

Margin of Safety Review

Where a NOAEL is available for a chemical ingredient that is considered as a toxicological concern, the Margin of Safety (MoS) has been calculated as greater than 100 taking into consideration any known data on dermal absorption and bioavailability. It is generally accepted that the MoS should be a least 100 to declare a substance safe for use in a finished product and the safety of this formulation is further supported by this uncertainty factor.

See Appendix One for a toxicological review of the formulation ingredients

Exposure Scenario

N.B: Exposure data are derived from the SCCS Notes of Guidance, 12th revision (SCCS/1647/22); the RIVM Report 320104001/2006, Cosmetics Fact Sheet.

Product Class: Skin products	**IFRA Category:** Category 9
Product Subclasses: Skin cleansing products, Soap products, General Bodywash	**Product Group:** SOAP
Product Group: Cosmetic	**Part of body exposed to undiluted**: Apply on general body area
Product Name: Ammoya Naturals Turmeric & Kojic Acid Soap	

Targeted Population: Adult

Amount per application (g): 18.67	**Number of applications per day**: Once per day
Physical Form: Solid	**Total Amount applied per day (g)**: 18.67
Skin Surface Area of Application (cm²): 17500	**Amount per Unit Area of Skin per day (mg/cm²/day)**: 0.4
Exposure Time Neat: Diluted immediately (Dilution factor 3)	**Estimated Daily Exposure (mg/kg/day)**: 2.79
Exposure Time Dilute: Diluted immediately.	**Retention Factor**: 0.01
Exposure Time Solvent Inhalation: Not Applicable	**Exposure Time Aerosol Inhalation**: Not Applicable

Fragrance Composition

The product contains a blend of essential oils, including Curcuma Longa (Turmeric) Root Oil, Lavandula Angustifolia (Lavender) Oil, Citrus Limon (Lemon) Peel Oil, Daucus Carota Sativa (Carrot) Seed Oil, Boswellia Carterii (Frankincense) Oil, Cananga Odorata (Ylang Ylang) Flower Oil, and Santalum Album (Sandalwood) Oil.

In order to confirm the acceptability of an essential oil, an IFRA Certificate confirming that the essential oil has been safety assessed by the manufacturer and meets the requirements of a recent amendment to the IFRA Code of Practice must be provided.

IFRA certificates have been provided for Curcuma Longa (Turmeric) Root Oil, Lavandula Angustifolia (Lavender) Oil, Citrus Limon (Lemon) Peel Oil, and Daucus Carota Sativa (Carrot) Seed Oil. However, the IFRA certificates do not specify which amendment of the IFRA Code of Practice the essential oils were reviewed under.

No IFRA certificates were provided for Boswellia Carterii (Frankincense) Oil, Cananga Odorata (Ylang Ylang) Flower Oil, or Santalum Album (Sandalwood) Oil.

To confirm the safety of the essential oils, the supplier must provide to the assessor IFRA Certificates that confirm that the essential oils have been reviewed against a specific and recent IFRA Code of Practice.

Microbiological Quality

Microbiological specifications:

To comply with the EN ISO 17516:2014 standard for Cosmetics — Microbiology — Microbiological limits, the following maximum limits apply:

Category 1: Products specifically intended for children under 3 years, eye area and mucous membranes.
Total Aerobic Mesophilic Microorganisms (Bacteria plus yeast and mould): ≤ 100 cfu/g or 100 cfu/ml of the product. Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Candida albicans must not be detectable in 1 g or 1 ml of the cosmetic product.
Category 2: Other cosmetic products.
Total Aerobic Mesophilic Microorganisms (Bacteria plus yeast and mould): ≤ 1000 cfu/g or 1000 cfu/ml of the product. Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Candida albicans must not be detectable in 1 g or 1 ml of the cosmetic product.

This product belongs to Category 2. A Microbial Limits Test was performed, and the results are as follows: Aerobic Mesophilic Bacteria <10 cfu/g, Yeast and Mold <10 cfu/g, and absence of *Candida albicans, Enterobacteriaceae, Escherichia coli,* Faecal Coliforms, *Pseudomonas aeruginosa, Salmonella* species, and *Staphylococcus aureus* (MSL Solution Providers Test Report dated 9/23/2024). The results are acceptable for a Category 2 product.

Preservative challenge test**:**

The efficacy of the preservation of a cosmetic product has to be assessed experimentally in order to ensure microbial stability and preservation during storage and use.

A Water Activity test was performed, and the water activity of the product was 0.558 (MSL Solution Providers Test Report dated 9/17/2024). Per the report, the product can be classed as microbiologically low risk according to ISO 29621:2017 and a preservative challenge test is not necessary.

Product Stability

Packaging compatibility of cosmetic products is an important safety consideration for cosmetic products irrespective of country of supply. It is, however, not a regulated compliance consideration for the purposes of this safety assessment. The supplier should ensure that, where it is relevant, this product meets all applicable restrictions before supplying this product to the marketplace.

Packaging Material Information

No information provided. Not a regulated compliance consideration for the purposes of this safety assessment.

Impurities/Traces/Prohibited Substances

Identification of the nature of relevant impurities that may be present must be stated, along with their concentrations, in order to consider their presence and assess the cosmetic product.

According to analytical testing, Turmeric and Kojic Acid Soap contains 62.79 ppm (i.e., 0.006279%) Diethanolamine (DEA) (Intertek Report of Analysis, dated 9/19/2024).

Exposure to DEA from Turmeric and Kojic Acid Soap is as follows:

Soap exposure = 0.19 g/day (SCCS Notes of Guidance[1])
DEA in Turmeric and Kojic Acid Soap = 0.19 g/day x 0.006279% = 0.0000119 g/day = **11.9 µg/day**

DEA has been listed on the State of California's Proposition 65 list as a carcinogen and a No Significant Risk Level (NSRL) of 5.6 µg/day was derived by Wang et al. (2014)[2]. The NSRL was derived from a chronic dermal study in mice. The NSRL can be adjusted for differences in dermal absorption between mice and humans.

Dermal Absorption (In vivo, Mice) = 27-58% [3]
Dermal Absorption (In vitro, Human Skin) = <1% [4]
Adjusted NSRL = 5.6 µg/day x (27%/1%) = **151 µg/day**

Thus, the exposure to DEA from Turmeric and Kojic Acid Soap (11.9 µg/day) is less than the adjusted NSRL (151 µg/day). There is an acceptable margin of exposure.

It was assumed that neither this product, nor the ingredients used in the product, contained any additional impurities/contaminants that would cause toxicity in a consumer.

Presence of Nanomaterials

No information provided. Not a regulated compliance consideration for the purposes of this safety assessment.

[1] Scientific Committee on Consumer Safety (2023). The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation, 12th Revision. Adopted May 15, 2023.
[2] Wang, B., Amacher, D. E., & Whittaker, M. H. (2014). Derivation of a No-Significant-Risk-Level (NSRL) for diethanolamine (DEA). Regulatory Toxicology and Pharmacology, 68(1), 76-84.
[3] Kirman, C. R., Hughes, B., Becker, R. A., & Hays, S. M. (2016). Derivation of a No-significant-risk-level (NSRL) for dermal exposures to diethanolamine. Regulatory Toxicology and Pharmacology, 76, 137-151.
[4] Kraeling, M. E. K., Yourick, J. J., & Bronaugh, R. L. (2004). In vitro human skin penetration of diethanolamine. Food and chemical toxicology, 42(10), 1553-1561.

Serious/Undesirable effects

On request, the supplier has not supplied information of any reports known to him of serious undesirable effect or undesirable effects on the cosmetic product, or where relevant, other similar cosmetic products and this cannot be commented upon. If the supplier is aware of an abnormally high level of customer complaints the supplier must bring this to the attention of the safety assessor and submit this formulation for reassessment and notify the competent authorities of corrective actions taken.

Specific Use Considerations

None.

Assessor's Credentials and Approval

This product was evaluated by H. REAMER who is qualified by education, training and experience to evaluate the safety of cosmetic product formulations.

H. REAMER, B.S. Toxicology, M.P.H.
Intertek Assuris

Date: December 18, 2024

This product was reviewed by G. LETELLIER who is qualified by education, training and experience to evaluate the safety of cosmetic product formulations.

G. LETELLIER, M.S. Toxicology, EUROTOX Registered Toxicologist (ERT), Diplomate of the American Board of Toxicology (DABT)
Intertek Assuris

Date: December 18, 2024

Appendix One: Product Formulation Data and Toxicological Review of Ingredients

Formulation

The chemical names shown below refer to the raw materials used to formulate this product. The identity of the raw materials may be based on alternative nomenclature such as IUPAC name, Chemical name, INCI name or generic trade name. Furthermore, there may be instances where several CAS number exist for the same chemical ingredient. Where this has occurred, the most appropriate substitute will have been used where one has not been provided.

INCI Name	% Concentration	% Active	Activity in Product	CAS No	Chemical Name
COCOS NUCIFERA (COCONUT) OIL	[redacted]	[redacted]	[redacted]	8001-31-8	COCOS NUCIFERA OIL
ELAEIS GUINEENSIS (PALM) OIL	[redacted]	[redacted]	[redacted]	8002-75-3	ELAEIS GUINEENSIS (PALM) OIL
GLYCERIN	[redacted]	[redacted]	[redacted]	56-81-5, 8013-25-0, 91052-08-3	GLYCERIN; GLYCEROL
AQUA	[redacted]	[redacted]	[redacted]	7732-18-5	AQUA (WATER)
SODIUM HYDROXIDE	[redacted]	[redacted]	[redacted]	1310-73-2	SODIUM HYDROXIDE
PROPYLENE GLYCOL	[redacted]	[redacted]	[redacted]	57-55-6	PROPYLENE GLYCOL, PROPYLENGLYCOLUM, PROPANE-1, 2-DIOL, 1,2-PROPANEDIOL
GOAT MILK	[redacted]	[redacted]	[redacted]		GOAT MILK
CARTHAMUS TINCTORIUS SEED OIL	[redacted]	[redacted]	[redacted]	8001-23-8	CARTHAMUS TINCTORIUS (SAFFLOWER) SEED OIL
SORBITOL	[redacted]	[redacted]	[redacted]	50-70-4	D-GLUCITOL
SORBITAN OLEATE	[redacted]	[redacted]	[redacted]	1338-43-8, 37318-79-9	SORBITAN OLEATE
AVENA SATIVA (OAT) PROTEIN EXTRACT	[redacted]	[redacted]	[redacted]	134134-87-5	AVENA SATIVA (OAT) PROTEIN EXTRACT
CURCUMA LONGA (TURMERIC) ROOT EXTRACT	[redacted]	[redacted]	[redacted]	84775-52-0	CURCUMA LONGA (TURMERIC) ROOT EXTRACT
KOJIC ACID	[redacted]	[redacted]	[redacted]	501-30-4	KOJIC ACID
TITANIUM DIOXIDE	[redacted]	[redacted]	[redacted]	13463-67-7, 1317-70-0, 1317-80-2	TITANIUM DIOXIDE (CI 77891)
CURCUMA LONGA ROOT OIL	[redacted]	[redacted]	[redacted]	84775-52-0	CURCUMA LONGA ROOT OIL (RB)
LAVANDULA ANGUSTIFOLIA (LAVENDER) OIL	[redacted]	[redacted]	[redacted]	84776-65-8, 8000-28-0	LAVANDULA ANGUSTIFOLIA (LAVENDER) OIL (GENERIC)
CITRUS LIMON (LEMON) PEEL OIL	[redacted]	[redacted]	[redacted]	8008-56-8, 85085-28-5, 84929-31-7, 8020-19-7	CITRUS LIMON (LEMON) PEEL OIL (GENERIC)
DAUCUS CAROTA SATIVA (CARROT) SEED OIL	[redacted]	[redacted]	[redacted]	8015-88-1, 84929-61-3	DAUCUS CAROTA SATIVA (CARROT) OIL
BOSWELLIA CARTERII OIL	[redacted]	[redacted]	[redacted]	89957-98-2, 8016-36-2, 8050-07-5	BOSWELLIA CARTERII (FRANKINCENSE) OIL
CANANGA ODORATA (YLANG YLANG) FLOWER OIL	[redacted]	[redacted]	[redacted]	83863-30-3, 93686-30-7, 8006-81-3	CANANGA ODORATA (YLANG YLANG) FLOWER OIL (GENERIC)
SANTALUM ALBUM OIL	[redacted]	[redacted]	[redacted]	84787-70-2, 8006-87-9	SANTALUM ALBUM (SANDALWOOD) OIL

Toxicological Review of Ingredients

Chemical Name: COCOS NUCIFERA OIL			
Function:HAIR CONDITIONING MASKING PERFUMING SKIN CONDITIONING			
Regulatory Status (Toxicological Risk Assessment Report):			
Exposure	**NOAEL**	**Safety Factors**	**MoS**
		0	MoS For Adult:

Summary Data:

Cosmetic Functions : Hair Conditioning / Masking / Perfuming / Skin Conditioning. Cocos Nucifera Oil is the fixed oil obtained by expression of the kernels of the seeds of the Coconut, Cocos nucifera L., Palmaceae. According to the FDA VCRP program in 2019, the INCI name was used in 4353 cosmetic formulations. FDA 21CFR175.105, 21CFR175.300, 21CFR176.200, 21CFR176.210, 21CFR177.2800, 21CFR182.70: GRAS substance and indirect food additive (PCPC and CosIng).
CIR 1986:
Coconut Oil and its derivatives, Coconut Acid, Hydrogenated Coconut Acid, and Hydrogenated Coconut Oil, are used by industry as a convenient source of lower chain length fatty acids.
Composition: Coconut Oil is obtained by expression from the kernels of the seeds of Cocos nucifera. The primary constituents are trimyristin, trilaurin, tripalmitin, tristearin, and various other triglycerides. About 90% of the oil is saturated.
Method of manufacture:Coconut Oil is obtained from copra, where it is present in quantities of 60-70%. The expressed material has a water content of 4-10%.
Impurities: Coconut Oil is usually quite low in color bodies, pigments, phosphatides, gums, and other nonglyceride substances commonly found in much largerquantities in other vegetable oils. It may contain free fatty acids, low concentrations of sterols, tocopherol, and squalene. It is the presence of lactones at approximately 150 ppm that provides the characteristic coconut flavor. They arepresent as a series of b-lactones with 6, 8, 10, 12, and 14 carbon atoms. Crude samples of Coconut Oil contain traces of polycyclic aromatic hydrocarbons (PAH), particularly when the copra is smoke-dried. A combination of activated charcoal treatment and steam vacuum deodorization are the common refining methods most likely to remove PAH from edible oils. It can also contain aflatoxins.
In cosmetic products, Coconut Oil is used as a cleanser, foaming agent, or stabilizer at concentrations up to 50%. Acute, chronic, and subchronic oral toxicity studies indicate that Coconut Oil and Hydrogenated Coconut Oil are relatively nontoxic by ingestion. Neither compound produced significant skin or eye irritation in laboratory animals. No sensitization was reported. Clinical assessment of cosmetic products containing Coconut Oil produced very minimal skin irritation reactions. There was no indication that these ingredients were primary irritants, sensitizers, or phototoxic compounds following human testing. It is concluded that Coconut Oil, Coconut Acid, Hydrogenated Coconut Oil, and Hydrogenated Coconut Acid are safe for use as cosmetic ingredients.
Non cosmetic use: The traditional use of Coconut Oil is in the manufacture of soap, but it is also used in other industrial processes. Coconut Oil is now being incorporated into a wide variety of food products and medicines. The FDA regulates Coconut Oil and Coconut Fatty Acid as indirect food additives and classifies both materials as an inactive pharmaceutical ingredient for over-the-counter (OTC) rectal suppository preparations.
Acute oral toxicity: Undiluted Coconut Oil was not toxic to rats up to 5 g/kg administered by gavage.
Subchronic Oral Toxicity: Wistar rats (120 day old) of each sex were used to compare the effects ofdiets containing 25% Coconut Oil or 25% butterfat fed ad libitum for 90 days. Both experimental groups developed a progressive increase in fat content of the liver, which was 20-30% higher than controls by the end of the study. Fattychange of the liver was very slight. No other pathological change was found inany animal of any group.
Skin irritation: a 24-h occlusive patch test in rabbits with undiluted Coconut Oil was non irritant.
Skin sensitization: a Magnusson-Kligman Maximization test conducted in guinea pigs with coconut oil (5% for induction, 100% for topical booster, 50% and 100% for challenge) was non irritant and non sensitizing.
Eye irritation: Undiluted coconut oil administered to rabbit eye was minimally irritant.
Clinical data indicate that bar soap containing 13% coconut oil was non irritant nor sensitizing and not phototoxic.
CIR 2011:
Cocos nucifera (coconut) oil, oil from the dried coconut fruit, is composed of 90% saturated triglycerides. It may function as a fragrance ingredient, hair conditioning agent, or skin-conditioning agent and is reported in 626 cosmetics at concentrations from 0.0001% to 70%. The related ingredients covered in this assessment are fatty acids, and their hydrogenated forms, corresponding

fatty alcohols, simple esters, and inorganic and sulfated salts of coconut oil. The salts and esters are expected to have similar toxicological profiles as the oil, its hydrogenated forms, and its constituent fatty acids. Coconut oil and related ingredients are safe as cosmetic ingredients in the practices of use and concentration described in this safety assessment.
Coconut oil is used in baby products up to 0.3% (data from 2008).
Non cosmetic uses: Coconut oil is used in the manufacturing of soaps, edible fats,chocolate, candies, candles, and night lights. It is also used inplace of lard in baking, in cotton dyeing, and as a base for ointment.
Genotoxicity: saponified coconut oil is not genotoxic in Ames test.
Clinical data: Coconut oil was not an allergen at 100% concentration in 12 participants in a double-blind randomized controlled pilot study.
CIR 2017:
The Cosmetic Ingredient Review Expert Panel (Panel) assessed the safety of 244 plant-derived fatty acid oils as used in cosmetics. Oils are used in a wide variety of cosmetic products for their skin conditioning, occlusive, emollient, and moisturizing properties. Since many of these oils are edible, their systemic toxicity potential is low. Indeed, exposure to the oils from food use would result in a much larger systemic dose than that resulting from use in cosmetic products. Therefore, the review focused on potential dermal effects. The Panel concluded that the 244 plant-derived fatty acid oils are safe as used in cosmetics. Oils derived from edible vegetables, fruits, seeds, tree, and ground nuts have been safely consumed by, and applied to the skin of, humans for thousands of years. Although nuts, fruits, and vegetables themselves may cause allergic reactions in certain individuals, the refined oils derived from these plants generally pose no significant safety concern following oral exposure, and their general biology is well characterized due to extensive use in food materials.
The fatty acid composition of Cocos Nucifera (Coconut) Oil is mainly: lauric (44-52%), myristic (13-19%) and palmitic (8-11%) acids.
Coconut oil did not produce adverse effects in several therapeutic studies.
Margin of safety: Cocos Nucifera (Coconut) Oil is largely consumed and edible, no systemic toxicity is expected with the use of Cocos Nucifera (Coconut) Oil.
Ref.: CosIng database. Cocos Nucifera Oil.
PCPC online database. Cocos Nucifera (Coconut) Oil.
CIR report. Final Report on the Safety Assessment of Coconut Oil, Coconut Acid, HydrogenatedCoconut Acid, and Hydrogenated Coconut Oil. Journal of the American College of toxicology, Volume 5, Number 3, 1986.
CIR report. Final Report on the Safety Assessment of Cocos nucifera (Coconut) Oil and Related Ingredients. 2011.
CIR report. Safety Assessment of Plant-Derived Fatty Acid Oils. 2017.

Chemical Name: ELAEIS GUINEENSIS (PALM) OIL

Function:emollients

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
		0	MoS For Adult:

Summary Data:

Function in cosmetics: Emollient, Skin Conditioning, Occlusive. Elaeis Guineensis Oil is a natural oil obtained from the fruits of the Palmoil Tree, Elaeis guineensis, Palmaceae. VCRP Frequency of Use as of 01/2015 : 256 cosmetic formulations. Classified as an indirect food additive (21CFR175.105, 21CFR175.300,21CFR176.200, 21CFR176.210). (PCPC)

Palm Oil is obtained from the mesocarp of the Elaeis guineensis palm tree. It is not a fully saturated oil, and contains equal amounts of saturated and unsaturated fatty acids, expressed as percent of total fatty acids as follows: Saturated (50%), Monounsaturated (39%), and Polyunsaturated (10%).Copper and iron impurities have been detected in crude Palm Oil.The following heavy metal impurities have been detected in refined Palm Oil: iron (0.02~3.07 ppm), copper (0.03 ppm), and nickel (0.01--0.03 ppm). (CIR 2010)

Other uses: The major end use for Palm Oil in the importing countries is for the manufacture of compound cooking fats and margarine. (CIR 2010)

Acute toxicity: The acute oral toxicity of undiluted Palm Oil was evaluated using five rats. The two deaths that were reported

occurred at 1 and 6 days post intubation, respectively. The LD50 was greater than 5.0 g/kg, and the test substance was classified as slightly toxic. (CIR 2010)

Repeated-dose toxicity: The short-term oral toxicity of crude Palm Oil was evaluated using four groups of 10 weanling Wistar albino rats (5 males, 5 females per group). Groups of rats received the following diets ad libitum for 28 days: group I (protein-free diet), group II (10% refined groundnut oil with 10% casein protein in diet), group III (10% crude Palm Oil with 10% casein protein in diet), and group IV (10% refined palm-olein oil [refined Palm Oil l with 10% casein protein in diet). No adverse effects were observed and all values were comparable to control values.The subchronic oral toxicity of 15% untreated Palm Oil and 15% heated Palm Oil (220°C) was evaluated using Sprague-Dawley rats (10/sex/group). The growth of animals between 0 and 13 weeks was comparable between the two groups. Untreated Palm Oil (15%) and 15% heated Palm Oil were not toxic when administered orally to rats. The subchronic oral toxicity of crude Palm Oil was evaluated weanling Wistar albino rat (15/sex/group). Rats were fed diets containing 10% refined groundnut oil, 10% refined palm-olein oil, and 10% crude Palm Oil, respectively, for 90 days. No adverse effects were observed and all values were comparable to control values. In a 1-year study, rats were fed a diet consisting of 15% heated Palm Oil liquid fraction and 16% soybean protein. Growth rate inhibition was observed in the two groups (both sexes) fed heated oil in the diet.The serum cholesterol concentration was significantly greater in females fed the heated peanut oil diet when compared to the other dietary groups. Alkaline phosphatase activity was significantly greater in rats of both sexes fed heated oils than in those fed heated oil in the diet. This effect was accompanied by hepatic hypertrophy, which can be indicative of liver metabolic hyperactivity. (CIR 2010)

Ocular irritation:The ocular irritation potential of undiluted Palm Oil was evaluated using six rabbits. The total ocular irritation score (six rabbits) was 3 at day 1 post instillation and I at day 2 post instillation. All reactions had cleared by day 3. The investigators concluded that undiluted Palm Oil induced minimal ocular irritation. Two different hand creams containing 2.0% Palm Oil also induced minimal ocular irritation when tested according to the same procedure. A facial lotion containing 1.5% Palm Oil induced moderate ocular irritation in another ocular irritation study using six rabbits (same procedure). (CIR 2010)

Skin irritation: The primary skin irritation potential of undiluted Palm Oil was evaluated in a single-insult occlusive patch test using nine rabbits. The primary irritation index (PII) was 0.22 (maximum possible score = 8), and the test substance was classified as practically nonirritating. In a second study (same procedure), the PII was 0.67, and the test substance was classified as minimally irritating. (CIR 2010)

Skin sensitization: The skin sensitization potential of Palm Oil was evaluated in the Magnusson-Kligman Maximization Test using four groups of 10 female, albino guinea pigs of the Hartley strain. During induction, three pairs of sites per animal were injected with the following materials, respectively: 5% Palm Oil (1st group) /5% phenylacetaldehyde (2nd group),in propylene glycol, 5% Palm Oil (1st group) /5% phenylacetaldehyde (2nd group),in 50% aqueous Freund's Complete Adjuvant, and 50% Freund's Complete Adjuvant.In the booster phase, initiated 1 week after induction, an occlusive dressing pad containing full strength Palm Oil (0.5 ml) (1st group) /phenylacetaldehyde (25%) (2nd group)was applied over the induction injection sites. The only challenge reactions reported (mild--pink uniform erythema covering most of the contact area) were observed in the second test group challenged with 2% phenylacetaldehyde. The investigators concluded that Palm Oil was nonallergenic. The skin sensitization potential of 15% Palm Oil in petrolatum was evaluated in a modified Draize assay using 120 subjects. During induction, the test substance was applied under occlusive condition to skin sites on the scapular region of the back using a Finn Chamber. Each chamber contained 0.025 g of the test substance per application. 10 induction applications were made to each subject. Induction reactions were scored at 48 hours post application (Monday and Wednesday applications) and at 72 hours post application (Friday applications) according to the following scale: 0 (no reaction) to 4 (erythema, edema, and bullae). It was concluded that Palm Oil (15% in petrolatum) did not induce sensitization in either of the 110 subjects tested (CIR 2010)

Phototoxicity: The phototoxicity of a facial lotion containing 1.5% Palm Oil was evaluated in the phototoxicity yeast assay. Test cultures treated with 1.5% Palm Oil were irradiated with UV light for 18 hours, and evaluated for zones of inhibition at 48, 72, and 96 hours. The facial lotion was not classified as phototoxic. (CIR 2010)

Reprotoxicity: Many reprotoxicity studies have been performed with Palm Oil. It was concluded that crude Palm Oil had no adverse effect on several reproductive parameters. The reproductive toxicity of 15% untreated Palm Oil and 15% heated Palm Oil (220°C) was evaluated using Sprague-Dawley rats (10 males, 20 females per group). After feeding, 10 males were mated with 20 females from their respective groups over a period of 18 days. The matings resulted in 234 live young (untreated Palm Oil) and 205 live young (heated Palm Oil). Both the number of implantations per dam and the average number of live young per litter were considered acceptable for both groups. The number of embryo losses during gestation was comparable between groups fed untreated Palm Oil and heated Palm Oil. (CIR 2010)

Mutagenicity: The mutagenicity of refined and unrefined Palm Oil was evaluated using Salmonella typhimurium strains TA1537,

TA1538, TA97, TA98, TA100, and TA102. Both refined and unrefined Palm Oil induced reproducible weak mutagenicity only in strain TAI537. In two other assays, no consistent evidence of mutagenicity was found in any of the strains tested.The genotoxicity of Palm Oil was evaluated using bone marrow cells from 10 female mice. Three groups were dosed with Palm Oil supernatant, Palm Oil sediment, and a mixture of the two, respectively, by gavage for 5 consecutive days. Mice in each group received daily doses of 4.5 g/kg. Compared to the negative-control group, no statistically significant differences were observed in the frequency of chromosomal aberrations and the mitotic index in bone marrow samples from all three test groups. More than one aberration per cell was identified in bone marrow samples from the positive control. Compared to the negative control, results for the positive-control group were significant at the 1% level. (CIR 2010)

Carcinogenicity: Groups of young, female Sprague-Dawley were fed either a chow diet or semi-purified diet containing 5% corn oil or 20% corn oil, Palm Oil, lard or canola oil for approximately 6 weeks. Rates of cellular proliferation were lower in the mammary glands of rats fed chow, 5% corn oil, or 20% Palm Oil than in those fed the other diets. These results were in accordance with the concept that the fat content of the mammary gland is positively correlated with susceptibility to mammary cancer. The effect of dietary Palm Oils on mammary carcinogenesis was also evaluated using three groups of 20 female Sprague-Dawley rats (45 days old). The three groups were fed semisynthetic diets containing 20%, by weight, crude Palm Oil (CPO), 20% refined, bleached, deodorized palm oil (RBD PO), and 20% metabisulfite-treated Palm Oil (MCPO), respectively, for 5 months. The two groups of rats fed 20% CO and 20% SBO, respectively, appeared to develop mammary tumors earlier than the three Palm Oil-fed groups. However, differences in mean latency periods were not statistically significant. The final incidences of palpable mammary tumors were 85%, 90%, 65%, 70%, and 70% for CO, SBO, CPO, RBD PO and MCPO groups, respectively. Mammary tumor incidences (palpable and nonpalpable) for Palm Oil-fed rats were as follows: 20% RBD PO diet (27 palpable, 3 nonpalpable); 20% CPO (23 palpable, 2 nonpalpable); and 20% MCPO (23 palpable, 5 nonpalpable). The two groups fed 20% CO and 20% SBO in the diet, respectively, had significantly more mammary tumors than the three groups that were fed Palm Oil diets. (CIR 2010)

The CIR Expert Panel concluded that Elaeis Guineensis Oil is safe as used up to 13% in LO and 48% in RO products, up to 2% in eye area and incidental ingestion products, 48% in dermal contact and mucous membrane products, 34% in hair products (CIR 2017).

Ref.: PCPC Online database. https://online.personalcarecouncil.org/jsp/IngredientDetail.jsp?monoid=9328 January 4, 2019
CIR Final report. Safety assessment of Safety Assessment of Elaeis Guineensis (Palm) Oil, Elaeis Guineensis (Palm) Kernel Oil, Hydrogenated Palm Oil and Hydrogenated Palm Kernel Oil. IJT 19(S2):7-28, 2000
CIR Final report. Safety assessment of plant-derived fatty acid oils. IJT 36(Suppl. 3):51-129, 2017

Chemical Name: Glycerin; Glycerol

Function: Denaturant / Humectant / Solvent /Conditioner, Viscosity Decreasing Agent

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
ORAL	8000 mg/kg bw/day	0	MoS For Adult: 9988.4

Summary Data:

Function: Denaturant / Humectant / Solvent /Conditioner, Viscosity Decreasing Agent.
Glycerin is a sweet-tasting simple polyol compound with three hydrophilic hydroxyl groups that are responsible for its solubility in water and its hygroscopic nature. The glycerol backbone is central to all lipids known as triglycerides. Used extensively in cosmetics, toiletries and pharmaceutical products for over 100 years and is generally recognized for its low-risk health effects. Consumer exposure to glycerin will occur principally through dermal and oral exposure. Upon contact, skin may feel warm due to the absorption of moisture from the skin. The majority of the toxicological information on this material is from human data. Toxic doses of glycerol, as with all chemicals, can be obtained when administered in sufficient quantities. However, health individuals can easily tolerate doses of up to 1.5 g/kg or less with only slight diuresis occurring. Glycerol is absorbed from the intestinal tract and is metabolized to carbon dioxide and glycogen in the liver (OECD SIDS, 2002; CIR, 2015).
According to CIR's Expert Panel, glycerin is safe in cosmetics in the present practices of use and at concentrations up to 78.5% in leave-on products and 68.6% in rinse-off products (CIR, 2015). According to 21CFR182.1320, glycerin is generally recognized as safe (GRAS) when used in accordance with good manufacturing practices.
Acute toxicity: Low acute toxicity (oral and dermal LD50> 4g/kg; Inhalation LC50 (rat)> 570 mg/m3/hr). Adverse effects in humans

following oral administration of glycerol include mild headache, dizziness, nausea, vomiting, thirst, and diarrhea. A single prolonged exposure to glycerin is not likely to be absorbed in significant amounts through the skin and so is not likely to cause toxicity (OECD SIDS, 2002; CIR, 2015).
Irritation: Non-irritant on skin in the Draize test. Very low eye irritation potential. 0.1 mL undiluted glycerol was instilled in the eyes of 6 rabbits) caused no evidence of irritation after 1, 24 and 72 hours and after 7 days. The overall irritation score using the Draize system was 0-2. Causes slight irritation on topical application to the eyes. Regularly used as ophthalmic solution; repeated application of 100% glycerol to the surface of human eye has been shown on microscopic examination to cause reversible changes in the appearance of the endothelium (OECD SIDS, 2002; CIR, 2015).
Sensitization: Non-sensitizing. No reported evidence of skin sensitization potential in human and in animal testing (OECD SIDS, 2002; CIR, 2015).
Photo-induced toxicity: No data available which indicates phototoxicity including irritation or sensitization potential (OECD SIDS, 2002; CIR, 2015).
Repeat dose toxicity: Repeated oral exposure to glycerol did not induce adverse effects other than local irritation of the gastro-intestinal tract. No toxicity effects observed in a 2-year study in rats orally administered ~ 10 g/kg/day (i.e., 20%) in the diet and in a 90-day study in rats administered 50000 or 200000 ppm in the diet. The NOEL in the 90-day study was concluded as 50000 ppm (~ 5000 mg/kg/day). An oral NOAEL of 8000 mg/kg bw/day can be assigned based on a 2-year repeated dose study in rats where no effects were observed at the highest dose tested (20% glycerin; equivalent to 8000 mg/kg bw/day in males and 10000 mg/kg/day in females) (OECD-SIDS, 2002). For inhalation exposure to aerosols, the NOAEC for local irritant effects to the upper respiratory tract is 165 mg/m3 and 662 mg/m3 for systemic effects (OECD SIDS, 2002; CIR, 2015).
Genotoxicity: Non mutagenic or genotoxic in bacterial assay and in vitro chromosome aberration studies with or without metabolic activation (OECD SIDS, 2002; CIR, 2015).
Carcinogenicity: Non-carcinogenic according to a chronic carcinogenicity study where glycerin was administered for up to 2 years in the diet of rats and according to the OECD-SIDS Expert Panel (OECD SIDS, 2002)
Reproductive/developmental toxicity: Effects on fertility and reproductive performance were not observed in a 2-generation study with glycerol administered by gavage (NOAEL 2000 mg/kg/day). No maternal toxicity or teratogenic effects were seen in the rat, mouse or rabbit at the highest dose levels tested in a guideline comparable teratogenicity study (NOEL >1180 mg/kg/day) (OECD SIDS, 2002).
Other data (human): Ingestion of 30 ml of glycerol thrice daily for a period of 50 days by normal human subjects was found to be harmless. However, a few cases of reactions such as lowered blood sugar and unconsciousness, following intravenous or oral doses have been reported in susceptible individuals (OECD SIDS, 2002; CIR, 2015).
Dermal absorption: When applied to unbroken skin, pure glycerin apparently is not appreciably absorbed. However, glycerin may be absorbed in potentially harmful amounts when applied in large quantities to severe burns (second or third degree) over large areas of the body as part of a cream or other topical application. Absorption under such circumstances can elevate serum osmolality and may result in osmotic shock (OECD SIDS, 2002; CIR, 2015). Worst case dermal absorption of 100% is assumed.
Margin of Safety: NOAEL: 8000 mg/kg/day (2-year repeated dose, rat, oral; OECD-SIDS, 2002); DAp = 100% (default)
References: OECD SIDS (2002). Initial Assessment Report for SIAM 14, 2002.
ECHA. REACH Dossier for Glycerin (CAS No. 56-81-5; EINECS No. 200-285-9).
CIR (2015). Safety Assessment of Glycerin as Used in Cosmetics. Final Report. 12/09/2014.
21CFR582.1320 - Code of Federal Regulations Title 21 (fda.gov). Accessed 7/14/2023.

Chemical Name: AQUA (Water)

Function: Solvent - Dissolves other substances

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
		0	MoS For Adult:

Summary Data:

Function : Solvent. Simply water unlikely to cause irritation, allergy or harm. Used in many cosmetic products as a solvent and necessary to sustain biological life. The source of water should be known, monitored to GMP and either a deionised or high purity grade free from toxins, pollutants and bacteriological contamination should be used in cosmetic products.

Chemical Name: Sodium hydroxide

Function: Sodium hydroxide is used as buffering and denaturant in the cosmetics (Coslng, 2013). In detergents it acts as pH adjuster. For purposes of labelling it isn't cited, it is a non-ionic surfactant.

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
		0	MoS For Adult:

Summary Data:

Cosmetic Functions: Buffering / Denaturant. Sodium hydroxide (NaOH) is a strong alkaline substance that dissociates completely in water into the sodium ion (Na+) and hydroxyl ion (OH-). Used in the manufacture of chemicals, rayon, soap and detergents amongst other products. Sodium hydroxide toxicity depends on the concentration of the sodium hydroxide solution and the duration of its contact with tissue. Normally used to neutralise a product so is rarely present in the finished product. It is controlled under the EU Cosmetic Regulations (Annex III/1,15a): Maximum permitted varies with product. Maximum permitted pH = 11 for general use as pH adjuster. Permitted at the following concentration according to the product type with the conditions of use and warnings included on the product label: (a) Nail cuticle solvent- 5%; Contains alkali. Avoid contact with eyes. Can cause blindness. Keep out of the reach of children. (b) Hair straightener– 2% (general consumer use) - Contains alkali. Avoid contact with eyes. Can cause blindness. Keep out of reach of children. 4.5% (professional use) - For professional use only. Avoid contact with eyes. Can cause blindness. (c) pH adjuster for depilatories maximum pH of 12 – Keep out of the reach of children. Avoid contact with eyes.

Sodium hydroxide acts locally, exerting a strong corrosive action whose mechanism is not known, and causes almost immediate degeneration of the tissue, which can result in rapid absorption of sodium hydroxide into the circulating system and distribution with the body water. It dissociates completely in water, blood, and cytoplasm and is not metabolized. Sodium is a normal constituent of the blood and an excess is excreted in the urine. A significant amount of sodium is taken up via the food because the normal uptake of sodium via food is 3.1-6.0 g per day. Exposure to NaOH could potentially increase the pH of the blood. However, the pH of the blood is regulated between narrow ranges to maintain homeostasis. Via urinary excretion of bicarbonate and via exhalation of carbon dioxide, the pH of blood is maintained at the normal physiological pH of 7.4-7.5. Therefore, NaOH is not expected to be systemically available in the body under normal handling and use conditions. Sodium hydroxide is corrosive to all body tissues; concentrated vapours cause serious damage to the eyes and respiratory system. Ingestion of sodium hydroxide, which occurs frequently in children, can cause severe necrosis, with stricture of the esophagus and death. Contact with the skin can result in dermatitis, loss of hair, and necrosis due to irritation. Skin types vary in sensitivity to caustic irritation.

Acute toxicity: Limited animal data is available on acute systemic dermal toxicity; clipped skin of adult mice was painted with 50% NaOH and rinsed off at various intervals. Mortality was observed when left on for 30 minutes or longer. However, no mortality was reported when rinsed off immediately. No acute inhalation or oral studies have been conducted with sodium hydroxide. Human case reports indicate that the degree and type of injury after ingestion of NaOH depend on the physical form. Solid NaOH produces injury to the mouth and pharynx and is difficult to swallow. On the other hand liquid NaOH is easily swallowed, being tasteless and odourless, and is more likely to damage the oesophagus and stomach.

Irritation: Corrosive. Exposure to sodium hydroxide solid or solution can cause skin and eye irritation. Direct contact with the solid or with concentrated solutions causes thermal and chemical burns leading to deep-tissue injuries. Very strong solutions of sodium hydroxide can hydrolyze proteins in the eyes, resulting in ulceration, perforation and opacification of the cornea or, in extreme cases, blindness. Inhalation of sodium hydroxide dust, mist, or aerosol may cause irritation of the mucous membranes of the nose, throat, and respiratory tract. Contact with 25-50% solutions produces immediate irritation, while after contact with solutions of 4% or less, irritation may not develop for several hours. Based on human data concentrations of 0.5 - 4% were irritating for the skin but no irritant effect were observed on application of 0.05%. Available animal data indicate that non-irritant level was 0.2-1.0%, while the corrosive concentration was 1.2%. In occupational exposure, concentration of up to 1.0 mg/m3 did not cause respiratory tract irritation.

Sensitisation: Not sensitising. NaOH was negative in human skin sensitisation study. Despite the long and widespread use, no human cases of skin and/or respiratory sensitisation have been reported with it.

Mutagenicity/Genotoxicity: Both the in vitro and the in vivo genotoxicity studies indicated no evidence for a mutagenic activity.

Repeat dose toxicity: No adequate data available by the oral, dermal or inhalation routes. A limited oral drinking water study with rats revealed effects on growth. However, this is not considered a toxicological response; NaOH neutralises the acid environment in the stomach which decreases the digestion and the absorption of food. Marzulli and Maibach (1975; as cited in BEST, 1984) applied sodium hydroxide solutions to the backs of human subjects in occluded patches renewed daily for 21 days. No irritation was reported at the lowest concentration studied, 0.05%; NaOH was found to be mildly irritating at 0.5% and severe irritation was seen with solutions of 4% or 5%. This data suggests that the NOAEL for localized effects on dermal application is 0.05%. No data have been found concerning carcinogenicity, reproduction or developmental toxicity of sodium hydroxide. It is not classified for carcinogenicity.

Photo-induced toxicity: No data available which indicate that sodium hydroxide is phototoxic.

Other data (human): Human poisoning cases indicate that less than 10 grams taken orally is fatal. In addition, controlled dermal exposures with concentrated sodium hydroxide have resulted in intercellular edema, erythema, decomposition of keratin material, and destruction of the epidermis. It has been observed that there may be a latency period between dermal contact and the onset of a sensation of irritation or burning. Exposure to sodium hydroxide mist may cause multiple small burns and temporary hair loss.

Dermal / percutaneous absorption: No data available. Degeneration of epidermal tissue on application would result in absorption but it dissociates completely in water, blood and cytoplasm and is therefore, not systemically available.

Margin of Safety: Inadequate data available to identify a NOAEL; therefore MoS cannot be calculated. Sodium hydroxide acts as buffering agent and is expected to be neutralized in action and therefore, not available systemically.

References:

Board of Environmental Studies and Toxicology (BEST). Emergency and Continuous Exposure Limits for selected Airborne Contaminants, Volume 2, 1984 : Sodium Hydroxide; Page 87-94. Accessed on 04/03/2013 at: www.nap.edu/openbook.php?record_id=690&page=87

EU Risk Assessment Report for Sodium Hydroxide

The Office of Environmental Health Hazard Assessment (OEHHA): Determination of Acute Reference Exposure Levels for Airborne Toxicants March 1999. Sodium Hydroxide. Accessed on 04/03/2013 at: http://oehha.ca.gov/air/acute_rels/pdf/1310932A.pdf

Chemical Name: Propylene Glycol, Propylenglycolum, Propane-1, 2-diol, 1,2-Propanediol

Function: Humectant / Solvent / Skin Conditioning

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
ORAL	1700 mg/kg bw/day	Not reported	MoS For Adult: 636763.5

Summary Data:

Functions: Humectant / Solvent / Skin Conditioning.
Propylene glycol (PG) is one of the most commonly used humectants in cosmetic formulations, topical pharmaceutical preparations, and food additive amongst other applications. Since 1942, it has been included in New and Non-Official Remedies as a proper ingredient for pharmaceutical products. The toxicity of PG has been extensively reviewed by various Expert Panels including the Cosmetic Ingredient Review Experts who considered it safe in cosmetic products at up to 50% (CIR, 2012).
PG is generally regarded to be of low order of toxicity. Very high acute doses of PG may however lead to lactic acidosis. Symptoms of acute PG intoxication in animals include CNS depression and narcosis. Individuals with compromised hepatic or renal function

would be less apt to clear propylene glycol, and hence would be more susceptible to toxicity due to high blood levels. PG is rapidly absorbed on oral administration. Following oral gavage, approximately 52% of the radiolabeled dose was excreted in the urine with the remaining radioactivity exhaled as CO2 (~20.2%). Only a small fraction (5%) was found in the feces. In humans, absorbed PG undergoes metabolism to lactic acid and are rapidly cleared from the system (t1/2 =2 hours). However, a small number of studies suggest that elimination of PG in infants is slower than in adults; prolonged t1/2 in infants in the range of 10.8 – 30 hours (NTP-CERHR, 2004). Available information indicates that the dermal absorption of PG across intact human skin is slow and limited. As demonstrated in hairless mouse, much of the uptake amount after dermal application remains in the upper layers of skin and is not penetrated into dermis or absorbed systemically. However, PG may act as a penetration enhancer for some chemicals probably by alteration of barrier function or an induced increase in the solution capacity within the stratum corneum (CIR, 2012). The low vapor pressure of propylene glycol in combination with the short half-life before saturation of metabolism suggests that significant absorption from the nasal mucosa would not occur on inhalation exposure. Of an average of 263 mL of nebulized aerosol, 8.1 mL containing 10% PG was retained per hour, corresponding to about 0.8 g of compound, which in turn amounts to 0.09 g/kg per 8 hours. Therefore, it can be concluded that under normal conditions of exposure, PG via inhalation is of limited toxicological relevance (NTP-CERHR, 2004). PG was moderately cytotoxic to human fibroblasts and keratinocytes, but it induced only a few toxic effects when administered orally in animal studies (NTP-CERHR, 2004).

Acute toxicity: Low acute toxicity. The reported oral LD50 for PG in various animal species ranges from 8 to 25 g/kg. The dermal LD50 was > 2000 mg/kg when applied under occlusion to the clipped skin of rabbits (ECHA, 2023). The LC50 (rabbits, 2 h exposure) was > 317042 mg/m³ air (10000 ppm) which indicates low acute inhalation toxicity (ECHA, 2023). A lethal oral dose of propylene glycol has not been reported for humans, but it is estimated that the human lethal oral dose is >15 g/kg for a 70 kg person (NTP-CERHR, 2004).

Skin irritation: Application to skin of rabbit under occlusion in a standard test was non-irritating; primary irritation index, PII =0 (REACH Dossier). Based on the results from a Guideline 404 skin irritation test along with previous study data, it was not a skin irritant, producing a negligible response after 4 hours occluded contact (SIDS, 2001). Humans displayed no effects as a result of open or occluded exposure to propylene glycol for up to 10 days; Rabbits displayed no effects as a result of open or occluded exposure to propylene glycol for up to 10 days; Guinea pigs displayed no effects as a result of open exposure to propylene glycol for up to 10 days; when propylene glycol was applied under occlusive patches increased skin -fold thickness was seen from 7 to 10 days after application (SIDS, 2001). The dermal irritation potential of 100% propylene glycol was evaluated with male hairless SKH1 hr/hr mice. Propylene glycol was instilled in polyvinyl chloride cups (vol 0.3 cm3) on the dorsal side of 3 mice for 24 h. At the end of the 24 h, the animals were killed, and a sample of the exposed skin was examined microscopically. Propylene glycol was minimally irritating, with a total score of 7 (maximum score =77) (CIR, 2012).

Eye irritation: Undiluted PG is minimally irritating to the eye, inducing slight transient conjunctivitis. Results of a guideline study (OECD 405 method) demonstrated that undiluted propylene glycol was minimally irritating to the eyes, producing slight transient conjunctivitis which resolves by 24-48 hours (SIDS, 2001).

Skin sensitization: PG was non-sensitizing in Magnusson-Kligman guinea pig maximization test, split adjuvant test, and in mouse local lymph node assay, LLNA (REACH Dossier). The stimulation index (SI) reported in the LLNA was 1.2 and 1.6 for 50% and 100% solution, respectively. Several sensitization/allergenicity assays of propylene glycol were performed in guinea pigs. No sensitization observed in these assays (concentrations was not specified) (CIR, 2012). In a 4-wk use study completed with 26 male subjects following the same procedure, a deodorant stick containing 65.8% propylene glycol also did not demonstrate a potential for eliciting dermal irritation or sensitization (CIR, 2012). Thirty-day use studies were completed with 26 male, 40 female, and 24 male subjects to evaluate the potential for deodorant sticks containing 35, 65, 2 and 73% propylene glycol, respectively to induce dermal irritation and/or sensitization. None of the subjects had any irritation or sensitization reactions, and the researchers concluded that the deodorant sticks containing 35, 65.2 or 73% propylene glycol did not demonstrate a potential for eliciting dermal irritation or sensitization (CIR, 2012)

Photo-induced toxicity: Propylene glycol did not absorb in the UVA or UVB range, hence phototoxicity is not expected. (CIR, 2012).

Photo-allergenicity was not reported in a provocative photo-patch test in human volunteers with PG (CIR, 2012). Repeat dose toxicity: Rats were fed for 2 years on diets containing 0, 6250, 12500, 25000 and 50000 ppm propylene glycol (ca. 0, 200, 400, 900 and 1700 mg/kg bw/day (males); 0, 300, 500, 1000 and 2100 mg/kg bw/day (females). No significant adverse effects noted clinically, on body weight, food consumption, at necropsy or on microscopic examination. A NOAEL of 1700 mg/kg bw/d was identified. Another study in rats fed PG for 2 years reported slight liver damage (described as centrilobular atrophy, bile duct proliferation and fatty degeneration) at daily doses of 4.9% (~ 3000 mg/kg bw/d). In dogs fed 8% (2000 mg/kg bw/d) and 20% (5000 mg/kg bw/d) PG in the diet, hemolysis was observed at the high dose; the NOAEL under the study conditions was 2000 mg/kg bw/d. When administered to rats in drinking water over 140 days, a NOAEL of 13200 mg/kg bw/d was identified (ECHA, 2023). The lowest reported NOEL of 1700 mg/kg bw/d identified in the 2-year study is considered appropriate in characterizing the safety margin.

Reproductive/developmental toxicity: The reproductive and developmental toxicity data for PG have been evaluated by NTP-CERHR in 2004. The Panel concluded that reproduction and development was not significantly impaired by PG. In a continuous breeding study, PG was administered in the drinking water of mice at doses of 0, 1.0, 2.5, and 5.0% (mean exposures of 0, 1,819,

4,796, and 10,118 mg/kg/day based on water consumption) to parental generation 1-week prior to and during cohabitation (14-week period). No adverse effects on any measure of reproduction including fertility, litter size, pup weight and sex ratio were observed (ATSDR, 1997). There was no effect on the reproductive capacity of offspring from the high dose group. No major adverse effects were reported in teratogenicity studies with PG (doses: 0, 16, 74.3, 345 or 1600 mg/kg bw/d) conducted in mouse, rat, hamster and rabbits, respectively.

Genotoxicity: Mutagenic or genotoxicity potential was not detected in vivo in assays with PG. Propylene glycol was not a genetic toxicant as demonstrated by a battery of in vivo (micronucleus, dominant lethal, chromosome aberration) and in vitro (bacterial and mammalian cells and cultures) studies (OECD, 2001). Lack of clastogenicity was demonstrated in vivo in mouse micronucleus test and no mutations were reported in dominant lethal assay in rats dosed 30, 2500 and 5000 mg/kg bw. In vitro, PG was negative in bacterial mutation assays and induced no chromosome aberration in human lymphocytes. However, a positive chromosomal aberration was noted in one study when incubated with Chinese hamster's fibroblast at cytotoxic concentration. Based on the weight of evidence, the chemical structure, and the metabolism, it is considered that PG is neither mutagenic nor genotoxic (NTP-CERHR, 2004).

Carcinogenicity: No evidence for carcinogenicity was observed in any of the chronic toxicity studies. The potential carcinogenicity was examined in a mouse skin painting study; there was no increase in dermal tumors or change in longevity after chronic treatment with propylene glycol.

Human data: There are few case reports concerning PG and hand dermatitis or atopic dermatitis in humans from topical preparations and ingestion of PG in sensitized individuals has produced flares of dermatitis (Lakind et al. 1999). Skin testing of 42 healthy volunteers showed that 100% propylene glycol caused faint, patchy erythema with edema in 40% of the tested subjects. In another study, an acute dermal exposure of eczema patients to 0.2 and 22.8 mg/cm2 of propylene glycol caused skin edema and erythema in 3.8% of the 823 patients that were skin tested. The authors concluded that PG has marginal irritant properties (ATSDR, 2007). High levels of propylene glycol in the plasma can lead to an increase in the osmolality gap. Propylene glycol is oxidatively converted to lactic and pyruvic acids which, if present in sufficient amounts, contribute to a metabolic acidosis. However, acidosis from propylene glycol is not as severe as that due to ethylene glycol. Serum levels of PG > 180 mg/L has resulted in toxicity in adults. In one case, an 11-year-old child receiving oral doses of 2–4 mL per day for 13 months as a component of a vitamin D preparation (estimated dose 4–8 g/kg bw/day) resulted in seizures and CNS depression. In a case of acute propylene glycol poisoning (the amount ingested not specified), the patient developed metabolic acidosis (pH of 7.29) with an osmolality gap of 51 mmol/kg. The serum level of PG was 400 mg/dL (ATSDR, 1997). Acute respiratory acidosis and cardiorespiratory arrest were reported in an 8-month-old infant with second-and third-degree burns after acute dermal treatment with silver sulfadiazine containing a high amount of propylene glycol. The dose of propylene glycol was 9,000 mg/kg/day (ATSDR, 1997).

Others: In vitro, embryonic development was reportedly reduced or inhibited in cultures of mouse zygotes exposed to PG (CIR, 1994). A further study examining the in vivo induction of cytogenetic aberrations found an increase in frequency of premature centrosphere separation (PCS) with 1300 – 5200 mg/kg PG. In zygotes from PG-dosed mice, hyperploidy was increased (NTP-CERHR, 2004).

Dermal absorption: Considering that PG is highly water soluble, the dermal absorption through intact human skin would be very limited. However, clinical studies indicate that once the stratum corneum is impaired (removed such as in burns or irritated), dermal absorption may be more pronounced. In vitro study using human skin under occlusive conditions reported a percutaneous absorption of 0.1%; the cumulative dermal penetration 24h post –application was 0.14 (± 0.11). The dermal penetration/uptake over a 24-hr period of PG from a cosolvent solution through hairless mouse skin was reported as 57%; although much of the uptake amount remained within the outer layers of the skin and was not detected in the dermis (the inner layer). Further evidence that PG does not reach the dermis was reported in a study with PG applied to the fingertip of a human volunteer and the depth of dermal penetration measured over a period of time intervals. The authors suggested that PG molecules diffuse into the stratum corneum only to a depth of 6-7 µm, approximately. It has been reported that hairless mouse skin overestimates absorption of PG by human skin and is not considered to be a reliable model (ATSDR, 1997). Thus, considering the high-water solubility and the in vitro data on human skin, the dermal absorption of PG is conservatively estimated at 1%.

Margin of Safety: NOAEL: 1700 mg/kg bw/d (2-year, repeat dose, rat, oral, ECHA, 2023) ; Dermal Absorption (Dap) = 1% (ATSDR, 1997)

References: CosIng (2023) Propylene glycol
OECD SIDS (2001) Initial Assessment Report, 2001. Propylene Glycol CAS No. 57-55-6.
ECHA (2023) REACH Dossier for Propane-1,2-diol.
CIR (1994) Final Report on the safety Assessment of Propylene Glycol and Polypropylene Glycols. JACT 13(6):437-491, 1994.
CIR (2012) Safety Assessment of Propylene Glycol, Tripropylene Glycol, and PPGs as Used in Cosmetics. IJT 31(Suppl 2):245-260, 2012.
NTP-CERHR (2004) Monograph on the Potential Human Reproductive and Developmental Effects of Propylene Glycol. NIH Publication No. 04-4482.
ATSDR. 1997. Toxicological Profile for Propylene Glycol.
Lakind et al. (1999) A review of the comparative mammalian toxicity of ethylene glycol and propylene glycol, Crit Rev Toxicol.

1999 Jul;29(4):331-65.

Chemical Name: Goat Milk			
Function: Skin-Conditioning Agent			
Regulatory Status (Toxicological Risk Assessment Report):			
Exposure	**NOAEL**	**Safety Factors**	**MoS**
		0	MoS For Adult:

Summary Data:

Goat Milk is whole milk obtained from goats. It is used as a Skin-Conditioning Agent. Per VCRP porgram (FDA), it was used in 53 cosmetics in 2019.
Dairy goats have been traditionally used for milk production across the globe, and in particular Asia, Africa and Europe, which produce 58.4%, 24.1% and 14.2% of world's goat milk, respectively.
Due to unavailability of cow milk, goat milk and its products are important daily food sources of protein, phosphate and calcium for the people of developing countries. Goat milk differs from cow or human milk in having higher digestibility of protein and fat, alkalinity, buffering capacity, and certain therapeutic values in medicine and human nutrition. Goat milk and cow milk contain substantially higher protein and ash, but lower lactose, than human milk. Goat milk is also of great importance to infants and patients who suffer from cow milk allergy. Cow's milk allergy is the most frequent allergy in the first years of life, so milk from other mammalian species, including goat, has been suggested as possible alternatives. However, goat milk allergy has also been showed.
To date goat milk accounts for less than 1.6% of the dairy production worldwide
Potential health benefits from the consumption of goat milk were recently reviewed, including hypoallergenicity, and improvements in gastro-intestinal disorders, Fe and Cu absorption, growth rates, bone density, and blood levels of vitamin A, Ca, thiamine, riboflavin, niacin, and cholesterol, however, claims around human health still mostly rely on anecdotal evidence, which is also used in industry promotional material and within the media

Milk is widely consumed as a source of nourishment. It is not irritating to eyes; in susceptible individuals contact with the skin or by inhalation may result in allergic symptoms or irritation. It is not suitable for those individuals with susceptibility to milk. This must be labeled. It should not be used on damaged skin.

Margin of safety: Based on the long history of safe use of Goat Milk in food, no margin of safety calculation is deemed necessary. DAp = 100% (default value).

References: Park - Encyclopedia of Animal Science - In book: Encyclopedia of Animal Science, Edition: 2nd, Chapter: Goat Milk: Composition, Characteristics - Publisher: CRC Press, Editors: W.G. Pond and N. Bell. Stergiadis et al. - Comparative Nutrient Profiling of Retail Goat and Cow Milk - Nutrients. 2019 Oct; 11(10): 2282. Rubio-Martín et al. - Comparison of the Effects of Goat Dairy and Cow Dairy Based Breakfasts on Satiety, Appetite Hormones, and Metabolic Profile - Nutrients. 2017 Aug; 9(8): 877.

Chemical Name: Carthamus Tinctorius (Safflower) Seed Oil			
Function: Masking/Skin Conditioning			
Regulatory Status (Toxicological Risk Assessment Report):			
Exposure	**NOAEL**	**Safety Factors**	**MoS**
		0	MoS For Adult:

Summary Data:

Cosmetic functions: Antioxidants; Fragrance Ingredients; Skin-Conditioning Agents [1]
Definition: Carthamus Tinctorius (Safflower) Seed Oil is the oily liquid obtained from the seeds of Carthamus tinctorius. It consists principally of the triglycerides of linoleic acid. [1] The seeds contain 25 to 37% of oil. [2] The composition of Safflower Oil used in cosmetics consists principally of about 68 percent linoleic, 26 percent oleic, 2 percent palmitic, and trace amounts of arachidic and linolenic acids. [3] Linoleic acid is considered to be an essential fatty acid necessary for growth particularly in children, drying of the skin, to maintain cell membrane integrity, to regulate cholesterol metabolism and for synthesis of hormones and hormone-like substances. [2] JECFA has established an acceptable ADI for linoleic acid. [4]
Uses: Safflower Oil is a golden yellow, edible drying oil. Safflower Oil has a long and extensive history of use in food products and is used in a wide variety of products, including alkyd resins, paints, varnishes, linoleum, medicines, dietetic foods, and hydrogenated shortening. [2] It has a GRAS status as an indirect food additive according to FDA. [1] [2]
The Cosmetic Ingredient Review Expert Panel (Panel) assessed the safety of 244 plant-derived fatty acid oils as used in cosmetics. Oils are used in a wide variety of cosmetic products for their skin conditioning, occlusive, emollient, and moisturizing properties. Since many of these oils are edible, their systemic toxicity potential is low. Indeed, exposure to the oils from food use would result in a much larger systemic dose than that resulting from use in cosmetic products. Therefore, the review focused on potential dermal effects. The Panel concluded that the 244 plant-derived fatty acid oils are safe as used in cosmetics. Oils derived from edible vegetables, fruits, seeds, tree, and ground nuts have been safely consumed by, and applied to the skin of, humans for thousands of years. Although nuts, fruits, and vegetables themselves may cause allergic reactions in certain individuals, the refined oils derived from these plants generally pose no significant safety concern following oral exposure, and their general biology is well characterized due to extensive use in food materials [3].
Acute toxicity: LD50 > 5g/kg (mouse, oral) [2] LD50 > 50 mg/kg in (mouse, intraperitoneal). [1]
Ocular irritation: Six rabbits received a single ocular application of undiluted Safflower Oil. The eye irritancy of Safflower Oil under these test conditions was minimal. Three products containing Safflower Oil were evaluated by-modified Draize eye irritation studies using 6 rabbits per product. The moisturizer contained 3 percent Safflower Oil, and 2 night creams contained either 3 percent or 5 percent Safflower Oil. Under the conditions of the test, all 3 products classified as nonirritants to eyes. [2]
Dermal irritation and sensitization: Undiluted Carthamus tinctorius (safflower) seed oil was minimally irritating in a repeat open patch test using rabbits and was not a primary irritant or sensitizer in a maximization study using guinea pigs. Cosmetic formulations containing 3% to 5% Carthamus tinctorius (safflower) seed oil were not irritating to humans in occlusive patch tests. In a HRIPT, Carthamus tinctorius (safflower) seed oil at 30% in a massage oil was not a dermal irritant or sensitizer. [3]
Mutagenicity/Genotoxicity: The genetic toxicity of safflower oil (100 to 10000 µg/plate) was assessed by testing in an AMES test in Salmonella typhimurium strains TA97, TA98, TA100 and TA1535 in presence or absence of S9. It was not mutagenic
Repeated-dose toxicity: Repeated dose toxicity studies have been directed toward fatty acid metabolism rather than the toxic effects of safflower oil. However, these studies indicate that ingestion of up to 15% safflower oil is not toxic to animals. [2]
Reproductive toxicity: A study investigated the effects of maternal dietary fat intake on completed gestations, maternal behavior, and neonatal brain size, physical development, and behavioral development. Female rats were fed standard commercial diets at all times except during gestation and lactation periods. The dams fed Safflower Oil had fewer completed gestations and poorer maternal behavior during lactation with regard to nest construction, keeping young in the nest, and time spent with the young. The pups of dam fed Safflower Oil had smaller brains at births. No further information is available. [2]
Carcinogenicity: A 2-year study was conducted in order to evaluate the effects of various concentrations of an oil very high in polyunsaturated fat (safflower oil), an oil containing high levels of polyunsaturated and monounsaturated fats (corn oil), and an oil containing saturated medium-chain fatty acids (tricaprylin) on the incidence and pattern of neoplasms in the F344/N rat. Each vehicle was administered by gavage at volumes of 2.5, 5, or 10 mL/kg body weight once daily for 5 days per week. These studies demonstrate that safflower oil and tricaprylin do not offer significant advantages over corn oil as a gavage vehicle in long-term rodent studies. Corn oil, safflower oil, and tricaprylin each caused hyperplasia and adenoma of the exocrine pancreas, decreased incidences of mononuclear cell leukemia, and reduced incidences or severity of nephropathy in male rats. [5]
Photo-induced toxicity: Products containing up to 5% Safflower oil were negative for human skin photosensitization (no further information) [6]
Dermal/Percutaneous absorption: Safflower Oil is absorbed through the skin. [2] Dap of 100% by default as no further information is available.
Margin of Safety calculation: Carthamus Tinctorius (Safflower) Seed Oil is consumed and edible, no systemic toxicity is expected with the use of Carthamus Tinctorius (Safflower) Seed Oil.
The CIR Expert Panel concluded that Carthamus tinctorius seed oil is safe in current practices of use and concentration up to 84% (nail products), with a maximum concentration in dermal contacts products of 72% (leave-on and rinse-off) [3].
Ref.:
[1] PCPC Online database. Carthamus Tinctorius (Safflower) Seed Oil. Visited on May 2020. Available on:https://online.personalcarecouncil.org/jsp/IngredientDetail.jsp?monoid=9367
[2] CIR. Final Report on the Safety Assessment of Safflower Oil. JACT Vol.4 No 5, 1985.
[3] CIR. Safety assessment of Plant-derived fatty acid oils. IJT 36(Suppl. 3):51-129, 2017.

[4] JECFA - Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives - LINOLEIC AND LINOLENIC ACID (MIXTURE). Visited on May 2020. Available on:http://www.inchem.org/documents/jecfa/jeceval/jec_1285.htm [5] NTP. Comparative Toxicology Studies of Corn Oil, Safflower Oil, and Tricaprylin in Male F344/N Rats as Vehicles for Gavage. [6] CIR Compendium 2012. Abstracts, discussions and Conclusions of Cosmetic Ingredient Safety Assessments.

Chemical Name: D-Glucitol

Function: Humectant / Plasticiser /Skin Conditioning / Flavoring Agent / Fragrance Ingredient

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
ORAL	50300 mg/kg bw/day	0	MoS For Adult: 235508.9

Summary Data:

Cosmetic Functions : Humectant / Plasticiser /Skin Conditioning / Flavoring Agent / Fragrance Ingredient.
Sorbitol is a hexahydric sugar alcohol that occurs naturally in plants and animals. It is widely used in the food industry as an ingredient in many food products, and medically, sorbitol is used in parenteral nutrition as a source of carbohydrate. It has a long history of use as food ingredient/additive and there have been no indications of significant harmful effects reported. Sorbitol is hygroscopic. About 80% of an orally administered dose is absorbed. Once absorbed, it is rapidly metabolised by the liver to several intermediates, but ultimately to glucose. Sorbitol is well utilised by the body as an energy source, and consequently, very little of an oral dose is eliminated in the urine and faeces. The only consistent adverse effect found in animals or humans is mild gastrointestinal effects (GI) such as gas, bloating, abdominal discomfort, and diarrhoea.
Acute toxicity: Sorbitol was practically non-toxic in acute oral studies in laboratory animals (LD50: 7.1 to 25.7 g/kg bw) and short-term toxicity studies in humans demonstrates that it does not cause any adverse effect other than mild gastrointestinal effects even at high dose levels of between 10-50 g (JECFA, 1974; CIR, 2019).
Irritation: Non-irritating. There is no data available indicating that sorbitol has skin, eye (mucous membrane) or respiratory tract irritation potential.
Sensitisation: Non-sensitising. No data available in animals and sorbitol is rarely associated with elicitation of allergic dermatitis in humans including occupational exposure.
Mutagenicity/Genotoxicity: Sorbitol is not genotoxic in a wide range of in vitro and in vivo mutagenicity tests: an Ames test with and without metabolic activation, chromosomal aberration assays using CHO cells and Chinese hamster lung fibroblasts without metabolic activation, and host-mediated assays of mutagenicity in mice using Salmonella strains G46 and TA1530, and Saccharomyces cerevisiae strain D3 as indicator strains (CIR, 2019).
Repeat dose toxicity: No toxic effects were noted in rats when 5% sorbitol was given in the diet for 3 months corresponding to 5 g/kg bw/day. Administered intravenously to rabbits, no effect on blood chemistry, body weight, survival, or organs at doses of 2.5, 5.0, or 10 mL/kg of a 20% sorbitol solution (500 mg/kg bw/d, 1000 mg/kg bw/d, and 2000 mg/kg bw/d) given daily for 3 months. Sorbitol was fed to weanling rats for two years at dietary levels of 0, 1, 5, or 10%. The two highest dose levels were supplemented with casein to maintain a 25% dietary protein level. A few of the treated animals had diarrhoea during the first 2 months at the 10% feeding level (12 g/kg bw/day). No toxicological effects were reported; the NOAEL was > 12000 mg/kg bw/d. In another 2-year chronic toxicity study, rat fed 20% sorbitol in the diet (~7.5 g/kg bw/d) had enlarged cecum, lower body weight gain, absolute thyroid weight and increased incidence of adrenal medullary hyperplasia. There is no evidence for reproduction, teratogenicity or developmental toxicity potential shown with sorbitol in numerous studies conducted in laboratory animals even at high doses of 1600 – 7800 mg/kg bw/d. Treatment-related tumours were not reported in the chronic toxicity studies which indicates that sorbitol lacks carcinogenicity activity (JECFA, 1974; CIR, 2019).
Other data (human): Sorbitol causes laxation because of its osmotic effects and poor absorption by the small intestine which results in increased transit time through the colon. In humans, the laxative threshold is 10-20 g of sorbitol liquid and 50 g of crystalline sorbitol; a study in 86 volunteers at a dose level of 25 g/day in two doses did not cause laxation. According to the results of dietary survey conducted by the US National Research Council (NRC), the average daily dietary intake of sorbitol ranges from 770 mg/day (154 mg/kg bw/d) in babies to ~30.1g/day (503 mg/kg bw/d) in adults or a maximum of 55.4 g/day (924 mg/kg bw/d). (FDA, 1972)
Dermal / percutaneous absorption: No data available. However, it is assumed that the absorption through the skin would be lower than that of the oral routes; thus, the oral absorption value of 80% is used as conservative estimate (JECFA, 1974; CIR, 2019).

In their Safety Assessment of Mannitol, Sorbitol, and Xylitol as Used in Cosmetics, the CIR Expert Panel concluded that Mannitol, Sorbitol, and Xylitol are safe in cosmetics in the present practices of use and concentration described in the safety assessment.
The reported uses of sorbitol are up to 70% in RO, 20% in LO products, 4.9% in eye area products, 70% in incidental ingestion and mucous membrane products (toothpaste), 31.9% in dermal contact products, 10.9% in hair products.
Margin of Safety: 503 mg/kg bw/d (average daily dietary intake; FDA, 1972); a minimal margin of exposure of 1 is considered sufficient. Virtually, this POD can be multiplied by 100, POD = 50,300 mg/kg bw/day, and a MoS of 100 is therefore considered as sufficient. DAP: 80% (default)
References: JECFA, Substance: Sorbitol (CASRN 50-70-4). 1974.
CIR, Safety Assessment of Mannitol, Sorbitol, and Xylitol as Used in Cosmetics. 2019.
FDA. SCOGS. Evaluation of the Health Aspects of Sorbitol as a Food Ingredient. Dec. 1972.

Chemical Name: Sorbitan oleate

Function: Surfactant/Emulsifier

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
ORAL	1000 mg/kg bw/day	0	MoS For Adult: 3745.7

Summary Data:

Function: Surfactant/Emulsifier. Sorbitan ester are waxy solids or viscous liquids. These esters are mono-, di-, and triesters of fatty acids and sorbitol. They are used in a variety of products including skin care products, moisturizers, cleansing products, and eye and facial makeup. The sorbitan esters are produced by reacting the polyol, sorbitol, with a fatty acids (caprylic, coconut oil-derived fatty acids, isostearic, oleic, stearic, isostearic, olive oil-derived fatty acids). Sorbitol and the fatty acids are naturally occurring chemicals and are used in cosmetic products. Used as thickeners in food and cosmetics and is FDA approved. Low potential to cause skin or eye irritancy. Low oral toxicity (LD50, rat >5000 mg/kg). The CIR have completed an authoritative review on the use of sorbitan laurate and other sorbitan esters for their suitability in cosmetic products.
Sorbitan esters show low toxicity by oral and dermal routes and subchronic and chronic toxicity is low. They are metabolized back to sorbitan and commons esters and then excreted. The lowest LD50 was 31,000 mg/kg for sorbitan stearate. The rat LD50 values from acute toxicity studies of sorbitan laurate ranged from 33,600 mg/kg to 41,500 mg/kg. Thirty male rats were fed a diet with 5% sorbitan stearate, equivalent to 5,000 mg/kg/day for 2 years. No effects on clinical signs, mortality, bw, feed consumption, hematology, clinical chemistry, gross or microscopic lesions, or pathology were reported. Gravid female Wistar rats, 20 per group, were dosed once daily by gavage with 0, 500, or 1,000 mg/kg/day sorbitan stearate on days 0 to 20 of gestation, and the animals were killed. The NOAEL for maternal toxicity and for teratogenicity was 1,000 mg/kg/day. No test article-related embryotoxic results were reported.
Not a dermal irritant and not reported as a dermal toxicant. Chronic studies in animal produced no effects when the ester concentration in the diet was 40%. Not reported as a skin sensitizer on intact skin but may cause sensitization on damaged skin. May induce cutaneous irritation in humans. Not reported as photosensitizers. Little potential for reproductive and developmental effects and do not show carcinogenic or mutagenic effects. At high concentration, cocarcinogenicity and tumour promotion (10% in mice) in dermal studies is observed but these concentrations are higher than what would be used in cosmetic products (typically 5%) Inhalation is not expected to be a route of exposure given their high molecular weight, volatility and melting point.
In an addendum to their original report the CIR added that the sorbitan esters were to be relatively nontoxic via ingestion in acute and long-term studies, minimal to mild skin irritants. Sorbitan esters did not act as sensitizing agents. The fatty acid component, tested alone, typically caused only slight irritation and sensitization, and was not photosensitizing. Sorbitan esters were not ocular irritants. These esters and their corresponding fatty acids were not mutagenic. In clinical tests, sorbitan esters were generally minimal to mild skin irritants and were nonsensitizing, but Sorbitan Sesquioleate did produce an allergic reaction in fewer than 1% of patients with suspected contact dermatitis and addition of Sorbitan Sesquioleate to the components of a fragrance mix used in patch testing increased both irritant and allergic reactions to the fragrance mix.
The CIR concluded that sorbitan oleate is safe in cosmetics in the present practices of use and concentration. The reported uses are up to 3% in LO and 7% in RO products, 0.08% in eye area products, 0.8% in incidental ingestion products, 7% in dermal contact products, 3% in hair products.
NOAEL = 1,000 mg/kg/day (reprotoxicity study on sorbitan stearate in rats, read-across); DAp = 100%
References: CIR, Safety Assessment of Sorbitan Estersas Used in Cosmetics, IJT 38(Suppl. 2):60-80, 2019. CIR, Final Report on the Safety Assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan

Palmitate, and Sorbitan Trioleate, JACT 4(3):65-121, 1985.

Chemical Name: Avena Sativa (Oat) Protein Extract

Function: Skin-Conditioning Agent

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
		0	MoS For Adult:

Summary Data:

Avena Sativa (Oat) Protein Extract is the extract of Avena Sativa (Oat) Kernel Protein. and Avena Sativa (Oat) Kernel Protein is a protein obtained from the kernels of oats, Avena sativa. It is used as a Skin-Conditioning Agent.
According to American Herbal Products Association and the Botanical Safety Handbook, Avena sativa (oat) is part of the safety class 1: Herbs that can be safely consumed when used appropriately.
In its Safety Assessment of Avena sativa (Oat)-Derived Ingredients as Used in Cosmetics, the CIR Expert Panel reviewed Avena Sativa (Oat) Protein Extract.
The Panel acknowledged that A. sativa grains are used extensively in both animal feed and human food and the plant parts are used in animal feed, resulting inmuch larger oral exposures than would result from cosmetic uses.Therefore, the Panel was not concerned about the systemictoxicity potential of most of these cosmetic ingredients.
In clinical tests with different products containing different Avena sativa (Oat)-Derived Ingredients, tested at concentrations between 0.003 to 43.3% in 485 to 5725 volunteers, the test substances were non-irritating, non-phototoxic, non-photoallergenic, non-allergenic and not ocular irritating.
The CIR Expert Panel discussed the potential for these ingredients to cause Type 1 reactions in individuals. In the previous CIR report of hydrolyzed wheat protein, the Panel limited the size of proteins to 3500 or less. The data provided for this assessment indicate that the ingredients in this report do not have the properties required to induce Type 1 hypersensitivity, thus the Panel concluded that these products had a low potential to cause sensitivity. Additionally,the Panel was not as concerned about the potential for protein in Avena sativa-derived ingredients to cause Type I reactions because, compared to wheat, soy, eggs, and nuts, oats are not considered to be a major food allergen.
The CIR Expert Panel concluded that Avena Sativa (Oat) Protein Extract is safe as used in the present practices of use and concentrations when formulated to be non-sensitizing, i.e. up to 1.5% in rinse-off dermal contact products. Avena sativa (oat) kernel extract reported use are up to 25% in leave-on dermal contact products.
Reference: CIR - Safety Assessment of Avena sativa (Oat)-Derived Ingredients as Used in Cosmetics - January 15,2015.

Chemical Name: Curcuma Longa (turmeric) Root Extract

Function: Fragrance Ingredient

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
ORAL	500 mg/kg bw/day	0	MoS For Adult: 17921.1

Summary Data:

Curcuma Longa (Turmeric) Root Extract is the extract of the roots of Curcuma longa [1]. Turmeric (Curcuma longa) is a plant of the ginger family named Zingiberaceae which is native of South Asia. Turmeric powder, with typical deep orange yellow color, is extensively used as a spice in curries and Indian cuisine. In India, the biggest producer of turmeric, it is also known since ancient times for its cosmetic and wound healing properties. Traditionally, turmeric paste was applied to the bride before marriage in some regions of India to give glow to the skin and to keep harmful bacteria away from the body. In the Ayurvedic medicine,

turmeric is thought to have many medicinal properties.
Uses [2]: The ground rhizome (turmeric) is permitted for food use and in many Asian countries; the use of turmeric as a food spice, colorant and medicine has a long tradition. Turmeric is applied topically for the treatment of acne, wounds, boils, bruises, blistering, ulcers, eczema, insect bites, parasitic infections, hemorrhages and skin diseases like herpes zoster and pemphigus. The Food and Drug Administration classifies turmeric as a substance Generally Recognized as Safe (GRAS) (Essential oils, oleoresins (solvent-free), and natural extractives (including distillates)) (21CFR182.20).
Composition: Carbohydrate is the main component of turmeric root (69.4% by mass) [2]. It also contains a mixture of curcuminoids with curcumin making up 90% of the curcuminoid content. The curcumin content of the Curcuma longa rhizome varies from 0.6 to 5% of the dry mass [2]. The essential oil from turmeric (5.8% of total mass) contains mainly sesquiterpenes (53% of essential oil). They include turmerones, curcumene, zingiberene [2]. In a publication, the turmeric essential oil major components were a-turmerone (42.6%), b-turmerone (16.0%) and ar-turmerone (12.9%) [6]. Mineral matter is present at 3.5%, moisture at 13.1% and protein at 6.3% of total mass [2].
Activities [2]: A number of studies have been conducted investigating the various pharmacological activities including anti-mutagenic, antioxidant, antifungal, hepatoprotective, wound healing and antidiabetic effects. Results of these studies which did not consider the toxicity suggest that turmeric extract has low order of toxicity in acute and repeated exposures.
Toxicological data on turmeric and constituents [2, 4, 5]:
- Acute toxicity: A single feeding of 30% turmeric diet to rats produced no toxic effects [2]. Acute administration of turmeric essential oil (TEO) was done as single dose up to 5 g per kg body weight in Wistar rats. There were no mortality, adverse clinical signs or changes in body weight; water and food consumption. The LD50 was > 5 g per kg body weight [5]. The LD50 of orally administered turmeric oleoresin in mice and rats could not be determined at doses up to 10 g/kg [4]. No toxic effects were observed after rats, guinea pigs, and monkeys were administered 2.5 g/kg turmeric powder or 0.3 g/kg of an alcoholic turmeric extract [4].
- Repeated-dose toxicity: In a sub chronic toxicity study, liver toxicity had been reported with turmeric, but most of these incidents involved large dietary doses (turmeric 0.2%, 1.0%, 5.0%) or turmeric ethanolic extract (0.05%, 0.25%) given to mice or rats. In mice fed for 14 days with a diet containing 1% and 5% turmeric, hepatotoxicity was observed. Rats fed with turmeric 1% for the same period showed no adverse effect. The rats fed turmeric at a dose of 5% of their diet for a period of 90 days showed a reduction in body weight gain and hepatotoxicity [2]. In a subchronic toxicity study with turmeric essential oil (TEO) from Curcuma longa L. which the main component was ar-turmerone (61.79%), TEO was orally administered to rats daily for 13 weeks at doses of 0.1, 0.25 and 0.5 g/kg b.wt. in rats. There were no mortality, adverse clinical signs or changes in body weight; water and food consumption. Indicators of hepatic function such as aspartate aminotransferase (AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) were unchanged in treated animals compared to untreated animals. It did not alter total cholesterol, triglycerides, markers of renal function, serum electrolyte parameters and histopathology of tissues. The results of the study indicated that the TEO was safe in rats (NOAEL) up to an oral dose of 0.5 g/kg for 13 weeks [5]. In mice and rats administered turmeric oleoresin (79-85% curcumin) daily in food at doses of 0, 1000, 5000, 10,000, 25,000, or 50,000 ppm (equivalent to average daily doses for rats of 50, 250, 480, 1300, or 2600 mg/kg in males and 60, 300, 550, 1450, or 2800 mg/kg in females and for mice 150, 750, 1,700, 3,850, or 7,700 mg/kg bw in males and 200, 1,000, 1,800, 4,700 or 9,300 mg/kg in females) for 13 weeks, an increase in liver weights was observed at the 5000 ppm dose and above; no histopathological lesions were observed, nor were there any significant differences in hematology, clinical chemistry, or urinalysis parameters, although some animals were noted to have stained fur and discolored feces and urine [4].
- Genotoxicity: No mutagenic effects were found in the Ames tests for curcumin and turmeric extracts. No effects on chromosomal damage, pregnancy rate, number of dead embryos, total implants and mutagenic effects were observed in mice fed with turmeric (0.5% ~ 500 mg/kg/d) or curcumin (0.015%) [2,4]. Turmeric essential oil (TEO) from Curcuma longa L. did not produce any mutagenicity to Salmonella typhimurium TA-98, TA-100, TA-102 and TA-1535 with or without metabolic activation. Administration of TEO to rats (1 g/kg b.wt.) for 14 days did not produce any chromosome aberration or micronuclei in rat bone marrow cells and did not produce any DNA damage as seen by comet assay [5].
- Carcinogenicity [2]: Curcumin is considered to be not carcinogenic. Long-term (103-weeks) carcinogenicity studies have been performed in mice and rats, fed ad libitum diets containing 0, 2000, 10.000 or 50.000 mg/kg turmeric oleoresin (79%-85% curcumin). These doses were equal in males/females to daily doses of 0, 220/320, 1520/1620 or 6000/8400 mg turmeric oleoresin/kg in mice and to 0, 80/90, 460/440 or 2000/2400 mg turmeric oleoresin/kg bw/day in rats. It was concluded that curcumin is not carcinogenic.
- Reprotoxicity: The reproductive toxicity of curcumin was studied in Wistar rats [2]. It was concluded that the no observed adverse effect level (NOAEL) for reproductive toxicity of curcumin, fed in the diet for two successive generations to rats in this study, was 850-960 mg/kg per day for male rats and 1000-1100 mg/kg for females for F0 and F1 generations, respectively. The JECFA group [5, 6] considered that the small body weight reduction in the F2 pups of the highest dose group prevented this from being regarded as a no adverse effect level, and so allocated an ADI for curcumin of 0–3 mg/kg based on the intake of 250–320 mg/kg (male and female) in the mid-dose group as the NOEL.
- Sensitization [2]: With respect to topical use, rare cases of allergic contact dermatitis have been reported. In an 18-month study on the topical use of curcumin to treat skin and mucous membrane cancers, scalp itching was observed in 1 patient of 62

patients. Patch testing led to allergic reactions (not further classified) in persons who were regularly exposed to the substance or who already had dermatitis of the fingertips. Few allergic reactions (skin rash) occurred in people not previously exposed to curcumin.
- Human: There have been rare reports of adverse effects in humans from consuming turmeric powder added as food additive. No major side effects have been reported in clinical studies with turmeric extract or curcumin, the active component. Side effects were not reported in patients with rheumatoid arthritis treated with 1200 mg/day of curcumin for two weeks; assuming 60kg adult, this is equivalent to 20 mg/kg/d [2]. Also, no toxic effects were observed after three months oral intake of 8,000 mg (133.3 mg/kg/day) or 2.2 g/day (36.7 mg/kg/day) of turmeric for 4 months [2, 4]. Curcumin has been found to stimulate the gall bladder thus the use of curcumin or turmeric is contraindicated in patients with obstruction of the biliary tract [2].
Moreover, a publication [3] investigated the safety of a curcuminoid-essential oil complex (CEC) containing a specific ratio of curcuminoids and essential oil of turmeric containing turmerones (ratio not provided, at least 95% of curcuminoid complex). The CEC was tested in different studies according to OECD guidelines: In an acute oral toxicity in mice and rats, the LD50 for mice and rats were both higher than 5,000 mg/kg. In an oral 90-day repeated dose toxicity test in rats, CEC was administered orally at a dose of 100, 500 or 1,000 mg/kg. No observable toxic effects were induced compared to the control group. The NOAEL can be considered to be 1,000 mg/kg/day (highest dose tested). In an Ames test, CEC was non-mutagenic when tested up to 5,000 µg/plate, compared with the untreated control. Similarly, the results of the chromosomal aberration test in vivo indicated that CEC was non-mutagenic at a dose of 2,000 mg/kg in rats. In the mammalian micronucleus test in vivo, no effects were observed in the micronuclei at either 24 or 48 h following treatment with CEC, compared with their negative control counterparts. As no significant effect was seen in the treated animals, it was concluded that CEC did not exhibit any mutagenic potential. In conclusion, CEC was observed to be non-toxic and safe, and was supported by evidence from investigations of acute toxicity, repeated dose toxicity and mutagenicity.
According to the Botanical Safety Handbook from the American Herbal Products Association [4], Curcuma longa L. rhizome is from the safety class 1, i.e. herb that can be safely consumed when used showing history of safe traditional use, no case reports of significant adverse events with high probability of causality, no significant adverse events in clinical trials, no identified concerns for use during pregnancy or lactation, no innately toxic constituents, toxicity associated with excessive use is not a basis for exclusion from this class, and minor or self-limiting side effects are not bases for exclusion from this class appropriately.
Based on the whole data and the fact Curcuma Longa (Turmeric) Root Extract (> 65% turmerones) has often a composition close to turmeric essential oil (approx. 70% turmerones), the most relevant point of departure available is the NOAEL of 0.5 g turmeric essential oil (TEO)/kg/day from the 13-week repeated-dose toxicity study in rat [5].

Margin of safety: NOAEL = 500 mg/kg/day available (13-week toxicity study in rats with turmeric essential oil containing 61.79% ar-turmerone – [5]); DAp: 100% (default value)
References: [1] PCPC. [2] European Medicines Agency (EMA). Committee on herbal medicinal products assessment report on Curcuma longa L. Rhizoma. EMEA/HMPC/456848/2008. November 2009. Re-assessed in November 2017. Assessment report on Curcuma longa L. (C. domestica Valeton), rhizome. Draft revision. EMA/HMPC/749518/2016. [3] MADAN L. AGGARWAL et al. Systematic and comprehensive investigation of the toxicity of curcuminoid-essential oil complex: A bioavailable turmeric formulation. MOLECULAR MEDICINE REPORTS 13: 592-604, 2016. [4] Botanical Safety Handbook from the American Herbal Products Association. Second Edition. 2013 edition. [5] Liju, Jeena, Kuttan, 2013. Acute and subchronic toxicity as well as mutagenic evaluation of essential oil from turmeric (Curcuma longa L). Food Chem Toxicol. 2013 Mar;53:52-61. [6] Avanço et al., 2017. Curcuma longa L. essential oil composition, antioxidant effect, and effect on Fusarium verticillioides and fumonisin production. Food Control 73 (2017) 806e813

Chemical Name: Kojic Acid

Function: Antioxidant, Skin Whitening

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
ORAL	2 mg/kg bw/day	28-day study (UF = 3)	MoS For Adult: 421.7

Summary Data:

Cosmetic functions: Antioxidant and Skin Whitening

Kojic Acid is a heterocyclic compound that functions as an antioxidant and skin whitening agent in cosmetic products. VCRP Frequency of Use as of 01/2021: 87 (PCPC). It is produced by filamentous fungi including *Aspergillus* and *Penicillium* (CIR, 2010). Kojic Acid is used primarily used in hand, neck, and face products.

In 2010, the Cosmetic Ingredient Review (CIR) Expert Panel assessed the safety of Kojic Acid. The ingredient was reported to be used in eye lotions at up to 1%, face and neck preparations at up to 2%, and body and hand preparations at up to 1%. The Panel concluded that the use of Kojic Acid in cosmetic products is safe at up to 1% based on dermal sensitization and skin lightening at higher concentrations (CIR, 2010).

In 2022, the Scientific Committee on Consumer Safety (SCCS) reviewed Kojic Acid and determined that, on the basis of the safety assessment, and considering the concerns related to potential endocrine disrupting properties of Kojic acid, Kojic acid is not safe when used as a skin lightening agent in cosmetic products at concentrations of up to 1%. In the SCCS's opinion, the use of Kojic acid as a skin lightening agent in cosmetic products is safe for the consumer up to a maximum concentration of 0.7% Kojic acid in the final product. As Kojic acid is sometimes added to peeling agents, a weakened skin barrier may be of additional concern because of greater dermal absorption. Only the topical use of Kojic acid in cosmetics has been considered in this Opinion. Other uses (e.g. food) of natural or synthetic sources have not been considered. Their assessment covered only the face, neck and hands areas of applications.(SCCS, 2022).

In 2024, the EU Regulation 1223/2009 has been updated and kojic acidc added to the Annex III (entry 375): it must not be used at more than 1% face and hand products. No other uses are allowed.

Acute Toxicity: Oral LD50s of 5100 mg/kg in mice and 1800 to >2000 mg/kg in rats (SCCS, 2022). Dermal LD50 was >2000 mg/kg in rats (SCCS, 2022).

Skin irritation: A single dose of 0.5 g Kojic Acid in 0.5 mL water was not irritating to the intact or abraded skin or rabbits when applied under occlusion for 24 hours (SCCS, 2022).

Eye irritation: Kojic Acid induced very weak hyperemia in the eyes of rabbits when a single dose of 3% Kojic Acid in an aqueous solution was applied (SCCS, 2022).

Skin Sensitization: Kojic Acid was non-sensitizing to the skin of guinea pigs in a Magnusson Kligman study. In a Buehler test, 2 out of 20 guinea pigs showed positive reactions, with erythema grades of 1 or 2, after the challenge application; the test substance was not considered to be sensitizing as less than 15% of animal were positive (OECD Guideline 406). The literature provides various case reports of individuals who had allergic reactions of varying severity to Kojic Acid-containing products. However, based on the available information, the SCCS concluded that "the occurrence of allergic contact dermatitis from Kojic acid is very low" (SCCS, 2022, p. 20).

Repeated Dose Toxicity: The SCCS described various 28-day, 90-day, and 6-month studies performed with rats and rabbits. They concluded that the most conservative NOAEL was from a 28-day oral study wherein male F344 rats received a diet of 0, 0.008, 0.03, 0.125, 0.5, or 2.0% Kojic Acid (calculated dose of 0, 5.85, 23.8, 95.3, 393.6, and 1387.3 mg/kg bw/day). 125-I uptake decreased at 23.8 mg/kg bw/day and higher. Additionally, histopathological changes including decreased colloid in the thyroid follicles and follicular cell hypertrophy in the thyroid were also observed at 23.8 mg/kg bw/day and above. A NOAEL of 5.85, rounded to 6 mg/kg bw/day, was determined (SCCS, 2022).

Reproductive Toxicity: Various one-generation studies showed no fertility effects related to Kojic Acid. NOAELs based on maternal toxicity and embryotoxicity ranged from 100 to 150 mg/kg bw/day in rats, 100 mg/kg bw/day in rabbits, and 30 mg/kg bw/day in mice (SCCS, 2022).

Mutagenicity/Genotoxicity: The SCCS (2022) indicated that positive findings in *in vitro* tests with Kojic Acid were not supported by *in vivo* tests that showed no genotoxic potential.

Carcinogenicity: Kojic Acid has shown to initiate thyroid follicular cell tumors in rats by interfering with thyroid hormone homeostasis. The SCCS (2022) reported that humans are less sensitive to this homeostasis disturbance and that Kojic Acid-induced hepatocarcinogenesis is “rather implausible under the normal cosmetic use” (p. 15).

Dermal Absorption: Nohynek et al. (2004) estimated the dermal absorption of Kojic Acid to be 17% based on an *in vitro* study with 14C-radiolabeled Kojic Acid.

Margin of Safety: NOAEL 28-day study in rats = 6 mg/kg bw/day + UF of 3 = 2 mg/kg bw/day (SCCS, 2022). DAp = 17%.

References:
Cosmetic Ingredient Review Expert Panel (CIR). (2010). Final Report of the Safety Assessment of Kojic Acid as Used in Cosmetics.
Nohynek, G. J., Kirkland, D., Marzin, D., Toutain, H., Leclerc-Ribaud, C., & Jinnai, H. (2004). An assessment of the genotoxicity and human health risk of topical use of kojic acid [5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one]. Food and chemical toxicology, 42(1), 93-105.
Personal Care Products Council. (2021). Ingredient Database - Kojic Acid.
Scientific Committee on Consumer Safety (SCCS). (2022). Opinion on Kojic Acid Corrigendum. SCCS/1637/21.

Chemical Name: Titanium Dioxide (CI 77891)

Function:UV Absorber - Protects the cosmetic product from the effects of UV-light UV Filter - Filters certain UV rays in order to protect the skin or the hair from harmful effects of these rays. All UV filters listed are substances on the positive list of UV filters (Annex VII of the Cosmetics Directive) Opacifying - Reduces transparency or translucency of cosmetics

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
ORAL	1000 mg/kg bw/day	0	MoS For Adult: 7491335.3

Summary Data:

Function: Opacifying/uv absorber. Titanium dioxide may be in the anatase or rutile form. Bioaccessibility data on titanium released from titanium dioxide were determined when exposed to synthetic biological media of varying pH and composition. Only a small fraction of titanium was released / dissolved from the titanium dioxide powder during exposure to any of the media matrices of varying acidity and composition. A trend with somewhat higher release rates with increasing acidity and exposure period was evident. Not classified in the EU. Titanium dioxide (dust) is classified by IARC as Category 2B, ''Possibly carcinogen to humans'' (IARC, 2010).

Food and Drug Administration (FDA) has authorized the use of titanium dioxide in food, in general, at a limit not to exceed 1% by weight of the food. It has approved the use of titanium dioxide for use in OTC sunscreen drug products at concentrations up to 25%. Per Annex VI of the EU Regulation 1223/2009, titanium dioxide (non nano) is allowed in cosmetics up to 25% as UV filter (In case of combined use of Titanium Dioxide and Titanium Dioxide (nano), the sum shall not exceed 25%).

Acute toxicity: Not acutely toxic or harmful by the oral, inhalation or dermal route. Acute oral toxicity studies in animals (rats or mice) with micro/non micro crystalline/coated/uncoated forms of titanium dioxide were conducted, in general, the LD50 >5000 mg/kg bw. The dermal LD50 for rats is determined to be >2000 mg/kg bw (SCCNFP, 2000). The inhalation LC50 in rats was > 2 mg/L (4 hour exposure).

Irritation: Non-irritating. Results of different skin irritation studies with various types of titanium dioxide showed varying degree of erythema and completely recovered at 72 hours after application. Results of animal studies demonstrated that coated and uncoated titanium dioxide is non-irritating to the eye (SCCNFP, 2000).

Sensitisation: No sensitisation was observed with both coated and uncoated titanium dioxide in both animal and human studies.

Mutagenicity/Genotoxicity: In vitro and in vivo studies indicate that titanium dioxide is non mutagenic or genotoxic. It was negative in a battery of standard assays. With respect to genotoxicity, the EFSA Panel concluded that TiO2 particles have the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations. No clear correlation was observed between the physico-chemical properties of TiO2 particles and the outcome of either in vitro or in vivo genotoxicity assays. A concern for genotoxicity of TiO2 particles that may be present in E 171 could therefore not be ruled out. Several modes of action for the genotoxicity may operate in parallel and the relative contributions of different molecular mechanisms elicited by TiO2 particles are not known. There was uncertainty as to whether a threshold mode of action could be assumed. In addition, a cut-off value for TiO2 particle size with respect to genotoxicity could not be identified (EFSA, 2021).

Repeat dose toxicity: Titanium dioxide did not show any adverse effects in 90-day and 28-day oral repeated dose toxicity studies in rats with a NOAEL of 1000 and 24,000 mg/kg bw/day, respectively. No adverse effects were observed in rats and mice orally exposed up to a dose of 3500 mg/kg bw/day over a period of 103 weeks in a carcinogenicity bioassay. Titanium dioxide is not absorbed to any relevant extent through human skin, thus no toxic effects can be expected via the dermal route of exposure. Titanium dioxide showed adverse pulmonary effects in chronic inhalation studies only at concentrations above the maximum tolerated dose (MTD) (REACH dossier, 2021)

Photo-induced toxicity: Titanium dioxide is neither photo-irritant nor photo-allergenic to rabbits and guinea pigs respectively. It showed no evidence of sensitization in human volunteers. Photo genotoxicity assays have been conducted with the results showing that titanium dioxide is not photogenotoxic (SCCNFP, 2000).

Human data: The working group of the International Agency for Research on Cancer (IARC) concluded that the epidemiological studies on titanium dioxide provide inadequate evidence of carcinogenicity (IARC Monograph, Volume 93, 2010). Others: Derived No Effect Level (DNEL) of 700 mg/kg bw/d for long term systemic exposure to titanium dioxide is given in the REACH Dossier.

Dermal / percutaneous absorption: In vitro percutaneous absorption studies with coated or uncoated titanium dioxide indicate no dermal absorption. The in vitro absorption of microfine zinc oxide and titanium dioxide through porcine skin was reported in the REACH dossier (accessed on 05/03/2013 at http://echa.europa.eu). Titanium dioxide was not recovered in the receptor fluid; the potentially absorbable dose (total in the skin, stratum corneum and epidermis) was 0.1- 0.5%. Titanium dioxide applied in an oil/water emulsion base to the external surface of the arms showed deposition of the substance in the upper layer of the stratum corneum without any evidence of absorption reported. “Worst case” dermal absorption value of 0.5% is assumed.

Margin of Safety (MoS): NOEL: 1000 mg/kg bw/d; Dermal absorption (Dap): 0.5%

The ingredient is not acutely toxic by oral, dermal or inhalation routes. It is non to slightly dermal irritating, non to moderately eye irritating and non skin sensitising. It is non mutagenic, non genotoxic andnon phototoxic or photosensitizing. Titanium Dioxide is suspected of causing cancer by inhalation route. No evidence that it is carcinogenic by other routes.

Reproductive/developmental toxicity: No information is readily available on the ingredient’s reproductive/developmental toxicity.

An extended one-generation reproduction toxicity (EOGRT) study was performed in male and female rats according to OECD TG 443 and good laboratory practice (GLP) compliance. In the F0 generation, E 171 was administered in the diet at doses of 0, 100, 300 or 1,000 mg/kg bw per day from 10 weeks prior to mating until weaning of the F1 generation. The F1 generation received these diets from weaning until PND 4 or 8 of the F2 generation. The F2 generation was exposed through the milk until the termination of the study on PND 4 or PND 8. No effects on general and organ toxicity and reproductive and developmental toxicity up to a dose of 1,000 mg/kg bw per day, the highest dose tested were reported under this study (EFSA, 2021).

As per recent EFSA opinion (2021), on the basis of all currently available evidence along with all the uncertainties, in particular the fact that genotoxicity concern could not be ruled out, the EFSA Panel concluded that E 171 can no longer be considered as safe when used as a food additive. However, as per the information available in recent SCCS opinion (SCCS/1617/20), available safety data show the absence of systemic effects including lack of reproductive and developmental toxicity or carcinogenic effects following exposures by the oral or dermal routes. The favourable safety profile of TiO2 is substantiated by the evaluations carried out by other authoritative and scientific bodies (EFSA, 2016; 2018 & 2019; ANSES, 2017 and US FDA, 2019 as cited in SCCS opinion). Overall, based on this information, with no or limited percutaneous absorption and other scientific literature on this ingredient, safety concerns are not expected with this ingredient for use in cosmetic products.

With regards to products which may lead to inhalation exposure to lungs, following restrictions as described below in accordance with per Annex III and VI should be complied with.

EU Regulatory update:

The third CMR Omnibus Regulation (EU) 2021/850, has been published in the Official Journal to the European Union on 28 May 2021. The Regulation will enter into force on the twentieth day following its publication in the Official Journal of the European Union and will apply from 1 October 2021. This date relates to the making available of cosmetic products on the market.

As per the Commission Regulation (EU) 2021/850, there would be an addition of an Annex III entry for titanium dioxide in EU Cosmetic regulation 1223/2009

The following Annex III restrictions only apply to titanium dioxide in powder form containing 1% or more of particles with aerodynamic diameter ≤10 µm:

1. face products in loose powder form: maximum concentration 25% and only to be used in the pigmentary form.
2. hair aerosol spray products: maximum concentration 1.4% for general consumers and 1.1% for professional use and only to be used in the pigmentary form.
3. other products: No maximum concentration, but not to be used in applications that may lead to exposure of the end-user's lungs by inhalation.

References:

ECHA (2013b) Registered substances. Titanium Dioxide.
EFSA (2004) European Food Safety Authority. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and materials in Contact with Food on a request from the Commission related to the safety in use of rutile titanium dioxide as an alternative to the presently permitted anatase form.
EPA (2013). Chemical: titanium dioxide. Retrived from EPA, United state Environmental protection Agency.
HSDB (2013) Hazardous Substances Data Bank. Titanium Dioxide.
IARC (2013) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.
NIOSH (2011). National Institute for Occupational Safety and Health. Occupational Exposure to Titanium Dioxide.
SCCNFP (2000). Opinion of the scientific committee on cosmetic products and non-food products intended for consumers concerning Titanium Dioxide.
REACH dossier 2021, Titanium Dioxide (CAS 13463-67-7)
EFSA (2021) Scientific Opinion on the safety assessment of titanium dioxide (E171) as a food additive. EFSA Journal 2021;19(5):6585, 130 pp. https://doi.org/10.2903/j.efsa.2021.6585
Scientific Committee on Consumer Safety (SCCS) OPINION on Titanium dioxide (TiO2) used in cosmetic products that lead to exposure by inhalation (SCCS/1617/20).
EU COMMISSION REGULATION (EU) 2021/850 of 26 May 2021
Committee for Risk Assessment RAC Opinion proposing harmonised classification and labelling at EU level of Titanium dioxide. Adopted 14 September 2017

Chemical Name: CURCUMA LONGA ROOT OIL (RB)

Function: Botanicals /Skin conditioning

Note: In the absence of NO(A)EL data, the Margin of Safety (MoS) has not been calculated.
Unless otherwise determined and in the absence of literature or other experimental data, a Dermal Absorption (DAp) of 100% is taken as the worst case scenario.
NO(A)EL: No Observed Adverse Effect Level; MoS: Margin of Safety; SED Systemic Exposure Dosage
Calculation of Margin of Safety: MoS = NO(A)EL / SED

References for skin surface area, exposures, body weight and application quantities are derived from EU guidance and literature sources.
These are held on file at Intertek.

The following conditions apply to this assessment:
1. This product was not evaluated for heavy metal or lead content by the undersigned.
2. This product was not assessed for compliance with regulations, other than as described above, by the undersigned.
3. This product has not been evaluated for potential physical injury such as choking hazard, aspiration risk, or mechanical irritation by the undersigned.
4. It was assumed that all ingredients in the product were disclosed and are accurate as listed in the report table, subject to valid request.
5. Based upon the information supplied, unless otherwise stated in this report and subject to a valid request, being made, it was assumed that neither this product, nor the ingredients used in the product, contained any impurities/contaminants that would cause toxicity in a consumer.
6. This evaluation is relevant solely to the conditions described herein. Any substitution of ingredients, increase in concentrations of use, or change of use pattern will necessitate a new evaluation.
"Valid request" refers to request from supplier of formulation to Intertek.
7. Toxicological profiles are stored within an in-house database at Intertek.

For European Legislation only: This formulation will be assessed by Intertek in accordance with PART B , Annex I to Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (Official Journal L 342, 22 December 2009, pp. 59–209). The safety assessment is based upon the chemical specification and toxicological profile of the ingredients as supplied at the time of assessment and an assessment of the final cosmetic product. The supplier to this safety assessment is advised to ask for a new safety evaluation if any change in formulation occurs, change in raw materials used, abnormally high number of adverse events are recorded, changes in recommended uses or other circumstances that may affect the safety of this product.

END OF REPORT

This report is made solely on the basis of your instructions and/or information and materials supplied by you. It is not intended to be a recommendation for any particular course of action. Intertek does not accept a duty of care or any other responsibility to any person other than the Client in respect of this report and only accepts liability to the Client insofar as is expressly contained in the terms and conditions governing Intertek's provision of services to you. Intertek makes no warranties or representations either express or implied with respect to this report save as provided for in those terms and conditions. We have aimed to conduct the Review on a diligent and careful basis and we do not accept any liability to you for any loss arising out of or in connection with this report, in contract, tort, by statute or otherwise, except in the event of our gross negligence or willful misconduct.