PRODUCT INFORMATION FILE

This file (PIF - Product Information File) filled according to CE/1223/09 and related legislation in force regulation, which require it to keep available to the competent authorities a range of information about your product and reported below.

The information part of the dossier is to be considered confidential and access to the file is allowed only to the competent authorities and to specific checks by reasoned reason, as specified in the Regulation. The supervisory authority is responsible for maintaining the confidentiality of information.

Commercial Name

CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Product Category

q. skin care liquid

The product has been notified to the UE portal, CPNP, on . .

VITATEKA

First Printing Date	Last Checking
13.02.2025	20.02.2025

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PART 1 - Description of Cosmetic Product

Formula Code -

Commercial Name

CONCENTRATED CREAM BALM MUMIJO 12 HERBS

The product has been notified to the UE portal, CPNP, on . .

CPNP reference product:

First Printing Date 13.02.2025 **Last Checking** N° 1 on 20.02.2025

Liable Person Data

Name VITATEKA OÜ

Address MÕISA TEE 5, KOSTIVERE ALEVIK, JÕELÄHTME VALD, ESTONIA 74204 - (HR)

Phone N. +37258042133

Email Djan1983@gmail.com

N° REA

Manufacturer's data (who manufactures a cosmetic)

Name BIURO WHITE PHARMA SP Z O.O.

Address JANOWSKA 70/9 21500 BIAŁA PODLASKA (-)

Phone N. +48 518 242 716

Email biuro@whitepharma.pl

N° REA

Distributor's data (person placing a product on the market)

Name VITATEKA OÜ

Address MÕISA TEE 5, KOSTIVERE ALEVIK, JÕELÄHTME VALD, ESTONIA 74204 - (HR)

Phone N. +37258042133

Email Djan1983@gmail.com

N° REA

Extra UE Distributor's data (person placing a product on the market)

Name

Address ()

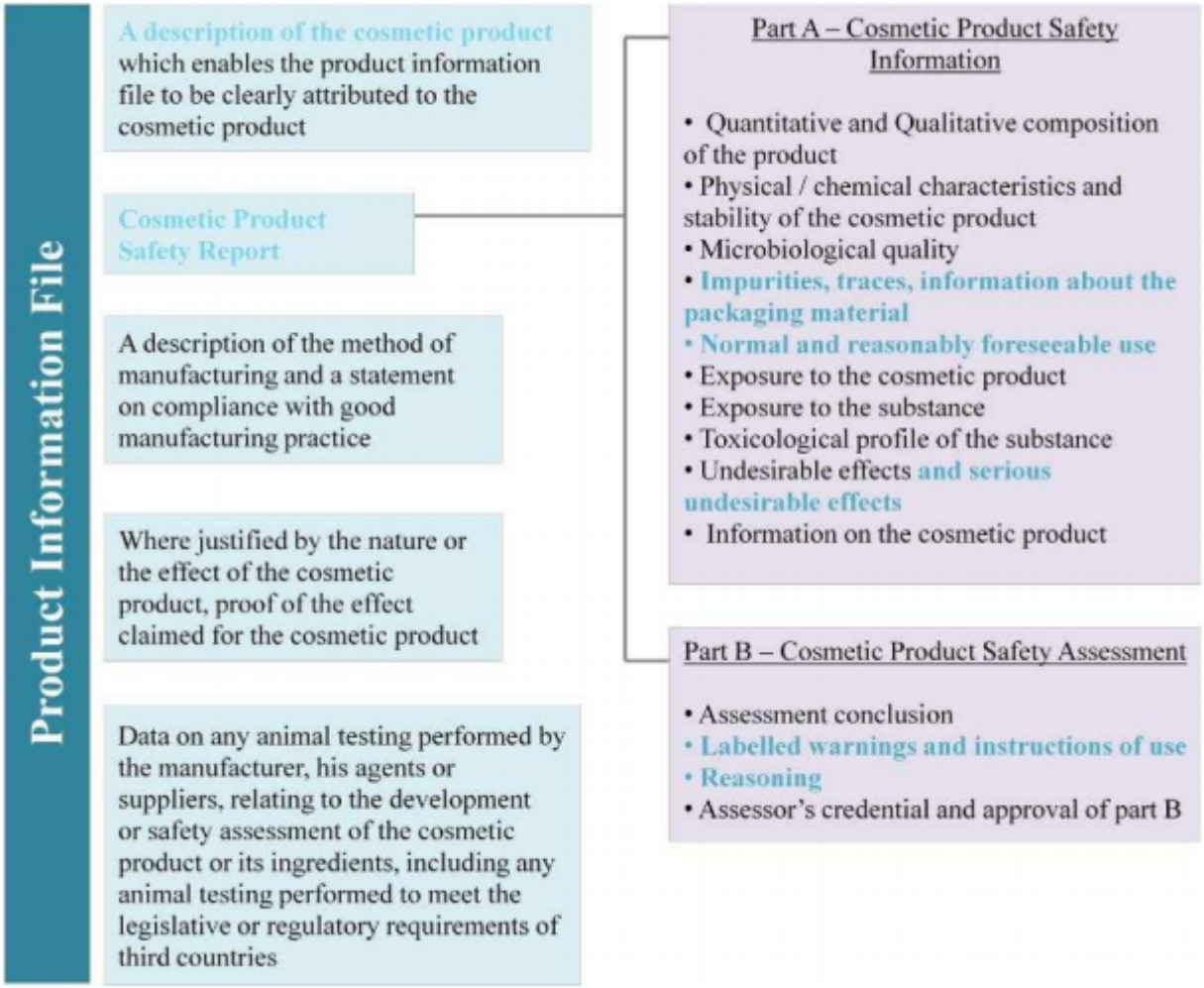
Phone N.

Email

N° REA

PIF to DISTRIBUTOR

PART 2
Relation on Cosmetic Product Safety (CPSR)



PART 2A - Information Regarding the Safety Profile of Cosmetic Product

Qualitative and Quantitative Composition of Cosmetic Product

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CPSR: Part A - Cosmetic Product Safety Information - Annex A1

Data processing: CHEMILAB, a software by PIF ITALIA s.r.l.

N	RAW MATERIAL TRADE NAME	% In Product	INCI NAME	*	% in Raw Mat.	CAS N.	EINECS N.	Funzionality
1	Purified water	57.500000	AQUA		100.0000	7732-18-5	231-791-2	SOLVENT
2	CETEARETH-25	5.000000	CETEARETH-25		100.0000	68439-49-6		CLEANSING, SURFACTANT - CLEANSING, SURFACTANT - EMULSIFYING
3	CETEARYL ALCOHOL	5.000000	CETEARYL ALCOHOL		100.0000	67762-27-0 / 8005-44-5	267-008-6	EMULSION STABILISING, OPACIFYING, SKIN CONDITIONING - EMOLLIENT, SURFACTANT - CLEANSING, SURFACTANT - EMULSIFYING, SURFACTANT - FOAM BOOSTING, VISCOSITY CONTROLLING
4	dimethycone	5.000000	DIMETHICONE		100.0000	63148-62-9 / 9006-65-9 / 9016-00-6		ANTIFOAMING, SKIN CONDITIONING, SKIN CONDITIONING - EMOLLIENT, SKIN PROTECTING
5	GLYCERYL STEARATE SE	5.000000	GLYCERYL STEARATE SE		100.0000	11099-07-3		SURFACTANT - EMULSIFYING
6	Isopropylmyristate	5.000000	ISOPROPYL MYRISTATE		100.0000	110-27-0	203-751-4	BINDING, FRAGRANCE, PERFUMING, SKIN CONDITIONING - EMOLLIENT
7	PARAFFINUM LIQUIDUM	5.000000	PARAFFINUM LIQUIDUM		100.0000	8012-95-1 / 8042-47-5	232-384-2	ANTISTATIC, SKIN CONDITIONING - EMOLLIENT, SKIN PROTECTING, SOLVENT

* The ingredients with asterisk have several restrictions (source COSING Cosmetic Ingredients and Substances).

PART 2A - Information Regarding the Safety Profile of Cosmetic Product

Qualitative and Quantitative Composition of Cosmetic Product

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CPSR: Part A - Cosmetic Product Safety Information - Annex A1 Data processing: CHEMILAB, a software by PIF ITALIA s.r.l.

8	CAMPHOR	1.000000	CAMPHOR	*	100.0000	464-49-3 / 76-22-2	207-355-2	DENATURANT, FRAGRANCE, PLASTICISER
9	Euxyl PE 9010	1.000000	PHENOXYETHANOL	*	91.5000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
10			ETHYLHEXYLGLYCERIN		8.5000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
11	HELIANTHUS ANNUUS SEED OIL	1.000000	HELIANTHUS ANNUUS SEED OIL		100.0000	84776-03-4 / 8001-21-6/ 164250-88-8	-/ 232-273-9/ -	SKIN CONDITIONING - EMOLLIENT, SKIN CONDITIONING - MISCELLANEOUS, SKIN CONDITIONING - OCCLUSIVE, SOLVENT
12	ALLANTOIN	0.500000	ALLANTOIN		100.0000	97-59-6	202-592-8	SKIN CONDITIONING, SKIN PROTECTING, SOOTHING
13	ALOE BARBADENSIS EXTRACT	0.500000	AQUA		94.0000	7732-18-5	231-791-2	SOLVENT
14			ALOE BARBADENSIS EXTRACT		5.0000	85507-69-3 / 94349-62-9	287-390-8	SKIN CONDITIONING
15			PHENOXYETHANOL	*	0.9000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
16			ETHYLHEXYLGLYCERIN		0.1000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
17	BENZYL NICOTINATE	0.500000	BENZYL NICOTINATE		100.0000	94-44-0	202-332-3	ANTISTATIC, SKIN CONDITIONING
18	BISABOLOL	0.500000	BISABOLOL		100.0000	515-69-5 / 23089-26-1	208-205-9	FRAGRANCE, SKIN CONDITIONING, SOOTHING
19	BLACKCURRANT OIL	0.500000	RIBES NIGRUM SEED OIL		100.0000	68606-81-5 / 97676-19-2	271-749-0 / -	SKIN CONDITIONING - EMOLLIENT
20	CAPSICUM ANNUUM FRUIT EXTRACT	0.500000	AQUA		89.0000	7732-18-5	231-791-2	SOLVENT

* The ingredients with asterisk have several restrictions (source COSING Cosmetic Ingredients and Substances).

PART 2A - Information Regarding the Safety Profile of Cosmetic Product

Qualitative and Quantitative Composition of Cosmetic Product

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CPSR: Part A - Cosmetic Product Safety Information - Annex A1

Data processing: CHEMILAB, a software by PIF ITALIA s.r.l.

21			CAPSICUM ANNUUM FRUIT EXTRACT		10.0000	84625-29-6	283-403-6	ANTI-SEBORRHEIC, ANTIMICROBIAL, ANTIOXIDANT, ASTRINGENT, HAIR CONDITIONING, SKIN PROTECTING
22			PHENOXYETHANOL	*	0.9000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
23			ETHYLHEXYLGLYCERIN		0.1000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
24	CHAMOMILLA RECUTITA FLOWER EXTRACT	0.500000	AQUA		49.0000	7732-18-5	231-791-2	SOLVENT
25			GLYCERIN		30.0000	56-81-5	200-289-5	DENATURANT, HAIR CONDITIONING, HUMECTANT, ORAL CARE, PERFUMING, SKIN CONDITIONING, SKIN PROTECTING, SOLVENT, VISCOSITY CONTROLLING
26			CHAMOMILLA RECUTITA FLOWER EXTRACT		20.0000	84082-60-0	282-006-5	FRAGRANCE, SKIN CONDITIONING
27			PHENOXYETHANOL	*	0.9000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
28			ETHYLHEXYLGLYCERIN		0.1000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
29	COSROMA TLJ011	0.500000	AQUA		64.0000	7732-18-5	231-791-2	SOLVENT
30			COLLAGEN		35.0000	9007-34-5	232-697-4	HAIR CONDITIONING, MOISTURISING, SKIN CONDITIONING
31			PHENOXYETHANOL	*	0.9000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
32			ETHYLHEXYLGLYCERIN		0.1000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
33	D-GLUCOSAMINE SULFATE	0.500000	GLUCOSAMINE SULFATE		100.0000	29031-19-4	249-379-6	SKIN CONDITIONING

* The ingredients with asterisk have several restrictions (source COSING Cosmetic Ingredients and Substances).

PART 2A - Information Regarding the Safety Profile of Cosmetic Product

Qualitative and Quantitative Composition of Cosmetic Product

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CPSR: Part A - Cosmetic Product Safety Information - Annex A1 Data processing: CHEMILAB, a software by PIF ITALIA s.r.l.

34	EUGENIA CARYOPHYLLUS BUD OIL	0.500000	EUGENIA CARYOPHYLLUS BUD OIL		100.0000	84961-50-2	284-638-7	FRAGRANCE, PERFUMING
35			EUGENOL	*	79.4200	97-53-0	202-589-1	DENATURANT, PERFUMING, TONIC
36			EUGENYL ACETATE	*	13.1000	93-28-7	202-235-6	FRAGRANCE
37			BETA-CARYOPHYLLENE	*	5.2100	87-44-5	201-746-1	FRAGRANCE, PERFUMING, SKIN CONDITIONING
38	HIPPOPHAE RHAMNOIDES OIL	0.500000	HIPPOPHAE RHAMNOIDES OIL		100.0000	225234-03-7 / 90106-68-6		SKIN CONDITIONING, SKIN CONDITIONING - EMOLLIENT
39	menthol	0.500000	MENTHOL	*	100.0000	1490-04-6 / 2216-51-5 / 89-78-1 / 15356-60-2	201-939-0 / 216-074-4 / 218-690-9	DENATURANT, FRAGRANCE, REFRESHING, SOOTHING
40	MUMIO ASPHALTUM PUNJABIANUM EXTRACT	0.500000	AQUA		79.0000	7732-18-5	231-791-2	SOLVENT
41			ASPHALTUM EXTRACT		20.0000			Anti-inflammatory, antioxidant, anti-acne
42			PHENOXYETHANOL	*	0.9000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
43			ETHYLHEXYLGLYCERIN		0.1000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
44	PROPOLIS EXTRACT WATER EXTRACT	0.500000	AQUA		45.0000	7732-18-5	231-791-2	SOLVENT
45			GLYCERIN		34.0000	56-81-5	200-289-5	DENATURANT, HAIR CONDITIONING, HUMECTANT, ORAL CARE, PERFUMING, SKIN CONDITIONING, SKIN PROTECTING, SOLVENT, VISCOSITY CONTROLLING
46			PROPOLIS EXTRACT		20.0000	85665-41-4	288-130-6	SKIN CONDITIONING
47			PHENOXYETHANOL	*	0.9000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE

* The ingredients with asterisk have several restrictions (source COSING Cosmetic Ingredients and Substances).

PART 2A - Information Regarding the Safety Profile of Cosmetic Product

Qualitative and Quantitative Composition of Cosmetic Product

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CPSR: Part A - Cosmetic Product Safety Information - Annex A1

Data processing: CHEMILAB, a software by PIF ITALIA s.r.l.

48			ETHYLHEXYLGLYCERIN		0.1000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
49	SODIUM CHONDROITIN SULFATE	0.500000	SODIUM CHONDROITIN SULFATE		100.0000	9007-28-7 / 9082-07-9	232-696-9	ANTISTATIC, HAIR CONDITIONING, SKIN CONDITIONING
50	SYMPHYTUM OFFICINALE ROOT EXTRACT	0.500000	AQUA		94.0000	7732-18-5	231-791-2	SOLVENT
51			SYMPHYTUM OFFICINALE ROOT EXTRACT		5.0000	84696-05-9	283-625-3	ANTI-SEBORRHEIC, SKIN CONDITIONING, SOOTHING
52			PHENOXYETHANOL	*	0.9000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
53			ETHYLHEXYLGLYCERIN		0.1000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
54	Tocopheryl acetate	0.500000	TOCOPHERYL ACETATE		100.0000	7695-91-2 / 58-95-7	231-710-0	ANTIOXIDANT, SKIN CONDITIONING
55	BOSWELLIA SERRATA EXTRACT	0.100000	PROPYLENE GLYCOL		50.0000	57-55-6	200-338-0	FRAGRANCE, HUMECTANT, SKIN CONDITIONING - HUMECTANT, SKIN CONDITIONING - MISCELLANEOUS, SOLVENT, VISCOSITY CONTROLLING
56			AQUA		40.0000	7732-18-5	231-791-2	SOLVENT
57			BOSWELLIA SERRATA EXTRACT		10.0000	97952-72-2	308-366-6	SKIN CONDITIONING
58	Citric Acid	0.100000	CITRIC ACID		100.0000	77-92-9 / 5949-29-1	201-069-1	BUFFERING, CHELATING, FRAGRANCE
59	COMARUM PALUSTRE ROOT EXTRACT	0.100000	AQUA		94.0000	7732-18-5	231-791-2	SOLVENT
60			HYDROLYZED COMARUM PALUSTRE ROOT/STEM EXTRACT		5.0000		-	SKIN CONDITIONING
61			PHENOXYETHANOL	*	0.9000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE

* The ingredients with asterisk have several restrictions (source COSING Cosmetic Ingredients and Substances).

PART 2A - Information Regarding the Safety Profile of Cosmetic Product

Qualitative and Quantitative Composition of Cosmetic Product

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CPSR: Part A - Cosmetic Product Safety Information - Annex A1

Data processing: CHEMILAB, a software by PIF ITALIA s.r.l.

62			ETHYLHEXYLGLYCERIN		0.1000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
63	dl-alfa-tocopherol care	0.100000	TOCOPHEROL		100.0000	54-28-4 (gamma)/ 16698-35-4(beta) / 10191-41-0 (DL) / 119-13-1 / 1406-18-4 / 1406-66-2 / 2074-53-5 (DL) / 59-02-9 (D)/7616-22-0	200-201-5 / 240-747-1 / 233-466-0 / 204-299-0 /215-798-8 / - / 218-197-9 / 200-412-2 / -	ANTIOXIDANT, FRAGRANCE, SKIN CONDITIONING - MISCELLANEOUS, SKIN CONDITIONING - OCCLUSIVE
64	INULA HELENIUM ROOT EXTRACT	0.100000	PROPYLENE GLYCOL		50.0000	57-55-6	200-338-0	FRAGRANCE, HUMECTANT, SKIN CONDITIONING - HUMECTANT, SKIN CONDITIONING - MISCELLANEOUS, SOLVENT, VISCOSITY CONTROLLING
65			AQUA		30.0000	7732-18-5	231-791-2	SOLVENT
66			INULA HELENIUM EXTRACT		20.0000	84012-20-4	281-666-1	FRAGRANCE, SKIN CONDITIONING
67	JUNIPERUS COMMUNIS FRUIT EXTRACT	0.100000	PROPYLENE GLYCOL		50.0000	57-55-6	200-338-0	FRAGRANCE, HUMECTANT, SKIN CONDITIONING - HUMECTANT, SKIN CONDITIONING - MISCELLANEOUS, SOLVENT, VISCOSITY CONTROLLING
68			AQUA		30.0000	7732-18-5	231-791-2	SOLVENT
69			JUNIPERUS COMMUNIS FRUIT EXTRACT		20.0000	84603-69-0	283-268-3	PERFUMING, SKIN CONDITIONING

* The ingredients with asterisk have several restrictions (source COSING Cosmetic Ingredients and Substances).

PART 2A - Information Regarding the Safety Profile of Cosmetic Product

Qualitative and Quantitative Composition of Cosmetic Product

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CPSR: Part A - Cosmetic Product Safety Information - Annex A1 Data processing: CHEMILAB, a software by PIF ITALIA s.r.l.

70	MEDICAGO SATIVA EXTRACT	0.100000	PROPYLENE GLYCOL		50.0000	57-55-6	200-338-0	FRAGRANCE, HUMECTANT, SKIN CONDITIONING - HUMECTANT, SKIN CONDITIONING - MISCELLANEOUS, SOLVENT, VISCOSITY CONTROLLING
71			AQUA		30.0000	7732-18-5	231-791-2	SOLVENT
72			MEDICAGO SATIVA EXTRACT		20.0000	84082-36-0	281-984-0	TONIC
73	RETINYL PALMITATE	0.100000	RETINYL PALMITATE		100.0000	79-81-2	201-228-5	SKIN CONDITIONING, SKIN CONDITIONING - MISCELLANEOUS
74	RHUS GLABRA EXTRACT	0.100000	PROPYLENE GLYCOL		50.0000	57-55-6	200-338-0	FRAGRANCE, HUMECTANT, SKIN CONDITIONING - HUMECTANT, SKIN CONDITIONING - MISCELLANEOUS, SOLVENT, VISCOSITY CONTROLLING
75			AQUA		30.0000	7732-18-5	231-791-2	SOLVENT
76			RHUS GLABRA EXTRACT		20.0000	90106-33-5	290-256-1	ANTISEBORRHOEIC / ASTRINGENT / SKIN CONDITIONING
77	TAMUS COMMUNIS EXTRACT	0.100000	PROPYLENE GLYCOL		50.0000	57-55-6	200-338-0	FRAGRANCE, HUMECTANT, SKIN CONDITIONING - HUMECTANT, SKIN CONDITIONING - MISCELLANEOUS, SOLVENT, VISCOSITY CONTROLLING
78			AQUA		30.0000	7732-18-5	231-791-2	SOLVENT

* The ingredients with asterisk have several restrictions (source COSING Cosmetic Ingredients and Substances).

PART 2A - Information Regarding the Safety Profile of Cosmetic Product

Qualitative and Quantitative Composition of Cosmetic Product

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CPSR: Part A - Cosmetic Product Safety Information - Annex A1

Data processing: CHEMILAB, a software by PIF ITALIA s.r.l.

79		TAMUS COMMUNIS EXTRACT		20.0000	84961-63-7	-	HUMECTANT, SKIN CONDITIONING, SKIN PROTECTING

* The ingredients with asterisk have several restrictions (source COSING Cosmetic Ingredients and Substances).

Part 2A
Physical/Chemical and Stability Features of Cosmetic Product

CPSR: Part A - Cosmetic Product Safety Information - Annex A2

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

PURITY AND ANALYTICAL SPECIFICATIONS OF RAW MATERIALS ARE CONTAINED ON THE RELEVANT CERTIFICATES OF ANALYSIS / SALES SPECIFICATIONS, WHICH ARE HELD BY THE MANUFACTURER. RAW MATERIAL PHYSICAL CHARACTERISTICS AND SUPPLIERS' HAZARD CLASSIFICATIONS ARE GIVEN IN THE SAFETY DATA SHEETS, WHICH ARE HELD BY MANUFACTURE. THE PHYSICAL/CHEMICAL SPECIFICATION (FOR DETAILES SEE POINT 9. OF MSDS) OF THE INGREDIENTS ARE WELL KNOWN (COSING, COSMOBASE, CIR, ECHA, PUBCHEM) AND COMMONLY USED IN SIMILAR PRODUCTS. THEIR INCLUSIONS IN THE FINISHED PRODUCT AT THE SPECIFIED CONCENTRATIONS DO NOT GIVE RISE TO ANY CONCERNS. TO DETERMINE PHYSICAL AND CHEMICAL PROPERTIES OF RAW MATERIAL WERE USED METHODS: GRAVIMETRIC, POTENTIOMETRIC, CHROMATOGRAPHIC, TITRIMETRIC METHODS. EVALUATION METHOD OF RAW MATERIAL'S PURITY ARE SHOWN IN TDS, COA AND MSDS. ALL THOSE DOCUMENTS ARE ATTACHED. REGARDING ANY TRACES AND IMPURITIES FROM THE RAW MATERIALS PLEASE REFER TO TABLE 1 OF PART A QUANTITATIVE AND QUALITATIVE COMPOSITION OF THE COSMETIC PRODUCT AND SECTION 8. TOXICOLOGICAL PROFILE OF THE SUBSTANCES.

FOR THE PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE COSMETIC PRODUCT: SEE THE ATTACHED TECHNICAL SHEET OF THE FINISHED PRODUCT.

FOR THE PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE SUBSTANCES OR MIXTURES, SEE THE TECHNICAL DATA SHEETS / SAFETY DATA SHEETS / OTHER STATEMENTS ATTACHED.

THE PRODUCT HAS PASSED 90 DAY STABILITY TEST, BASE ON METHODS:
1. EUROPEAN MEDICINES AGENCY -REPRODUCTION AND/OR DISTRIBUTION OF THIS DOCUMENT IS AUTHORISED FOR NON COMMERCIAL PURPOSES ONLY PROVIDED THE EMEA IS ACKNOWLEDGED AUGUST 2003 CPMP/ICH/2736/99 ICH TOPIC Q 1 A (R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTSSESNSORIAL TESTS ARE PERFORMED VISUAL EVALUATION OF REFERENCE SAMPLE STORED AT AMBIENT CONDITIONS (ROOM TEMPERATURE): A STABLE PRODUCT IS CONSIDERED AS PRODUCT THAT MEETS THE PARAMETERS AND SPECIFICATION AS SET BY THE CLIENT.
2. COSMETICS EUROPE: GUIDELINES ON STABILITY TESTING OF COSMETIC PRODUCTS ALL RIGHTS RESERVED TO CTFA AND COSMETICS EUROPE MARCH 2004
3. SCIENTIFIC COMMITTEE ON CONSUMER SAFETY SCCS THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION 10TH REVISION.
CONCLUSION: THE PRODUCT MEETS THE STATED REQUIREMENTS OF THE MANUFACTURER. FOR DETAILES SEE STABILITY TEST PROTOCOL.
PHYSICAL/CHEMICAL CHARACTERISTICS OF THE INGREDIENTS (SUBSTANCES AND MIXTURES) PURITY AND ANALYTICAL SPECIFICATIONS OF RAW MATERIALS ARE CONTAINED ON THE RELEVANT CERTIFICATES OF ANALYSIS / SALES SPECIFICATIONS, WHICH ARE HELD BY THE MANUFACTURER.
SINCE THE TESTS WERE CARRIED OUT ON THE PRODUCT UNDER EXTREME CONDITIONS AND WITHIN 90 DAYS OF TESTING THE PRODUCT PACKED IN THE ORIGINAL PACKAGING, UNDER THE ABOVE CONDITIONS, NO VISIBLE, PHYSICO-CHEMICAL CHANGES WERE FOUND AND NO DEFORMATIONS OF THE PACKAGING, PLUS MICROBIOLOGICAL TEST DO NOT LET YOU DOUBT THE STABILITY OF THE PRODUCT. IT CAN BE CONCLUDED THAT THE SHELF LIFE OF THE PRODUCT IS 30 MONTHS.

VITATEKA

TECHNICAL DATA SHEET

Formula Code -

CONCENTRATED CREAM BALM MUMIJO 12 HERBS

First Printing Date . . **Last Checking** N° 1 on 20.02.2025

PRODUCT DESCRIPTION

Product Family 3. Non rinse-off Products

Product Category Creams, emulsions, lotions, gels and oils for the skin (hands, feet, face, etc.)

Product Type q. skin care liquid

CREAM BALM

INGREDIENTS

AQUA DIMETHICONE ISOPROPYL MYRISTATE CETEARETH-25 CETEARYL ALCOHOL GLYCERYL STEARATE SE PARAFFINUM LIQUIDUM HELIANTHUS ANNUUS SEED OIL CAMPHOR PHENOXYETHANOL RIBES NIGRUM SEED OIL MENTHOL SODIUM CHONDROITIN SULFATE ALLANTOIN BENZYL NICOTINATE BISABOLOL EUGENIA CARYOPHYLLUS BUD OIL HIPPOPHAE RHAMNOIDES OIL TOCOPHERYL ACETATE GLUCOSAMINE SULFATE EUGENOL GLYCERIN PROPYLENE GLYCOL COLLAGEN CITRIC ACID TOCOPHEROL ASPHALTUM EXTRACT CHAMOMILLA RECUTITA FLOWER EXTRACT RETINYL PALMITATE PROPOLIS EXTRACT ETHYLHEXYLGLYCERIN EUGENYL ACETATE CAPSICUM ANNUUM FRUIT EXTRACT BETA-CARYOPHYLLENE SYMPHYTUM OFFICINALE ROOT EXTRACT ALOE BARBADENSIS EXTRACT MEDICAGO SATIVA EXTRACT TAMUS COMMUNIS EXTRACT JUNIPERUS COMMUNIS FRUIT EXTRACT INULA HELENIUM EXTRACT RHUS GLABRA EXTRACT BOSWELLIA SERRATA EXTRACT HYDROLYZED COMARUM PALUSTRE ROOT/STEM EXTRACT

PHYSICAL / CHEMICAL / MICROBIOLOGICAL CHARACTERISTICS

Phisical State	LIQUID	**Viscosity**	CHARACTERISTIC
Color	CHARACTERISTIC	**Density**	N/A
Fragrance	CHARACTERISTIC	**Centrifuge**	N/A
pH	-		
PAO (Period After Opening)	12	**Use preferably within:**	36

Other Informations

Microbiological Specifications Based on available information from the ingredient specifications (see section A. Quantitative and qualitative composition–specification of ingredients. To evaluate microbiology of ingredients those methods were used: ISO21149 (aerobic mesophilic bacteria, result: < =100 CFU/g), ISO16212 (Yeasts and Moulds at 25°C, result < =10 CFU/g), ISO21150 (Escherichia coli; result Absent in 1g), ISO22718 (Staphylococcusaureus; result Absent in 1g), ISO22717 (Pseudomonas aeruginosa; result Absent in 1g), ISO18416 (Candida albicans; result Absent in 1g). Based on above mentioned result ingredients used can be assessed as microbiologically safe. Detailed data of methods and results presented in TDS and CoA

TEST DESCRIPTION	Result
Enumeration of aerobic mesophilic bacteria	<=100 CFU/g
Enumeration of Yeasts and Moulds at 25°C	<=10 CFU/g
Detection of Escherichia coli	Absent in 1g
Detection of Staphylococcus aureus	Absent in 1g
Detection of Pseudomonas aeruginosa	Absent in 1g
Detection of Candida albicans	Absent in 1g

MANUFACTURING

Production of creames:
1. Water purification by doble distillation and UV treatment
2. Water heating until 80 0C
3. In separate tank mixing and homogenesation of fatty compounds at known temperature. It is mixture B
4. In separate tank mixing and homogenesation of oils, salts, complexing agent, preservative. It is mixture B
5. Adding of mixture A to pre-heated water and mixing and homogenesation process continue.
6. Waiting when mixture A with water will cool until 45 0C
7. Adding of mixture B to cooled mixture A with water tank and continue mixing approx.. more 30 minutes
8. Adding to mix A, B with water extracts, skin softeners
9. Continue whole mix of compounds A, B, water, extract approx. more 45 minutes until final mix will be done.

Formula Code -

CONCENTRATED CREAM BALM MUMIJO 12 HERBS

First Printing Date . . **Last Checking** N° 1 on 20.02.2025

PACKAGING

Packaging
1. Preparing and disinfection of filling's inventar, can, caps and environment around
2. Adding ready mix to filling inventar and put to can after caping.
3. Already packed product labeling and goes to the stock.

200 ml PE tube with PP cap

INSTRUCTIONS AND WARNINGS FOR USE

This product's presentation is in accordance with a Regulation no 1223/2009 of the European Parliament and of the Council about the labelling of cosmetic product. Restricted ingredients are properly listed on the package. Instruction of use: Apply the cream to the body in light circular movements 3 - 5 minutes until complete absorption 2 - 3 times a day. Cream is designed for daily use. All use instructions are written on the label.

FIRST AID MEASURES

Avoid contact with eyes, open wounds and mucose membranes. Keep out of reach of children. Contraindications: individual intolerance to the components. In case of allergic reactions, discontinue use and consult a doctor.

HANDLING AND STORAGE

Keep at a temperature 5°C - 25°C

To determine physical and chemical properties of raw material were used methods: gravimetric, potentiometric, chromatographic, titrimetric methods.
Evaluation method of raw material's purity are shown in TDS, CoA and msds. All those documents are attached.
Final product:
Phisical State evaluation method: visual observation
pH evaluation method; potentiometry method (electric pH meter) were used.
Viscosity evaluation method: visual observation
Fragrance evaluation method: smell assessment method
Color evaluation method: visual observation

Part 2A
Microbiological Quality

CPSR: Part A - Cosmetic Product Safety Information - Annex A3

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Microbiological test were done according methods: ISO21149; ISO16212; ISO21150; ISO22718; ISO22717. Results presented in TDS of final product, detailed data of test presented in test raport.

No Challange test is carried out as the product do not pose any risk to consumers under normal conditions of use. The product not intended for using persons under 3 years. DUE TO THE FACT THAT THE COMPOSITION CONTAINS NATURAL AND SYNTHETIC ANTISEPTICS AND ANTIOXIDANTS, AS WELL AS OILS (TOTAL MORE THAN 25%) DUE TO WHICH THE EFFECT OF AIR OXYGEN, HUMIDITY AND BACTERIA ON THE PRODUCT IS REDUCED. BASED ON STATEMENT (1) OF 3.3.2. Microbiological quality of the finished cosmetic product OF Guidelines on Annex I to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products, PRODUCT BELONGS TO low microbiological risk. According to the above and the microbiological quality passed test of finish product, it can be concluded that there is no need for an ISO11930 PRESERVATIVE EFFICACY „CHALLANGE“ TEST.

For the PAO / DEADLINE SEE attachment.

PAO EVALUATION / DEADLINE

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

PAO 12 MONTHS

PAO not applicable, since expairy date of product 30 months.

Part 2A
Information Regarding Impurities, Residues and Packaging Material

CPSR: Part A - Cosmetic Product Safety Information - Annex A4

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Laminated tube with a protective membrane.
Type of the Laminate: ABL (laminate with aluminum barrier layer)
Material of Shoulder: High-pressure polyethylene
Material of cap: polypropylene
Type of printing: flexo, UV paints and lacquer.
Packaging material is stable under normal conditions of use.
Packaging material has proper certificate of conformity. The manufacturer is ensured that packaging is of cosmetics quality and is chosen as not to lead to deterioration of the product.

Raw Materials Impurities List

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Data processing: CHEMILAB, a software by PIF ITALIA s.r.l.

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product
1	CETEARYL ALCOHOL	5.000000	PARAFFIN	8002-74-2	232-315-6	0.5	0.025

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	COGNIS METHOD 970059	NON TOXIC UNDER CLP	

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product
2	dl-alfa-tocopherol care	0.100000	ASCORBIC ACID	50-81-7	200-066-2	0.5	0.0005

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	EP	non toxic under CLP	

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product
3			Colecalciferol	67-97-0	200-673-2	0.5	0.0005

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	EP	Acute Tox. 2: H330 , H310 , H300; STOT RE 1: H372	% weight >=3 STOT RE 1 H372; 0,3<= % weight <3 STOT RE 2 H373

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product
4			RETINOL	68-26-8	200-683-7	0.5	0.0005

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	EP	Aquatic Chronic 4: H413; Eye Irrit. 2: H319; Repr. 1B: H360; Skin Sens. 1: H317	

Raw Materials Impurities List

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Data processing: CHEMILAB, a software by PIF ITALIA s.r.l.

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product
5	dl-alfa-tocopherol care	0.100000	CYANOCOBALAMIN	68-19-9	200-680-0	1.5	0.0015

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	EP	non toxic under CLP	

IMPURITY CHEMICAL NAME	CAS N.	% In Product	SED Adults	NO(A)EL	MOS Adults	MOS 10 Years	MOS 5 Years	MOS 12 Months	MOS 6 Months	MOS Birth
PARAFFIN	8002-74-2	0.025000	0.003696	5.000	1353	1353	1353	1353	1353	1353
CYANOCOBALAMIN	68-19-9	0.001500	0.000222	200.000	900901	900901	900901	900901	900901	900901
RETINOL	68-26-8	0.000500	0.000074	4.000	54054	54054	54054	54054	54054	54054
Colecalciferol	67-97-0	0.000500	0.000074	1.000	13514	13514	13514	13514	13514	13514
ASCORBIC ACID	50-81-7	0.000500	0.000074	2000.000	27027027	27027027	27027027	27027027	27027027	27027027

Part 2A
Normal and Reasonably Predictable Use

CPSR: Part A - Cosmetic Product Safety Information - Annex A5

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

The commercial history of the product, and of the raw materials it is made of, testify the optimal tolerability of the same, this is evidenced from the fact that in no case has been come to acquaintance of undesirable reactions.
Under normal conditions of use no cases of intoxication or irritation were found.
The information from the raw material suppliers and literature shows that the components of the formula do not have an irritant or skin sensitising effect. In the event that this happens, appropriate information material will be included in this dossier.
Acute toxicity, carcinogenicity, mutagenicity and teratogenesis effects assessed by national or international official bodies are unknown. For more details on how to use it, see the section "Instructions and instructions for use" in the product data sheet attached. Instruction of use: Apply the cream to the body in light circular movements 3 - 5 minutes until complete absorption 2 - 3 times a day. Cream is designed for daily use. Avoid contact with eyes, open wounds and mucose membranes. Keep out of reach of children. Contraindications: individual intolerance to the components. In case of allergic reactions, discontinue use and consult a doctor.

Part 2A
Exposure to Cosmetic Product

CPSR: Part A - Cosmetic Product Safety Information - Annex A6

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Product Family	3. Non rinse-off Products
Product Category	Creams, emulsions, lotions, gels and oils for the skin (hands, feet, face, etc.)
Product Type	q. skin care liquid
Application Area	This product is considered as a leave-on product intended to use on 10% of body area
Another possible use	
For Children Under 3 Years	No
Estimated application in g/day	7.82
Relative Qty in mg/kg bw/day	14.78
Dap/100 retention factor in g	1.00

Part 2A
Exposure to ingredients and Toxicological profile

CPSR: Part A - Cosmetic Product Safety Information - Annex A7

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Estimated daily quantity of cosmetics (g/day)	7.82	Relative Qty in mg/kg bw/day	14.78	Dap/100 retention factor in g	1.00

INCI Name	CAS N.	*	% In Product	SED Adults	NO(A)EL	MOS Adults	MOS 10 Years	MOS 5 Years	MOS 12 Months	MOS 6 Months	MOS Birth
AQUA	7732-18-5		60.354000	8.922736	45000.00	**5043**	**5043**	**5043**	**5043**	**5043**	**5043**
CETEARETH-25	68439-49-6		5.000000	0.739200	1000.00	**1353**	**1353**	**1353**	**1353**	**1353**	**1353**
CETEARYL ALCOHOL	67762-27-0 / 8005-44-5		5.000000	0.739200	750.00	**1015**	**1015**	**1015**	**1015**	**1015**	**1015**
DIMETHICONE	63148-62-9 / 9006-65-9 / 9016-00-6		5.000000	0.739200	1000.00	**1353**	**1353**	**1353**	**1353**	**1353**	**1353**
GLYCERYL STEARATE SE	11099-07-3		5.000000	0.739200	1000.00	**1353**	**1353**	**1353**	**1353**	**1353**	**1353**
ISOPROPYL MYRISTATE	110-27-0		5.000000	0.739200	1000.00	**1353**	**1353**	**1353**	**1353**	**1353**	**1353**
PARAFFINUM LIQUIDUM	8012-95-1 / 8042-47-5		5.000000	0.739200	1624.00	**2197**	**2197**	**2197**	**2197**	**2197**	**2197**
CAMPHOR	464-49-3 / 76-22-2	*	1.000000	0.147840	250.00	**1691**	**1691**	**1691**	**1691**	**1691**	**1691**
HELIANTHUS ANNUUS SEED OIL	84776-03-4 / 8001-21-6/ 164250-88-8		1.000000	0.147840	9250.00	**62568**	**62568**	**62568**	**62568**	**62568**	**62568**
PHENOXYETHANOL	122-99-6	*	0.947400	0.140064	500.00	**3570**	**3570**	**3570**	**3570**	**3570**	**3570**
ALLANTOIN	97-59-6		0.500000	0.073920	450.00	**6088**	**6088**	**6088**	**6088**	**6088**	**6088**

* The ingredients with asterisk are restrictive (source COSING Cosmetics Ingredients and Substances).

The possible absence of NO(A)EL is duly justified in Annex B3 of this P.I.F.
With regard to the toxicological data of the substances, see Safety Data Sheets of the previously attached substances.

The values "SED Adults" and "MOS Adults" are calculated taking as reference the average weight of an adult person equal to 60 kg.

The value of the MOS obtained is related for the various ages by means of a coefficient which derives from the ratio between the surface of the skin and the body mass in the various ages. It is higher in children than in adults, below the reference thresholds:
- Adult; MoS 100
- At 10 years, 1.3 times higher; MoS 130
- At 5 years, 1,5 times higher; MoS 150
- At 12 months, 1,6 times higher; MoS 160
- At 6 months 1,8 times higher; MoS 180
- Infants 2,3 times over; Mos infants 230

Part 2A
Exposure to ingredients and Toxicological profile

CPSR: Part A - Cosmetic Product Safety Information - Annex A7

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Estimated daily quantity of cosmetics (g/day)	7.82	Relative Qty in mg/kg bw/day	14.78	Dap/100 retention factor in g	1.00

BENZYL NICOTINATE	94-44-0		0.500000	0.073920	20.00	**271**	**271**	**271**	**271**	**271**	**271**
BISABOLOL	515-69-5 / 23089-26-1		0.500000	0.073920	200.00	**2706**	**2706**	**2706**	**2706**	**2706**	**2706**
EUGENIA CARYOPHYLLUS BUD OIL	84961-50-2		0.500000	0.073920	1000.00	**13528**	**13528**	**13528**	**13528**	**13528**	**13528**
GLUCOSAMINE SULFATE	29031-19-4		0.500000	0.073920	2149.00	**29072**	**29072**	**29072**	**29072**	**29072**	**29072**
HIPPOPHAE RHAMNOIDES OIL	225234-03-7 / 90106-68-6		0.500000	0.073920	9220.00	**124729**	**124729**	**124729**	**124729**	**124729**	**124729**
MENTHOL	1490-04-6 / 2216-51-5 / 89-78-1 / 15356-60-2	*	0.500000	0.073920	188.00	**2543**	**2543**	**2543**	**2543**	**2543**	**2543**
RIBES NIGRUM SEED OIL	68606-81-5 / 97676-19-2		0.500000	0.073920	10000.00	**135281**	**135281**	**135281**	**135281**	**135281**	**135281**
SODIUM CHONDROITIN SULFATE	9007-28-7 / 9082-07-9		0.500000	0.073920	1000.00	**13528**	**13528**	**13528**	**13528**	**13528**	**13528**
TOCOPHERYL ACETATE	7695-91-2 / 58-95-7		0.500000	0.073920	500.00	**6764**	**6764**	**6764**	**6764**	**6764**	**6764**
EUGENOL	97-53-0	*	0.397100	0.058707	300.00	**5110**	**5110**	**5110**	**5110**	**5110**	**5110**
GLYCERIN	56-81-5		0.320000	0.047309	10000.00	**211376**	**211376**	**211376**	**211376**	**211376**	**211376**
PROPYLENE GLYCOL	57-55-6		0.300000	0.044352	5300.00	**119499**	**119499**	**119499**	**119499**	**119499**	**119499**
COLLAGEN	9007-34-5		0.175000	0.025872	8600.00	**332406**	**332406**	**332406**	**332406**	**332406**	**332406**
ASPHALTUM EXTRACT			0.100000	0.014784	33.30	**2252**	**2252**	**2252**	**2252**	**2252**	**2252**
CHAMOMILLA RECUTITA FLOWER EXTRACT	84082-60-0		0.100000	0.014784	4000.00	**270563**	**270563**	**270563**	**270563**	**270563**	**270563**

* The ingredients with asterisk are restrictive (source COSING Cosmetics Ingredients and Substances).

The possible absence of NO(A)EL is duly justified in Annex B3 of this P.I.F.
With regard to the toxicological data of the substances, see Safety Data Sheets of the previously attached substances.

The values "SED Adults" and "MOS Adults" are calculated taking as reference the average weight of an adult person equal to 60 kg.

The value of the MOS obtained is related for the various ages by means of a coefficient which derives from the ratio between the surface of the skin and the body mass in the various ages. It is higher in children than in adults, below the reference thresholds:
- Adult; MoS 100
- At 10 years, 1.3 times higher; MoS 130
- At 5 years, 1,5 times higher; MoS 150
- At 12 months, 1,6 times higher; MoS 160
- At 6 months 1,8 times higher; MoS 180
- Infants 2,3 times over; Mos infants 230

Part 2A
Exposure to ingredients and Toxicological profile

CPSR: Part A - Cosmetic Product Safety Information - Annex A7

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Estimated daily quantity of cosmetics (g/day)	7.82	Relative Qty in mg/kg bw/day	14.78	Dap/100 retention factor in g	1.00

CITRIC ACID	77-92-9 / 5949-29-1		0.100000	0.014784	250.00	**16910**	**16910**	**16910**	**16910**	**16910**	**16910**
PROPOLIS EXTRACT	85665-41-4		0.100000	0.014784	1400.00	**94697**	**94697**	**94697**	**94697**	**94697**	**94697**
RETINYL PALMITATE	79-81-2		0.100000	0.014784	7.71	**522**	**522**	**522**	**522**	**522**	**522**
TOCOPHEROL	54-28-4 (gamma)/ 16698-35-4(beta) / 10191-41-0(DL) / 119-13-1 / 1406-18-4 / 1406-66-2 / 2074-53-5 (DL) / 59-02-9 (D)/7616-22-0		0.100000	0.014784	500.00	**33820**	**33820**	**33820**	**33820**	**33820**	**33820**
ETHYLHEXYLGLYCERIN	70445-33-9		0.088600	0.013099	100.00	**7634**	**7634**	**7634**	**7634**	**7634**	**7634**
EUGENYL ACETATE	93-28-7	*	0.065500	0.009684	230.00	**23751**	**23751**	**23751**	**23751**	**23751**	**23751**
CAPSICUM ANNUUM FRUIT EXTRACT	84625-29-6		0.050000	0.007392	2388.00	**323052**	**323052**	**323052**	**323052**	**323052**	**323052**
BETA-CARYOPHYLLENE	87-44-5	*	0.026050	0.003851	222.00	**57647**	**57647**	**57647**	**57647**	**57647**	**57647**
ALOE BARBADENSIS EXTRACT	85507-69-3 / 94349-62-9		0.025000	0.003696	11800.00	**3192641**	**3192641**	**3192641**	**3192641**	**3192641**	**3192641**
SYMPHYTUM OFFICINALE ROOT EXTRACT	84696-05-9		0.025000	0.003696	100.00	**27056**	**27056**	**27056**	**27056**	**27056**	**27056**
INULA HELENIUM EXTRACT	84012-20-4		0.020000	0.002957	83.00	**28069**	**28069**	**28069**	**28069**	**28069**	**28069**
JUNIPERUS COMMUNIS FRUIT EXTRACT	84603-69-0		0.020000	0.002957	120.00	**40582**	**40582**	**40582**	**40582**	**40582**	**40582**
MEDICAGO SATIVA EXTRACT	84082-36-0		0.020000	0.002957	166.00	**56138**	**56138**	**56138**	**56138**	**56138**	**56138**

* The ingredients with asterisk are restrictive (source COSING Cosmetics Ingredients and Substances).

The possible absence of NO(A)EL is duly justified in Annex B3 of this P.I.F.
With regard to the toxicological data of the substances, see Safety Data Sheets of the previously attached substances.

The values "SED Adults" and "MOS Adults" are calculated taking as reference the average weight of an adult person equal to 60 kg.

The value of the MOS obtained is related for the various ages by means of a coefficient which derives from the ratio between the surface of the skin and the body mass in the various ages. It is higher in children than in adults, below the reference thresholds:
- Adult; MoS 100
- At 10 years, 1.3 times higher; MoS 130
- At 5 years, 1,5 times higher; MoS 150
- At 12 months, 1,6 times higher; MoS 160
- At 6 months 1,8 times higher; MoS 180
- Infants 2,3 times over; Mos infants 230

Part 2A
Exposure to ingredients and Toxicological profile

CPSR: Part A - Cosmetic Product Safety Information - Annex A7

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Estimated daily quantity of cosmetics (g/day)	7.82	Relative Qty in mg/kg bw/day	14.78	Dap/100 retention factor in g	1.00

RHUS GLABRA EXTRACT	90106-33-5		0.020000	0.002957	5000.00	**1690903**	**1690903**	**1690903**	**1690903**	**1690903**	**1690903**
TAMUS COMMUNIS EXTRACT	84961-63-7		0.020000	0.002957	2500.00	**845451**	**845451**	**845451**	**845451**	**845451**	**845451**
BOSWELLIA SERRATA EXTRACT	97952-72-2		0.010000	0.001478	500.00	**338295**	**338295**	**338295**	**338295**	**338295**	**338295**
HYDROLYZED COMARUM PALUSTRE ROOT/STEM EXTRACT			0.005000	0.000739	300.00	**405954**	**405954**	**405954**	**405954**	**405954**	**405954**

* The ingredients with asterisk are restrictive (source COSING Cosmetics Ingredients and Substances).

The possible absence of NO(A)EL is duly justified in Annex B3 of this P.I.F.
With regard to the toxicological data of the substances, see Safety Data Sheets of the previously attached substances.

The values "SED Adults" and "MOS Adults" are calculated taking as reference the average weight of an adult person equal to 60 kg.

The value of the MOS obtained is related for the various ages by means of a coefficient which derives from the ratio between the surface of the skin and the body mass in the various ages. It is higher in children than in adults, below the reference thresholds:
- Adult; MoS 100
- At 10 years, 1.3 times higher; MoS 130
- At 5 years, 1,5 times higher; MoS 150
- At 12 months, 1,6 times higher; MoS 160
- At 6 months 1,8 times higher; MoS 180
- Infants 2,3 times over; Mos infants 230

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

ALLANTOIN (CAS: 97-59-6)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

450 -- - ECHA, European Chemical Agency. Additional information: Annex XI to the REACH Regulation provides for the waiver of additional animal testing in scenarios where adequate data exist, and further animal testing is not scientifically necessary to further the safety argument for the test substance. Given the preponderance of evidence, as well as the availability of a 2-year tumorigenicity study, it is scientifically unnecessary to generate additional mammalian data for Allantoin. - Allantoin is the end product of purine metabolism in most mammals, excluding humans and some non-human primates;
- Humans lack the enzyme necessary to convert uric acid to Allantoin, where most test species have this enzyme;
- Allantoin is endogenous in standard test species and thus chronic exposure is not of relevance;
- Allantoin is endogenous in humans as well;
- Normal endogenous levels of Allantoin in humans and standard test species are highly variable;
- QSAR using the OECD Toolbox Category Approach demonstrates a lack of repeated-dose toxicity for Allantoin;
- Hazard classification of Allantoin on the basis of chronic exposure is not warranted;
- Occupational exposure to Allantoin is not anticipated;
- Consumer exposure to Allantoin is limited to cosmetic and pharmaceutical use and is regulated accordingly.

Thus, the relevance of in vivo studies in non-humans is limited and further mammalian testing with Allantoin is scientifically unnecessary. The following LOELs were predicted for Allantoin: 989 mg/kg/day read-across value for rat and mouse; 1743 mg/kg/day trend analysis for rat; 1000 mg/kg/day read-across for rat.
Data and QSAR predictions (for molecules in the domain) indicate that repeated dose toxicity tests showed no effects for most endpoints at the highest dose tests (>450 mg/kg/day). The lowest reported effect concentration was 50 mg/kg/day (CAS 96 -31 -1).

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 (oral) rat 5 000 mg/kg bw
Additional information: In a reliable acute oral toxicity study, no mortality was recorded during the duration of the study. The LD50 was determined to be >5,000 mg/kg bw. No symptoms were noted during the observation period and no significant, treatment-related body weight changes were observed during the duration of the study. No abnormalities were detected upon gross examination of the principal organs of animals euthanized at the end of study.
In a study reported in the European Agency for the Evaluation of Medicinal Products summary report on Allantoin, the dermal LD50 in rats is more than or equal to 5,000 mg/kg bw.
No data are available via the inhalation route of exposure.

SKIN IRRITATION AND CORROSIVITY

not irritating
Additional information:
The primary skin irritation potential of Allantoin was investigated according to OECD test guideline no. 404. The test item was applied by topical semi-occlusive application of 0.5 g to the intact left flank of each of three young adult New Zealand White rabbits. The duration of treatment was four hours. The scoring of skin reactions was performed 1, 24, 48 and 72 hours after removal of the dressing. Each animal was assessed for erythema/eschar grades and for oedema grades, separately.
The test item did not elicit any skin reactions at the application site of any animal at any of the observation times (all scores 0). The test item caused no staining of the treated skin. No corrosive effects were noted on the treated skin of any animal at any of the measuring intervals and no clinical signs were observed. Thus, the test item did not induce significant or irreversible damage to the skin.
Based upon the referred classification data (Commission Directive 2001/59/EC of August 2001), Allantoin is considered to be "not irritating" to rabbit skin.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritating
Additional information:
A single dose of 100 mg of the test substance in its original form was placed into the conjuntival sac of the left eye of 6 male New Zealand White rabbits. The eyes were not rinsed after introduction of the test substance. The ocular reactions were observed one hour after the introduction and on day 2, 3, 4, 5 and 8.
No ocular reactions were observed after an introduction of 100 mg of test substance in 6 rabbits, at any of the time points.
The maximum irritation index was 0.
According to the scale of the EEC Directive 83/467/EEC, Allantoin was considered as non-irritant by the ocular route in the rabbit.

SKIN SENSITISATION

not sensitizer
Additional information:
Migrated from Short description of key information:
No sensitization was observed in a reliable local lymph node assay (LLNA) on Allantoin.
Justification for selection of skin sensitisation endpoint:
Study was conducted under GLP according to OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay).

DERMAL/PERCUTANEOUS ABSORPTION

Absorption rate - dermal (%): 16
6 hour exposure, the diffusion rate ranged from 6.9% to 20%

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
Well documented study by a reputable U.S. Government laboratory following a protocol equivalent/similar to OECD guidelines.
Allantoin was found to be non-mutagenic in the Ames Assay in the S. typhimurium TA1535, TA1538, TA98, TA100 bacterial strains.
In addition, male and female rats were fed 0.2% Allantoin in feed over a period of 2 years [approximate total doses of Allantoin throughout the whole exposure were 40 g/rat (male) and 28 g/rat (female)]. After 2 years, carcinogenic effects of the test animals were compared to those of control animals. Allantoin did not induce a significant increase in tumor incidences in the test animals and is therefore considered to be non-carcinogenic.

CARCINOGENICITY

not carcinogenic
Additional information:
Based on the weight of evidence, Allantoin does not meet the criteria for classification as a carcinogen according to EU Directive 67/548/EEC and Regulation 1272/2008.

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
Annex XI to the REACH Regulation provides for the waiver of additional animal testing in scenarios where adequate data exist, and further animal testing is not scientifically necessary to further the safety argument for the test substance. Given the preponderance of evidence, as well as the availability of a 2-year tumorigenicity study, it is scientifically unnecessary to generate additional mammalian data for Allantoin. - Allantoin is the end product of purine metabolism in most mammals, excluding humans and some non-human primates;
- Humans lack the enzyme necessary to convert uric acid to Allantoin, where most test species have this enzyme;
- Allantoin is endogenous in standard test species and thus chronic exposure is not of relevance;
- Allantoin is endogenous in humans as well;
- Normal endogenous levels of Allantoin in humans and standard test species are highly variable;
- QSAR using the OECD Toolbox Category Approach demonstrates a lack of repeated-dose toxicity for Allantoin;
- Hazard classification of Allantoin on the basis of chronic exposure is not warranted;
- Occupational exposure to Allantoin is not anticipated;
- Consumer exposure to Allantoin is limited to cosmetic and pharmaceutical use and is regulated accordingly.
Thus, the relevance of in vivo studies in non-humans is limited and further mammalian testing with Allantoin is scientifically unnecessary.

TOXICOKINETIC (ADME studies)

no bioaccumulation potential
Allantoin, (2,5-Dioxo-4-imidazolidinyl) urea or 5-Ureidohydantoin, is a colorless crystalline powder that is soluble in water at approximately 0.6%. It is endogenous in many mammals and some plants. In most mammals, it is the product of uric acid oxidation by purine catabolism. Potential exposure routes include dermal, oral, inhalation and intravenous, with dermal and oral predominating. Toxicokinetics of Allantoin are reasonably well studied..

Absorption

Absorption of Allantoin is route and vehicle dependent. Dermal absorption was as much as 16%, other routes resulted in absorption in range of 0.2% to 1.5% of the administered dose. No irritation or corrosivity was observed in the dermis of exposed test animals using a standard protocol.

Dermal

In a study of limited reliability due to the small number of human test subjects (n=6), Allantoin (1%) doses were prepared in both hydrophilic gel and oil/water emulsion vehicles. The doses (0.5 g) also contained 5000 I.U. heparin, 1% onion bulb extract, 20% azulan and 5% ethanolic extract of Anthodium chamomillae. The excess dose was quantitatively removed from the test subject's skin after 5 min. Allantoin absorption from the hydrophilic gel vehicle was 5% after 3 hr., and 6.9% after 6 hr. Similarly, absorption was 13% at 3 hr. and 15.4% at 6 hr. for the oil/water emulsion. No evidence of skin irritation or corrosion was reported.

Oral

In a study of limited reliability due to minimal reporting of methodology information and limited number of test subjects (n=1 per dose level), canines were dosed orally with Allantoin in capsules and in solution at 386 mg, 392 mg, 436 mg, 500 mg, 517 mg, 571 mg, 1440 mg and 1500 mg. Absorption was determined by measurement of blood levels of Allantoin, which were uniformly in the range of 1.2 mg to 2.0 mg.

Intravenous

In a study of limited reliability due to minimal reporting of methodology information and limited number of test subjects (n=1 per dose level), canines were dosed intravenously with a 0.6% solution of Allantoin for a delivered dose of 600 mg. Absorption was determined by measuring blood levels of Allantoin after 10 min., 50 min., 30 min., 70 min., 110 min., 2.5 hr., 3 hr., 3.5 hr., 4 hr. and 5 hr. Absorption reached a maximum of 9.5 mg 10 min. after administration of dose, then fell to 2.5 mg at 50 min followed by gradual decrease to baseline after 5 hr.

Inhalation

No inhalation absorption data are available.

Distribution

Because Allantoin is rapidly absorbed and excreted, distribution in tissues and fluids other than blood and urine has not been extensively studied. Allantoin distribution in blood and urine is discussed more fully in the context of absorption and excretion. However, distribution has been evaluated in the rumen of sheep and in the fetus of pregnant rhesus monkeys, further supporting the rapid absorption and excretion of Allantoin.

A reliable study (score 2) investigated the distribution of Allantoin in sheep. Test animals were dosed with 28 µCi of 4,5-14C labeled Allantoin and 15 mg unlabelled Allantoin in 10 mL isotonic saline via jugular cannula. Approximately 80% of the 14C Allantoin was recovered in the urine during the 12 hr. immediately post injection. This rose to 94% after 4 days. 14C Allantoin passed through the blood bicarbonate pool, suggesting that Allantoin is degraded in the gastrointestinal tract. A small amount of 14C Allantoin (4 % of the net

flux of allantoin through the blood pool) was apparently degraded to form bicarbonate-C in the rumen and postruminally as determined by examination of rumen contents sampled via cannula.

A study of indeterminant reliability tested the transfer of Allantoin from fetus to dam in rhesus monkeys. The fetus was surgically catheterized (femoral artery and vein) in utero, and the maternal aorta and vena cava were similarly catheterized. 14C Allantoin was infused into the fetal femoral artery. Testing of blood from the fetus and dam indicated little exchange of 14C.

Metabolism

Extensive literature reports that exogenous Allantoin is rapidly absorbed and excreted. Most mammals process purines to Allantoin yielding stable endogenous levels of Allantoin in both blood and urine. Purine catabolism yields hypoxanthine, which is converted to uric acid then xanthine by xanthine oxidase. Uric acid is converted to Allantoin by urate oxidase, followed by Allantoin excretion. Humans and some non-human primates do not possess urate oxidase, so in those species, uric acid is excreted directly.

Excretion

Allantoin, whether from exogenous dosing, or from endogenous sources related to the purine metabolic cascade, is rapidly and completely excreted. Extensive literature supports this conclusion, including several studies reported herein. In general, excretion of orally dosed Allantoin is species dependent, approximately 30% of the absorbed dose in rats and humans and 75% of the absorbed dose in canines. Excretion of intravenously or subcutaneously dosed Allantoin approaches quantitative levels regardless of species.

In a study of limited reliability due to the small number of human test subjects (n= 2 to 4), aqueous solutions of Allantoin were administered orally to the test subjects in two dosing schemes: (1) a single dose of 1000 ppm, and (2) four doses of 1500 mg at 2 hr. intervals. Similarly, test subjects were dosed intravenously at 50 mg, 75 mg, 100 mg and 240 mg in a Ringer's solution vehicle, and subcutaneously at 50 mg, also in a Ringer's solution vehicle. Absorbed dose recoveries were 19% - 34% for the oral route, 72% - 98% for the intravenous route, and 73% - 81% for the subcutaneous route.

In a study of limited reliability due to minimal reporting of methodology information and limited number of test subjects (n=1 per dose level), canines were dosed orally with Allantoin in capsules and in solution at 386 mg, 392 mg, 436 mg, 500 mg, 517 mg, 571 mg, 1440 mg and 1500 mg. Urinary recovery was in the 67% - 80% (absorbed dose) range. In a similar study, canines were dosed intravenously with a 0.6% solution of Allantoin for a delivered dose of 600 mg. Urinary recovery amounted to 98% of the absorbed dose. Another study involving intravenous dosing of canines with Allantoin (200 mg delivered) yielded similar results (88% - 92% recovery).

In a study of limited reliability due to minimal reporting of methodology information, rats (n=20) were dosed by gavage at an unreported dose level. Remarkable, however, is the fact that reported recoveries of absorbed dose (29% - 39%) were similar to those seen in human test subjects (19% - 34%).

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

BIBLIOGRAPHY

- Safety data sheets
-
-TOXNET database on toxicology

- ECHA database on REACH registered substances
- CIR Cosmetic Ingredients Review

ALOE BARBADENSIS EXTRACT (CAS: 85507-69-3 / 94349-62-9)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

11800 -- - EMA, https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-aloe-barbadensis-mill-and aloe-various-species-mainly-aloe-ferox-mill-and-its-hybrids-folii-succus-siccatus_en.pdf

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (mouse) 500 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

not classified as irritant / corrosive

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not classified as irritant / corrosive

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information: Morimoto et al. (1982) reported the results of the Ames test and the rec-assay for aloe crude extracts. The investigators found neither water nor methanol extracts (no further information available) of aloe to have mutagenic activity in Salmonella typhimurium strains TA98 or TA100. A water extract of aloe was reported to produce a positive effect in the rec assay using Bacillus subtilis. Marquardt et al. (1987) (cited in the unpublished report of Brusick (1994)) conducted a more thorough evaluation of aloe-extract in the Ames test. A wide range of mutant strains (TA97, TA98, TA100, TA102, TA1535, TA1537, and TA1538) was included, and “faecalase” (gut flora enzymes) was employed in order to breakdown any potentially active glycosides. The results of this investigation were negative with the maximum test concentration set at 3,000 µg/plate. Barbaloin was also reported negative in this study. In 1992 Cytotest Cell Research GmbH & Co. conducted a series of genetic tests using a batch of commercial aloe-extract (also cited in the unpublished report of Brusick, 1994). The Ames test (employing TA1535, TA1537, TA1538, TA98, and TA100) only produced a mutagenic effect in strain TA1537 at 5,000 µg/plate without and with S9 mix but not at the next lower concentration of 1,000 µg/plate. A mammalian cell assay for gene mutation conducted in V79 cells showed no evidence of mutagenicity with aloe extract in concentrations up to 1,000 µg/ml without S9 mix and up to 5,000 µg/ml with S9 mix. Aloe-extract was shown to be clastogenic in CHO cells. In the absence of S9 mix, aloe-extract induce significant increases in chromosome breakage at concentration of 3,000 µg/ml (30-hour harvest) and 4,000 µg/ml (24-hour harvest). No clastogenicity was observed with S9 mix at concentrations up to 4,750 µg/ml. However, an in vivo test for clastogenicity with aloe-extract (Bootman et al. 1987a, cited in the unpublished report of Brusick, 1994) produced no evidence of a response in the mouse micronucleus test at a maximum applicable dose of 1.5 mg/kg (orally)

CARCINOGENICITY

not carcirogenic
Additional information: A 2 years carcinogenicity study of Aloe, Aloe arborescens Miller var. natalensis Berger, a food additive was conducted for assessment of toxicity and carcinogenic potential in the diet at doses of 4% or 0.8% in groups of male and female Wistar Hannover rats. The whole leaf powder of Aloe arborescens, the same grade used as a food additive was mixed at concentrations of 0.0% (Control), 0.8%, and 4.0% into powdered basal diet and pelleted. The concentrations of aloenin and aloin (barbaloin and isobarbaloin) in the whole leaf powder of Aloe arborescens and the pelleted diet were measured and evaluated using high performance liquid chromatography. The concentrations of aloin and aloenin in the whole leaf powder after storage for 2 weeks were 0.83% and 1.91%, respectively. The concentrations of aloin and aloenin in the pelleted diet after 2 weeks of storage at room temperature were 0.0009% and 0.0022% for the 0.8% diet and 0.0179% and 0.0663% for the 4.0% diet. Both sexes receiving 4% showed diarrhoea, with loss of body weight gain. The survival rate in the 4% female group was significantly increased compared with control females after 2 years. Haematological and biochemical examination showed increase of RBC, Hb, and Alb in the 4% males. The cause of these increases could conceivably have been dehydration through diarrhoea. AST and Na were significantly decreased in the males receiving 4%, and Cl was significantly decreased in both 4% and 0.8% males. A/G was significantly increased in the 4% females, and Cl was significantly decreased (0.8%) in the female group. Histopathologically, both sexes receiving 4% showed severe sinus dilatation of ileocecal lymph nodes, and yellowish pigmentation of ileocecal lymph nodes and renal tubules. Adenomas or adenocarcinomas in the cecum, colon, and rectum were observed in 4% males but not in the 0.8% and control male groups. Similarly, in females, adenomas in the colon were also

observed in the 4% but not 0.8% and control groups. In conclusion, Aloe, used as a food additive, exerted equivocal carcinogenic potential at 4% high-dose level on colon in the 2 years carcinogenicity study in rats. The authors concluded that aloe is not carcinogenic at nontoxic-dose levels and that carcinogenic potential in at 4% high-dose level on colon is probably due to irritation of the intestinal tract by diarrhoea (Yokohira et al., 2009). The National Center for Toxicological Research (NCTR) conducted 14-day, 13-week, and 2 years carcinogenesis studies on the leaf extracts of Aloe vera plants. The Aloe vera plant extracts used in these studies were obtained from freshly harvested Aloe barbadensis Miller plants and were freeze dried (6% moisture) and gamma-irradiated to preserve quality. No other additives were used in their preparation. Solutions of non-decolorized extracts of Aloe vera leaves (DER and HAD content unknown) were added to the drinking water to groups of rats and mice for 2 years. Groups of 48 rats received solutions containing 0.5% (= 0.62 g Aloe vera whole-leaf extract per kg bw per day, 1% or 1.5% of Aloe vera extract in the drinking water, and groups of mice received solutions containing 1%, 2%, or 3% = 11.8 g Aloe leaf extract/kg bw/day of whole leaf Aloe vera extract. Similar groups of animals were given plain drinking water and served as the control groups. At the end of the study tissues from more than 40 sites were examined for every animal. In all groups of rats and mice receiving the Aloe vera extract, the rates of hyperplasia in the large intestine were markedly increased compared to the control animals. There were also increases in hyperplasia in the small intestine in rats receiving the Aloe vera extract, increases in hyperplasia of the stomach in male and female rats and female mice receiving the Aloe vera extract, and increases in hyperplasia of the mesenteric lymph nodes in male and female rats and male mice receiving the Aloe vera extract. In addition, cancers of the large intestine occurred in male and female rats given the Aloe vera extract, though none had been seen in the control groups of rats for this and other studies at this laboratory. The authors concluded that nondecolorized Aloe vera caused cancers of the large intestine in male and female rats and also caused hyperplasia of the large intestine, small intestine, stomach, and lymph nodes in male and female rats. Aloe vera extract also caused hyperplasia of the large intestine in male and female mice and hyperplasia of the mesenteric lymph node in male mice and hyperplasia of the stomach in female mice (Boudreau et al., 2013). The effects of long-term Aloe vera ingestion on age-related diseases were investigated using male specific pathogen-free (SPF) Fischer 344 rats. Experimental animals were divided into four groups: Group A, the control rats fed a semi-synthetic diet without Aloe vera; Group B, rats fed a diet containing 1% freeze-dried Aloe vera blended filet; Group C, rats fed a diet containing 1% charcoal processed, freeze-dried Aloe vera filet; and Group D, rats fed the control diet and given whole leaf charcoal-processed Aloe vera (0.02%) in the drinking water. This study demonstrates that life-long Aloe vera ingestion produced neither harmful effects nor deleterious changes. In addition, Aloe vera ingestion appeared to be associated with some beneficial effects on age-related diseases. Groups B exhibited significantly less occurrence of multiple causes of death, and a slightly lower incidence of fatal chronic nephropathy compared with Group A rats. Groups B and C rats showed the trend, slightly lower incidences of thrombosis in the cardiac atrium than Group A rats. Therefore, these findings suggest that life-long Aloe vera ingestion does not cause any obvious harmful and deleterious side effects (Ikeno et al., 2002).

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information: No teratogenic or foetotoxic effects were seen in rats after oral treatment with aloe extract (up to 1000 mg/kg) or aloin A (up to 200 mg/kg) (WHO, 1999). The pregnant rats were treated between the 10th and 13th day of the gestational period. A caesarean section was done on the 21st day post conception.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

TOXICOKINETIC (ADME studies)

not bioaccumulative
Additional information: data on the man

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

The ESCOP monograph mentioned an unpublished research report of a human pharmacokinetic study in 6 healthy volunteers (ref. 39 in 3). After oral administration of aloes (equivalent to 16.4 mg of hydroxyanthracene derivates) for 7 days, aloe-emodin was detected as a metabolite in the plasma only sporadically and with maximum concentrations of less than 2 ng/ml. In the same study rhein was detected in the plasma in concentrations ranging from 6-28 ng/ml after single dose administration. In 7-day administration there was no evidence of accumulation of rhein.In the pharmakokinetic study by Krumbiegel and Schulz (1993) therapeutic doses of two laxatives (Agiolax and Sennatin) were repeatedly administered to 10 healthy volunteers (18-32 years, male) in a two-way change-over design.4 single doses of Agiolax (6.3 g granulate containing 13,23 mg total anthronoids, including 7,62 mg potential rhein and 0,378 mg aloe-emodin) or Sennatin (2 tablets containing 20,36 mg total anthronoids including 13,06 mg potential rhein 0,4 mg potential aloe emodin) were given to the volunteers at 24 h intervals. Blood samples were collected up to 96 h after the first dose, and plasma levels of total aloe-emodin and rhein were determined simultaneously with a sensitive (lower limit of quantification: 0.5 ng aloe-emodin and 2.5 ng rhein per millilitre plasma) and specific fluorometric HPLC method. Aloe-emodin was not detectable in any plasma sample of any subject. Rhein concentration time courses showed highest levels of 150-160 ng/ml and peak maximaat 3-5 h and 10-11 h after dosing probably according to absorption of free rhein and rhein released from prodrugs (e.g. sennosides) by bacterial metabolism, respectively. The absorbed rhein anthrone is glucuronidised in the liver. One part of the glucuronides is excreted via the urine and cause the yellow or red-brown discolouration of the urine. The other part is excreted via the bile (Lemli et al. 1980; Stolk and Hoogtanders 1999)

BIBLIOGRAPHY

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- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EMA, European Medical Agency

ASPHALTUM EXTRACT (CAS:)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

33,3 -- - https://www.webmd.com/vitamins/ai/ingredientmono-1697/shilajit
Additional information:
When taken by mouth: Processed shilajit is possibly safe when used in doses of 2 grams daily for 45 days or up to 500 mg daily for up to 48 weeks. It seems to be well-tolerated. But there isn''t enough reliable information to know if crude or unprocessed shilajit is safe or what the side effects might be.
When applied to the skin: There isn''t enough reliable information to know if shilajit is safe or what the side effects might be.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

no data

SKIN IRRITATION AND CORROSIVITY

no data

MUCOSAE IRRITATION AND CORROSION (eye irritation)

no data

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

no data

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- WEBMD https://www.webmd.com/

BENZYL NICOTINATE (CAS: 94-44-0)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

20 -- - NIH, https://drugs.ncats.io/drug/S497LCF9C9

POD:In Vivo Use Guide
Patients not currently on NIASPAN must start ADVICOR at the lowest initial ADVICOR dose, a single 500 mg/20 mg tablet once daily at bedtime. The dose of ADVICOR should not be increased by more than 500 mg daily (based on the NIASPAN component) every 4 weeks. The dose of ADVICOR should be individualized based on targeted goals for cholesterol and triglycerides, and on patient response. Doses of ADVICOR greater than 2000 mg/40 mg daily are not recommended.
Route of Administration: Oral
In Vitro Use Guide
HepG2 cells were preincubated for 48 hours with varying concentrations of niacin (0 to 3.0 mmol/L) in DMEM containing 10% FBS media. Incubation of HepG2 cells with niacin significantly inhibited (by 12% to 15%) fatty acid esterification to produce TG as assessed by the incorporation of 3H-oleic acid into TG. 14C-acetate incorporation into cholesterol and phospholipids was unchanged. The activity of microsomal triglyceride transfer protein MTP), a carrier protein for lipids, was not altered by pretreatment of cells with niacin.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (mouse) 2188 mg/kg

SKIN IRRITATION AND CORROSIVITY

Causes skin irritation

MUCOSAE IRRITATION AND CORROSION (eye irritation)

Causes serious eye irritation

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

no data

MUTAGENESIS / GENOTOXICITY

no data

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

not bioaccumulative according: Log Pow 2.4

DATA ON MAN

no data

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EMA, European medical agency
- NIH, National Institute of Health

BETA-CARYOPHYLLENE (CAS: 87-44-5)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

222 -- - EFSA, https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2015.4069

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (mouse) ≥ 5,000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

not irritant for skin
Additional information:
The mean relative absorbance value of the test item, corresponding to the cell viability did not decrease (105.9%; threshold for irritancy: ≤ 50%), consequently the test item was not irritant to skin.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

The mean values for corneal opacity, iris lesions, redness of conjunctivae and oedema of conjunctivae (chemosis) were 0.0, 0.0, 1.2 and 0.8, respectively. All weak signs of irritation were reversible and 7 days after application of the test article all four animals were free of any signs of eye irritation. The test item should not be classified as irritating to the eye, according to the directive of the EEC commission 93/21/EEC and GHS/EU CLP criteria.

SKIN SENSITISATION

sensitising
Additional information:
A modified Freund's Complete Adjuvant Test (FCAT) sensitisation experiment was performed in female Dunkin-Hartley albino guinea pigs. Animals were induced on days 0, 6 and 10 with intradermal injections (0.1 mL) of β-Caryophyllene (6.8% w/w, Group A) or Caryophyllene oxide (7.3% w/w, Group B), or the vehicle control (FCA/water (1:1) emulsion). Challenge tests were performed on day 21, in which test material was administered to shaved flanks for 24 hours and reactions were assessed at 48 and 72 hours. Whilst challenge with caryophyllene oxide demonstrated dose-dependent sensitisation, β-Caryophyllene did not induce positive reactions in exposed animals, and is not considered to be a contact allergen. The study design was similar to the OECD 406 Guideline, used sufficient numbers of animals and was considered to be reliable with restriction (Klimisch 2).
A supporting LLNA was also conducted in mice using caryophyllene oxide or a mixture of hydroperoxides derived from photooxidation of beta-caryophyllene. The mice received 25 ul of the test material dissolved in acetone:olive oil (AOO) 4:1, on the dorsum of both ears for three consecutive days. Oxidized beta-caryophyllene (air exposed for 10 weeks) was tested in concentrations 30%, 10%, and 3% (w/v) (1.36, 0.45, and 0.14 M, calculated from the molecular weight of caryophyllene oxide) and the caryophyllene hydroperoxides (obtained from photooxidation with Bengal rose) in concentrations 15%, 5%, and 0.5% (0.63, 0.21, and 0.02 M). Five days after the initial treatment, all mice were injected intravenously through the tail vein with 20 uCi of [methyl-3H]thymidine (2.0 Ci/mmol, Amersham Biosciences, UK) in 250 ul phosphate-buffered saline (PBS). After 5 h the mice were sacrificed, the draining lymph nodes were excised and pooled for each group, and single cell suspensions of lymph node cells were prepared and examined for thymidine incorporation measured by beta-scintillation counting. Whilst challenge with caryophyllene oxide demonstrated a relatively weak sensitisation reaction in mice treated at a concentration of 30% caryophyllene oxide, the photooxidised hydroperoxide products from beta-caryophyllene induced a strong concentration-dependent sensitisation reaction in this assay. Caryophyllene has two isolated double bonds that are capable of reacting with dioxygen in triplet state (triplet oxygen) or singlet state (singlet oxygen). A reaction of caryophyllene with triplet oxygen yielding to autoxidation products requires the presence of light and air and the absence of anti-oxidants. A reaction of caryophyllene with singlet oxygen is a [2+2]-cycloaddition and requires the excitation of triplet oxygen. This excitation can be achieved by UV irradiation of a diluted, cooled solution of caryophyllene in a suitable solvent (e.g. chloroform) containing a sensitiser (e.g. Bengal rose). The solvent must be transparent to the UV radiation and must not quench the excited state of neither the sensitiser nor the singlet oxygen. Water does not have the necessary properties and aqueous preparations of caryohpyllene will not produce oxidation products from a reaction with singlet oxygen. For that reason, the EC3 value of 26.2% is considered to be the relevant value for β-caryophyllene. The study design was similar to the OECD 429 Guideline, used sufficient numbers of animals and was considered to be reliable with restriction (Klimisch 2).

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not genotoxic / mutagenic
Additional information:
In support of the in vitro data, no genotoxicity was observed in two in vivo genotoxicity studies (2009; 2014). The effects of β-caryophyllene on the number of sister chromatid exchanges (SCE) and the number of chromosome aberrations was determined in two separate experiments in male mice (2014). In the first experiment, Male Swiss-Webster mice (6 per group) were orally administered β-Caryophyllene (20, 200 and 2000 mg/kg) or the vehicle control (10% w/v corn oil). Positive control mice received Benzo-a-pyrene (200 mg BaP/kg). In a second experiment, mice orally administered β-Caryophyllene (20, 200 and 2000 mg/kg) were intraperitoneally injected with 200 mg/kg of BaP 30 minutes later. Mice were sacrificed 25 hours after administration and bone marrow was analysed by chromatid differential staining. No genotoxic effects were observed up to 2000 mg/kg β-Caryophyllene, as the number of SCE were not statistically significantly different between the control (mean 3.8 SCE) and test item concentrations (mean 4.1 SCE). No statistically significant differences were observed for the average generation time, numbers/types of chromosome aberrations or mitotic index between the test item treatments and the control. Furthermore, treatment with β-Caryophyllene ameliorated the genotoxicity of BaP at the high dose, suggesting the substance may be geno-protective. In addition, no genotoxicity or bone marrow cytotoxicity were observed up to 2000 mg/kg β-Caryophyllene in a mouse erythrocyte micronucleus assay (2009). The studies were considered reliable with restriction (Klimisch 2) and sufficient to fulfil the REACH information requirement. The in vivo data further support the conclusion that β-Caryophyllene is not genotoxic.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Sensitisation data (human)
Consecutive dermatitis patients (n = 1511) in 6 European dermatology centres were patch tested with 3.0% oxidation mixture of caryophyllene (containing 25% β-caryophyllene and 35% caryophyllene oxide) or 3.9% caryophyllene oxide in non-stabilised white petrolatum (2005). About 0.5% of the patients reacted to oxidized caryophyllene and 0.1% of patients reacted to caryophyllene oxide. Caryophyllene oxide gave positive reactions in only 2 out of 8 patients also reacting to the mixture of oxidized caryophyllene. This study is reliable with restrictions (Klimisch 2) as it is a large clinical study reported in a peer-reviewed journal and meets generally accepted scientific principles.

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EFSA, European Food Safety Agency

BISABOLOL (CAS: 515-69-5 / 23089-26-1)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

200 -- - ECHA, https://www.cir-safety.org/sites/default/files/bisabolol.pdf

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) 15,6 ml/kg

SKIN IRRITATION AND CORROSIVITY

irritant
Additional information:
Several studies looked at the effect of base creams containing up to 0.5% (−)-α-bisabolol on induced skin irritation in guinea pigs and human subjects. The bisabolol creams did not have an anti-irritant effect on the induced irritation. In one guinea pig study, the bisabolol cream appeared to worsen the induced cumulative irritation.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritant
Additional information:
Overall, based on the available data, racemic (+/-)-αlpha-Bisabolol is considered to be not irritating to eyes.

SKIN SENSITISATION

sensitizer
Additional informaton:
LLNA (acc. OECD 429, GLP): skin sensitizer (Symrise 2010; C97160)

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
α-Bisabolol in ethanol was not mutagenic, with or without metabolic activation, towards Salmonella typhimurium strains TA97, TA98, TA100, and TA1535 at concentrations up to 100 µg/plate, 7 or towards strains TA98 or TA100 at concentrations of 0-222 µg/plate. 8 Bisabolol was cytotoxic in strain TA100 when tested without metabolic activation. Bisabolol, at concentrations of 0.56-2.24 mM, was not genotoxic in the Drosophila wing spot assay (SMART)

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
In two developmental toxicity studies with (-)alpha-Bisabolol in rats and rabbits, the lowest toxic oral dose for both fetuses and dams was concluded to be between 1.0 and 3.0 mL/kg body weight. Accordingly, the observed NOAEL is set at 1.0 mL/kg bw/d (930 mg/kg bw/d). Adverse effects on prenatal development were only observed in rats and rabbits at doses that are also toxic to the dams and are well above the limit dose of 1000 mg/kg bw/d according to current standard test guidelines. Therefore, these findings are considered to be secondary to maternal stress. Furthermore, no teratogenic potential was observed at all dose groups tested. Therefore, under the given testing conditions, no impairment of the prenatal development by Bisabolol became evident.

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Case Reports
Seven pediatric patients had a history of intolerance to a moisturizer that contained bisabolol; six of the patients had atopic dermatitis. The patients were patch tested with 0.5 and 1% bisabolol (three patients) or 1 and 5% bisabolol in petrolatum, as well as with other moisturizer components. Four of the patients had positive reactions to up to 1% bisabolol (1/3 patients) or up to 5% bisabolol (3/4 patients); these subjects also had positive reactions to a sesquiterpene lactone mix and/or a Compositae mix. However, an additional 16 subjects (12 with atopic dermatitis) with intolerance to the same moisturizer did not react to patch testing with up to 5% bisabolol. A subject presented with dry, desquamative cheilitis of both lips, and a repeated open application test (ROAT) with the subject's lipstick resulted in an eczematous reaction. Subsequent patch testing with the lipstick and its components, including 5% bisabolol, produced a positive reaction to bisabolol and the formulation. Patch testing of 10 controls subjects with the same material had negative results.
The test material (10%; 5600 µg/cm2 (estimated)) did not indicate a potential for dermal irritation or allergic contact sensitization.

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

BOSWELLIA SERRATA EXTRACT (CAS: 97952-72-2)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

500 -- - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC3532773/#:~:text=As%20there%20was%20a%20decrease,and%20500%20mg%2Fkg%20B.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 2 000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

not classified as irritant
Additional information:
An in vitro skin irritation test using the Reconstructed Human Epidermis (SkinEthic RHE® model) was performed according to the OECD Guideline 439 and in compliance with GLP to predict the acute skin irritation potential of the test substance.
The test item was applied during 42 minutes, at the dose of 16 mg, to 3 living Reconstructed Human epidermis (SkinEthic RHE® model) previously moistened with 10 µL of distilled water. The treatment of the epidermis was followed by a rinse with 25 mL of DPBS and a 42 hours post-incubation period at 37°C, 5% CO2. Cell viability was then measured by enzymatic conversion of the vital dye MTT into a blue formazan salt that was quantitatively measured after extraction from tissues. Additionally, 2 living Human skin model surfaces were treated in the same manner but they were incubated in culture medium instead of MTT solution in order to generate nonspecific living colour controls.
The mean corrected percent viability of the treated tissues was 95.9%, versus 1.3% in the positive control (5% Sodium Dodecyl Sulfate). The mean percent tissue viabilities obtained with the positive control and negative controls were within the range of historical data and therefore validated the experiment.
Under the test conditions and in accordance with Regulation EC No. 1272/2008, the test item was considered as non-irritant to skin. It corresponds to UN GHS No Category. No hazard statement or signal word is required.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not classified as eye irritant
Additional information:
An ex vivo eye irritation study was performed according to the OECD Guideline 437 and in compliance with GLP to evaluate the possible ocular corrosive or severe irritating effects of the test item after administration on bovine corneas.
The test item was evaluated in two experiments. In both experiments, corneas obtained from freshly slaughtered calves were mounted in corneal holders. Both chambers of the corneal holder were filled with complemented MEM culture media (cMEM) and pre-incubated for 1 hour and 5 minutes (± 5 minutes) at +32°C. Three corneas for each treated series (test item formulation, positive control and vehicle control) were used.
Before treatments, a first opacity measurement was performed on each cornea using an opacitometer.
The test item, formulated at 20% in paraffin oil, was evaluated in these two experiments using a treatment time of 4 hours and using the open-chamber method. Vehicle and positive controls were applied using the same treatment time and the closed-chamber treatment method. At the completion of the treatment period, all items were removed from the front opening of the anterior chamber and the epithelia were rinsed.
A second opacity measurement was then performed.
After the second opacity measurement, the medium of the anterior chamber was removed and filled with a fluorescein solution. The holders were then incubated vertically for 90 minutes (± 5 minutes) at +32°C. At the end of the incubation period, the Optical Density of the solution from the posterior chamber of each holder was measured in order to determine the permeability of the cornea. Each cornea was then observed for opaque spots and other irregularities.
With one exception during the second experiment (mean OD490 nm of the vehicle control), all acceptance criteria were fulfilled during both experiments. The study was therefore considered as valid.
In first experiment, fluorescein fixation and/or residual amount of test item were observed on two of the three test item-treated corneas. No notable opaque spots or irregularities were observed on the remaining cornea. The mean In Vitro Irritancy Score (IVIS) of the test item-treated corneas was: 4.
Individual IVIS values of test item-treated corneas were: 1, 1 and 11. Two of the three corneas gave discordant predictions from the mean of all three corneas since the third corneas gave a higher IVIS principally due to the opacity value. As residual test item was noted over these corneas after the rinsing step, it was therefore not possible to determine if the high corneal opacity value noted for these corneas was due to the test item reacting with cell structures (i.e. protein precipitation, etc.) or only to these residuals amounts of test item which stuck to the cornea. Moreover, during this assay, results could be considered as borderline between "no category" and "no prediction can be made" since the mean IVIS was 4. In this context, the result in the first testing experiment was considered borderline and a second experiment was performed.
In the second experiment, fluorescein fixation and residual test item were observed on all the corneas treated with the test item. The mean IVIS of the test item-treated corneas was: 1. Individual IVIS values of test item-treated corneas were: 2, 0 and 1.
On the basis of the two experiments performed as part of this study, five out of the six test item-treated corneas gave a mean IVIS < 3, and the only IVIS > 3 could be related to a high corneal opacity value likely due to representative residual amounts of test item which stuck to the corresponding cornea. Residual amounts of test item were also noted on each test item-treated cornea in the second experiment, but amounts were not graded, and no significant increase in opacity was noted, suggesting only very few amount of test item remained onto these corneas.
As a consequence, based on the concordant results obtained on five out of six corneas during these two experiments, no additional experiment was performed and the test item was considered as a test chemical not requiring classification for eye irritation or serious eye damage (UN GHS No Category).
Under the experimental conditions of this study, the test item, the test item was identified as not requiring classification for eye irritation or serious eye damage (UN GHS No Category).

SKIN SENSITISATION

not sensitising
Additional information:
A maximalisation test was conducted in 25 healthy, male volunteers. Applications of the test material in petrolatum were made under occlusion to the same site on the forearms of all subjects for five alternate-day 48 hour periods. Patch sites were pretreated for 24 hours with 5% aqueous sodium lauryl sulfate (SLS) under occlusion. Following a ten day rest period, challenge patches were applied under occlusion to fresh sites for 48 hours. Challenge applications were preceded by 1-hour applications of 10% aqueous SLS under occlusion. Reactions were read on patch removal and 24 hours after patch removal. No effect was observed.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
In a reverse gene mutation assay in bacteria, performed according to the OECD Guideline 471 and in compliance with GLP, Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100, and Escherichia coli strain WP2uvrA were exposed to the test item at the following concentrations:
- Experiment 1 - Plate Incorporation Method: 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate, with and without S9-mix
- Experiment 2 - Pre-Incubation Method: 15, 50, 150, 500, 1500 and 5000 µg/plate, with and without S9-mix
Rat liver homogenate (10% liver S9 in standard co-factors) was used as a metabolizing system. Vehicle control, negative (untreated) and positive control groups were also included in mutagenicity tests.
The vehicle (dimethyl sulphoxide) control plates gave counts of revertant colonies within the normal range. All of the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies, both with or without metabolic activation. Thus, the sensitivity of the assay and the efficacy of the S9-mix were validated.
No visible reduction in the growth of the bacterial background lawn was noted at any dose level, either in the presence or absence of metabolic activation (S9-mix), in Experiment 1 (plate incorporation method) and in Experiment 2 (pre incubation method).
A test item precipitate (cream-coloured and greasy in appearance) was noted at and above 1500 µg/plate, this observation did not prevent the scoring of revertant colonies.
No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test item, either with or without metabolic activation (S9-mix) in Experiment 1 (plate incorporation method) and Experiment 2 (pre incubation method).
Under the test conditions, the test item is not considered as mutagenic in these bacterial systems.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- NIH, National library of Medicine

CAMPHOR (CAS: 464-49-3 / 76-22-2)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

250 -- - ECHA, European Chemical Agency

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 cut off (oral) rat > 5 000 mg/kg bw
LD50 (dermal) rat > 2 000 mg/kg bw
LC50 (inhalation) rat > 10 000 mg/m³ air
Additional information:
The LD50 of the test item “bornan-2-one” is greater than 2000 mg/kg body weight after single oral administration to Wistar rats.
Based on Annex 2d Test Procedure with a Starting Dose of 2000 mg/kg body weight of OECD Guideline 423 it can be concluded that the test item “bornan-2-one” is according to GHS criteria classified in Category 5 or Unclassified with a LD50 cut off value equal to or greater than 5000 mg/kg body weight, after single oral administration to Wistar rats.

SKIN IRRITATION AND CORROSIVITY

not irritating
Additional information:the log kow of target substance is 3.04, "Primary Irritation Index" is 1.43

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritating
Additional information:
Irritation parameter: maximum mean total score (MMTS) 1.43

SKIN SENSITISATION

not sensitising
In Chemico: Bibliographic source: QSAR toolbox v3.0, year 2012.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
In Vitro data: In conclusion, results from the present study thus suggest that citral, citronellal, (±)-camphor, (-).-menthol and 1,8-cineole are not mutagenic in the Ames test and that terpineol is weakly mutagenic to TA102 tester strain.

In vivo, year 1999: in the micronucleus test, animals are treated with a chemical and then the frequency of micronucleated cells is determined at some specified time after treatment. If a treated group of animals shows significantly higher frequencies of micronucleated cells than do the untreated control animals, then the chemical is considered to be capable of inducing structural and/or numerical chromosomal damage.
After a 24-hour exposure to the camphor, no dose-group of either sex showed a ~ignificant increase in micronucle iscompared to the control.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

NOAEL: 400 mg/kg bw/day, Study duration: subchronic. Species: rabbit

TOXICOKINETIC (ADME studies)

Details on absorption:
The plasma protein binding was determined by ultrafiltration with Zentriflow membranes of Amicon Inc. (Ryan and Hanna 1971; Vohland and Streichert 1978). A correction had to be made for the adsorption of camphor at the membrane. The protein binding was 61±6% at a concentration of 10 µg camphor/ml plasma.
Metabolite characterisation studies
Metabolites identified:
yes
Details on metabolites:
Metabolite Ret. time ((min: sec)) Mass fragments m/e (intensity %)
I 5-hydroxycamphor 5 : 34 M + 168 (48), 153 (29), 135 (6), 125 (48), 111(100), 109 (31)
II 5-ketocamphor 3 : 10 M + 166 (96), 151 (14), 138 (12), 109 (79), 95(48), 69 (100)
III 9-hydroxycamphor 7 : 51 M + 168 (19), 153 (38), 135 (7), 125 (13), 111(28), 109 (31), 108 (100), 107 (53)
IV 8-hydroxycamphor 6 : 50 M + 168 (19), 153 (4), 137 (15), 109 (18), 108(53), 95 (100)
V 3-hydroxycamphor 4 : 55 M + 168 (9), 153 (91), 135 (13), 108 (93), 107(100), 93 (60)
VI 8 or 9-camphor carbonic acidtrimethylsilylester 7 : 17 M + 254 (6), 239 (8), 226 (4), 225 (4), 108 (58), 93(19), 73 (100)
VII Isoborneole 1 : 10 M + 154 (1), 139 (8), 136 (6), 121 (7), 110 (20), 95(100), 93 (11)
Conclusions:
Interpretation of results (migrated information): bioaccumulation potential cannot be judged based on study results

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

- FDA, Food and Drug Administration
- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

CAPSICUM ANNUUM FRUIT EXTRACT (CAS: 84625-29-6)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

2388 -- - - ECHA, https://echa.europa.eu/et/registration-dossier/-/registered-dossier/32097/7/6/1

Additional information: Key study: Test method similar to OECD TG 408. In a 13-week subchronic study, paprika color showed little or no significant toxicity even with 5% supplementation in the diet. Thus, the NOAEL was concluded to be 5% in the diet (0.67 g/rat/day or 2948.4 mg/kg bw/day for male rats and 0.43 g/rat/day or 3197.4 mg/kg bw/day for female rats). Key study: Test method similar to OECD TG 452. In a 52-week chronic study, the NOEL was estimated to be 2.5% in the diet (1253 mg/kg bw/day) and the NOAEL was determined to be 5% in the diet (2388 mg/kg bw/day) for male rats, and for females, the NOEL was concluded to be 5% in the diet (2826 mg/kg bw/day)

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) 11 250 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

H315: Causes skin irritation

MUCOSAE IRRITATION AND CORROSION (eye irritation)

H319: Causes serious eye irritation.

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not classified as mutagenic / genotoxic
Additional information: According to JECFA2009 (1) extracts of chilli peppers of different levels of purity have been tested, with mixed, inconsistent and often contradictory results. The EFSA Panel (2) concluded that the limited information available from the open literature does not allow a reliable assessment of the genotoxicity of paprika extracts. Therefore, upon request of EFSA, two new GLP compliant genotoxicity studies using Paprika extract were performed: an OECD TG 471 mutation assay and a OECD TG 487in vitromicronucleus assay. Respective authors concluded that tested paprika extract did not induce mutation in the OECD test TG 471 mutation assay and did not induce micronuclei in cultured human peripheral blood lymphocytes. The Panel agreed with these conclusions. Based on these results, the EFSA Panel concluded that paprika extracts used as a food colour do not raise a genotoxic concern.

CARCINOGENICITY

not classified for carcinogenicity according to CLP Regulation (EC) no. 1272/2008.
Additional information: Key study: Test method similar to OECD TG 451. In a 104-week carcinogenicity study, paprika color was found not carcinogenic to male or female F344 rats with dietary concentration up to 5% (2052 mg/kg bw/day for males and 2324 mg/kg bw/day for females).

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

not bioaccumulative
Additional information:
Approved for using in FOOD industries

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

- SDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- JECFA, 2009. Safety evaluation of certain food additives and contaminants. WHO Food Additives Series No. 59, 2008. Available online: http://apps.who.int/iris/bitstream/10665/43823/1/9789241660594_eng.pdf
- EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2015. Scientific Opinion on the re evaluation of paprika extract (E 160c) as a food additive. EFSA Journal 2015;13(12):4320, 52 pp. doi:10.2903/j.efsa.2015.4320.

CETEARETH-25 (CAS: 68439-49-6)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

1000 -- - CIR, https://journals.sagepub.com/doi/pdf/10.1177/109158189901800306

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 8000 mg/kg bw
LD50 dermal (rabbit) > 2000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

mild irritant

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

MUCOSAE IRRITATION AND CORROSION (eye irritation)

mild irritant

SKIN SENSITISATION

not sensitizer
Additional information: clinical study in section DATA ON THE MAN

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
Cetyl alcohol (dose not specified) was not mutagenic in Salmonella typhimurium LT2 mutant strains in the spot test (Elder 1988a). Stearyl Alcohol was not mutagenic in the Ames assay, either with or without metabolic activation (Elder 1985). The review on Steareths reported that an unspecified alcohol ethoxylate did not induce chromosomal anomalies in either hamster bone marrow cells (following oral dosing of the hamsters) or in human leukocytes (which had been incubated with the test agent). The test agent was also nonmutagenic in the dominant lethal assay (male mice) (Elder 1988b). PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test; the maximum test concentration in both studies was 1 %. In the unscheduled DNA synthesis assay, a statistically significant increase in radioactive thymidine incorporation into rat hepatocyte nuclei was noted only at the highest concentration tested (0.1 %). PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay when tested at concentrations up to 150 gIL (Andersen 1993).

CARCINOGENICITY

not carcirogenic
Additional information:
Stearly Alcohol did not promote tumor formation in mice when tested with 7,12-dimethybenz{ a]anthracene DMBA (Elder 1985). The review on Steareths reported that a structurally undefined polyoxyethylene alkyl ether was neither a carcinogen nor a tumor promotor in a mouse skin-painting study (Elder 1988b). All of the carcinogenicity data available on the PEGs was specifically on PEG-8, which was used as a solvent control for a number of studies. PEG-8 was not carcinogenic when administered orally to mice (30 weeks of dosing), intraperitoneally to rats (6 months of dosing), subcutaneously (20 weeks of dosingrats; 1 year of dosing-mice), or when injected into the gastric antrum of guinea pigs over a period of 6 months (Andersen 1993).

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
For longer alkyl chains there is evidence of diminishing toxicity, and extrapolation to much longer chains such as expected in the Ceteareth moieties suggested to the CIR Expert Panel that there is no reproductive or developmental hazard posed by these Ceteareth compounds.

TOXICOKINETIC (ADME studies)

Gastrointestinal absorption of PEGs is dependent on the molecular weight of the compound. In general, the more solid the PEG compound, the less absorption that occurs. In both oral and i.v. studies, no metabolism was observed and the PEGs were rapidly eliminated unchanged in the urine and fees. In a study with human burn patients, monomeric ethylene glycol isolated in the serum following topical exposure to a PEG-based antimicrobial cream, indicating that PEGs are readily absorbed through damaged skin (Andersen 1993). Three creams containing 2, 3, and 5% w/w Ceteareth-20 were tested as possible vehicles for dermal delivery of the analgesic piketoprofen. The 2% (w/w) Ceteareth-20 cream also contained 1.8% piketoprofen, 3% polyoxyethylene sorbitan monolaurate, 2% sorbitan monolaurate, 24.9% long-chain alcohols mixture, and 66.3% water. The cream with 3% Ceteareth-20 also contained 1.8% piketoprofen, 30.2% long-chain alcohols mixture, and 65% water. The cream with 5% Ceteareth-20 also contained 1.8% piketoprofen and 93.2% long-chain alcohols mixture. The creams were applied to the clipped skin of albino rabbits (numbers not stated) such that 200 mg of the analgesic/kg body weight was applied. The formulation was left in contact with the skin for 72 hours. Blood samples were taken from the marginal ear vein prior to product application and at hourly intervals thereafter. The samples were analyzed by thin-layer chromatography for 4-biphenylacetate (BPA) content which is a metabolite of the analgesic. All three creams containing Ceteareth-20 enhanced absorption of the drug as compared to three creams which did not contain Ceteareths. The most effective penetration was achieved with the 2% Ceteareth-20 cream (which also contained other surfactants). Although comparable (though less) penetration was also reached with another cream that contained surfactants other than Ceteareth-20, the narrow time base of the blood level curve indicated loss of drug to capillary blood and, hence, elimination from the site of action. The 2% Ceteareth-20 cream offered rapid penetration as well as retention in the subcutaneous tissue such that the drug appeared in circulating blood. High plasma levels of the metabolite were noted with the 2% Ceteareth-20 cream and were attributed to rapid skin penetration via the piloseba- ceous glands. It was suggested that the lower penetration values for the 3 and 5% Ceteareth-20 creams were &dquo;due to lowering of the thermodynamic activity of piketoprofen by micellar trappings of the active compound or by interactions with the skin. Thus, when a combination of surfactants was used, the release rate of piketoprofen from the organic phase was increased by the formation of high activity coefficient surfactant-drug complexes; (Fabregas et al. 1986).

PHOTOINDUCED TOXICITY

not induce photo toxicity
Additional information: clinical study in section DATA ON THE MAN

DATA ON MAN

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CLINICAL STUDIES Dermal Irritation and Sensitization No skin sensitization was observed in 25 panelists who had been inducted and challenged with a cream containing 3.0% cetearyl alcohol. In skin irritation and sensitization studies, product formulations containing up to 8.4% cetyl alcohol produced no substantial evidence of irritation or sensitization. A 30°lo concentration of cetyl alcohol in petrolatum caused sensitization reactions in 11.2% of 330 subjects in a sensitization study. However, no positive sensitization reactions were observed with studies of formulations containing up to 5.0% cetyl alcohol. Photosensitization studies of products containing 1.0% and 4.0% cetyl alcohol were negative (Elder 1988a). Results of screening patch testing of large populations indicated a contact sensitization rate of 0.51 % for Stearyl Alcohol (19 of 3740 sensitized) (Elder 1985). Steareth-2, 60% in water, was not a primary irritant or a sensitizer to human skin. Steareth-2, 0.6°lo in a mousse, was a mild irritant. A body lotion containing 2.75% Steareth-2 and 2.25% Steareth-20 was not phototoxic. At a concentration of 60% in water, Steareth-10 was not an irritant, and Steareth-20 (also tested in formulation) was neither an irritant, sensitizer nor phototoxic to human skin (Elder 1988b). In clinical studies, PEG-6 and PEG-8 induced mild sensitization in 9% and 4~l0 of 23 male subjects tested, respectively. However, later production lots of PEG-6, as well as PEG-75, did not cause reactions in any of the 100 male and 100 female subjects tested. A product formulation containing 3% PEG-8 induced minimal to mild irritation (induction phase) in over 75% of 90 volunteers participating in a skin irritation and sensitization study. Responses (not classified) were noted in 22 subjects at the 24 hours challenge reading. Cases of systemic toxicity and contact dermatitis in burn patients were attributed to PEG based topical ointments. The ointment that induced systemic toxicity contained 63% PEG-6, 5% PEG-20, and 32 % PEG-75 (Andersen 1993).

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EMA, European medical agency

CETEARYL ALCOHOL (CAS: 67762-27-0 / 8005-44-5)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

750 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/16007/7/6/1. Additional information:

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) >10000 mg/kg bw
LD50 dermal (rabbit) >8000 mg/kg

It is concluded that the substance Alcohols, C16-18 does not meet the criteria to be classified for human health hazards for acute oral effects

Additional information:
Acute oral toxicity

Alcohols, C16-18 is from the category of Long Chain aliphatic Alcohols within a carbon chain length range of C6-C22. Considering the data for linear alcohols in the range 1-octanol to 1-docosanol and including unsaturated alcohols, the oral LD50values range from > 5000 mg/kg to well over 10,000 mg/kg, with most of values representing the

maximum administered dose.

ClinicalSigns. Few, if any signs of toxicity were reported following oral administration of the linear alcohols ranging from C6 to C22 alcohols. At doses approaching acute lethality loss of appetite, lethargy and diarrhoea was reported for most members of the linear alcohols. Animals surviving a large oral dose showed no evidence of any delayed or irreversible effects following acute administration of any of these alcohols. In decedents irritation of the gastro-intestinal tract and typical agonal changes were observed, however no substance specific observations could be recognised for any of the materials of this sub-category. There are no observations reported to suggest a potential for CNS depression following administration of a single oral dose of a linear alcohol within this category.

Conclusion:The category of the long chained aliphatic alcohols (linear and essentially linear) is of a low order of acute toxicity upon oral administration.Alcohols, C16-18 was not classified according to EU or GHS criteria.

Acute inhalation toxicity

Alcohols, C16-18 is from the category of Long Chain aliphatic Alcohols within a carbon chain length range of C6-C22.The available data cover the lower (1-hexanol and 1-octanol), intermediate (1-decanol, 1-dodecanol) and higher (1-tetradecanol, C16-18alcohols) chain-lengths of the linear alcohols subcategory.

The volatility of the category of aliphatic alcohols as a whole is low. Saturated vapour pressures for the higher chain alcohols are extremely low; for example the calculated concentration of a saturated atmosphere of 1-dodecanol and 1-octadecanol at ambient conditions is in the order of 10-2and 10-5mg/L, respectively. Most experimental studies used the maximum achievable vapour concentrations or aerosols for the assessment of the acute lethal concentration. For all substances tested the LC50values exceeded the maximum achievable vapour concentrations. Even the more volatile members of this category (e.g. 1-hexanol, C6-12 essentially linear alcohols [Types B and C], 1-heptanol and 1-undecanol) showed no evidence of toxicity after a single exposure for 1 – 6 hours

None of the acute inhalation studies provided any evidence of a potential for CNS depression for the category of aliphatic alcohols. This conclusion is further supported by data in mice indicating that inhalation of high concentrations (up toca. 10,000 ppm) of 1-heptanol for short periods of time did not induce anaesthesia.

Conclusion: Inhalation of vapours of long chained alcohols in the range C6-C22 at levels up to the saturated vapour pressure is unlikely to be associated with significant toxicity.Alcohols, C16-18 was not classified according to EU or GHS criteria.

Acute Dermal Toxicity

Alcohols, C16-18 is from the category of Long Chain aliphatic Alcoholswithin a carbon chain length range of C6-C22.

For the linear alcohols in the range, C6 - C10 most of the reported LD50values in rabbits are in the range 2000 - 4000 mg/kg. For the alcohols C12and higher the acute dermal

LD50values were 8000 mg/kg or higher. Although some incidental LD50values below 2000 mg/kg were reported, these values generally represented the maximum dose tested. Substances with a chain length beyond C18 have not been tested but on the basis of the consistent low acute dermal toxicity for alcohols with a chain-length of C16 and below and the consistently low oral acute toxicity for the category as a whole it is expected that aliphatic alcohols in the range C18 – C22 are of a low order of acute dermal toxicity.

Clinical signs.Occluded exposure for 24 hours generally caused local dermal irritation. There was a clear (inverse) relationship between the chain length and the severity of the dermal effects. The severity of the irritation was graded as moderate – severe for the lower members of this category; typical observations included erythema, oedema, wrinkling, desquamation and cracking. The grading of the local effects for the aliphatic alcohols with a longer carbon chain was reported as slight-moderate. Animals showing signs of significant local irritation displayed signs of toxicity such as general weakness, anorexia, lethargy; it is not possible to ascertain if these findings were secondary to the irritation or evidence of direct systemic toxicity.

Conclusion:The category of the long chained aliphatic alcohols is of a low order of acute toxicity upon dermal administration. Alcohols, C16-18 was not classified according to EU or GHS criteria.

SKIN IRRITATION AND CORROSIVITY

not irritant
Following a 24 hour semi-occlusive exposure to rabbit skin Alcohols, C16-18 is classified as non-irritant based on either EU or GHS criteria.
The alcohols with chain lengths of C16-18 are non-irritant to skin.

Based on the data that was reported a NOAEL following dermal administration of fatty alcohol blend for a minimum of 90 days was less than 100 mg/kg/day.
However the NOAEL has been based on a local irritation effect rather than a systemic effect. Therefore it is proposed (by the author of the EPSR) that on the basis of a lack of systemic effects reported in the study, the NOAEL following dermal administration of fatty alcohol blend for a minimum of 90 days is greater than 1000 mg/kg/day.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritant
Result: not irritating . Based on the Draize scores reported it is considered that Alcohols, C16-18 is not not an eye irritant according to either EU or GHS criteria.The alcohols with chain lengths of C16-18 are non-irritant to eye.

SKIN SENSITISATION

not sensitising

Additional information:
Respiratory sensitisation.

There are no Respiratory sensitisation studies available.

Due to the absence of chemical groups or other structural alerts this substance is not considered to exhibit an high hazard potential.

Alcohols, C16-18 is of low priority for further work based on a low hazard potential is of low priority for further work based on a low hazard potential.

There is no information available from single or repeated inhalation exposures in laboratory animals or from human experience allowing a conclusion on potential respiratory tract irritation and sensitisation of the aliphatic alcohols.

Therefore testing for Respiratory sensitisation does not need to be performed.

Migrated from Short description of key information:
There are no Respiratory sensitisation studies available.
Due to the absence of chemical groups or other structural alerts this substance is not considered to exhibit an high hazard potential.
Alcohols, C16-18 is of low priority for further work based on a low hazard potential is of low priority for further work based on a low hazard potential.
There is no information available from single or repeated inhalation exposures in laboratory animals or from human experience allowing a conclusion on potential respiratory tract irritation and sensitisation of the aliphatic alcohols.
Therefore testing for Respiratory sensitisation does not need to be performed.

DERMAL/PERCUTANEOUS ABSORPTION

A QSAR model predicts that the permeability of Alcohols, C16-18 to human skin is quite low. The permeability coefficient was determined to be 0.001 mg/cm2, which is around 1% of the skin penetration rate.
Predicted dermally absorbed coefficient was determined to be Kp (est)=2.04 cm/hr.

MUTAGENESIS / GENOTOXICITY

There are conclusive but not suffcient data for the classification of substance Alcohols, C16-18 with regard to mutagenicity/genetic toxicity. It is concluded that the substanceAlcohols, C16-18 does not meet the criteria to be classified for human health hazards for Mutagenicity-Genetic Toxicity

In vitro Studies

Bacterial tests

In a reliable study (Thompson, P.W. , 1996), performed according to OECD guideline 471, the C16 alcohol Kahlcol 6098 did not increase the reverse mutation rate in histidine dependent bacterial strains of Salmonella typhimurium in the presence or absence of metabolic activation at concentrations up to 5000 µg/plate. This concentration was not cytotoxic. Hexadecan-1-ol (C16) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

In a valid and reliable study (Iglesias G, J J Hlywka, J E Berg, M H Khalil, L E Pope and D Tamarkin,2002), behenyl alcohol (C22) did not increase the reverse mutation rate in histidine dependent bacterial strains of Salmonella typhimurium in the presence or absence of metabolic activation at concentrations up to and including 1000 µg/plate. It is concluded that the test substance is negative for mutagenicity in bacteria under the conditions of the test. Docosan-1-ol (behenyl alcohol (C22)) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

In a reliable study (Henkel KGaA.,1981), the C16 alcohol Lanette 16 (Lorol 16) did not increase the reverse mutation rate in histidine dependent bacterial strains of Salmonella typhimurium in the presence or absence of metabolic activation at concentrations up to 2500 µg/plate. There was some evidence of cytotoxicity in some strains at higher concentrations (500 and/or 2500 µg/plate) in the absence of metabolising fraction only. Hexadecan-1-ol (C16) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

In a reliable study (Thompson, P.W. ,1996) conducted according to OECD guideline 471, the C18 alcohol Kalcohl 8098 did not increase the reverse mutation rate in any of the histidine dependent bacterial strains of Salmonella typhimurium tested in the presence or absence of metabolic activation at concentrations up to 5000 µg/plate. The top concentration was not cytotoxic. It is concluded that the test substance is negative for mutagenicity to bacteria under the conditions of the test. Octadecan-1-ol (C18) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

In a reliable study (Henkel KGaA., 1981), conducted using a protocol similar to OECD guideline 471, the C18 alcohol Lanette 18 did not increase the reverse mutation rate in histidine dependent bacterial strains of Salmonella typhimurium in the presence or absence of metabolic activation at concentrations up to 2500 µg/plate. Slight cytotoxicity was evident at 2500 µg/plate. Octadecan-1-ol (C18) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

Non-bacterial test

In a reliable study (Iglesias G, J J Hlywka, J E Berg, M H Khalil, L E Pope and D Tamarkin,2002), according to a protocol that is similar to OECD 473, behenyl alcohol (C22) did not increase the incidence of chromosome aberrations in Chinese hamster V79 cells in the presence or absence of metabolising fraction at concentrations up to 20 ug/ml. There was no evidence of cytotoxicity at this dose level. Docosan-1-ol (behenyl alcohol (C22)) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

In vivo Studies

Dodecan-1-ol (C12) has been tested a reliable study (Henkel KGaA., 1992), conducted according to OECD guideline 474, no genotoxicity was seen in mice after a single oral dose of 5000 mg/kg bw. . The test substance, dodecan-1-ol is closely related to the registration substance, Alcohols, C16-18 and it is considered that read-across is valid.

In a reliable study (Iglesias G, J J Hlywka, J E Berg, M H Khalil, L E Pope and D Tamarkin,2002), behenyl alcohol (C22) did not increase the incidence of micronuclei in mouse

bone marrow cells after a single oral gavage dose of up to 500 mg/kg bw. Docosan-1-ol (behenyl alcohol (C22)) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

Stearyl alcohol (Hachiya N, Takeya A, Takizawa Y,1982), did not increase the incidence of micronucleated cells in mouse bone marrow erythrocytes following a single oral dose level up to and including 1450 mg/kg or a total of 2920 mg/kg adminstered as 4 doses in a 24 hour period. It is concluded that the test substance is negative for induction of micronuclei under the conditions of the test. Octadecan-1-ol (C18) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

Conclusion:Alcohols, C16-18 is from the category of Long Chain aliphatic Alcohols within a carbon chain length range of C6-C22 and do not have a genotoxic potential.

CARCINOGENICITY

not carcinogenic

Studies in animals.

Data availability.There are no data available for the category of the long chained alcohols reporting in detail about carcinogenicity studies according to current testing standards. Several of the linear alcohols have been tested in experimental investigations studying the potential for initiation, promotion or co-carcinogenicity, however as a rule these data have a low reliability and suffer from significant shortcomings regarding the reporting details, the number of animals, the use of non-standardised or unvalidated protocols, and lack of control of confounders (e.g. local irritation). As a whole the information available on carcinogenicity is regarded to have limited reliability.

Hexanol-1, 1-octanol, 1-decanol, 1-dodecanol, 1-tetradecanol, 1-hexadecanol and 1-octadecanol were tested in one or more mouse skin painting studies using applications 2 - 3 times weekly for periods up to 60 -70 weeks. Development of local skin tumours was not reported in any of these assays. All of these experiments were conducted as part of investigative studies into co-carcinogenicity or tumour promotion properties of aliphatic alcohols (Sicé, 1966; Bingham, 1969; Van Duuren, 1976).

The aliphatic alcohols were applied repeatedly over periods up to 60 weeks to the skin of mice that had been initiated or were co-exposed with carcinogens such as 7, 12-dimethylbenz[a]-anthracene or benzo[a]pyrene (B[a]P). In most of the experimental protocols the application of aliphatic alcohols induced significant dermal irritation at the site of treatment and led to formation of local tumours; in some cases a decrease in latency of tumour development or co-carcinogenicity was reported (Sicé, 1966; Van Duurenet al., 1976; Bingham, 1969).

In other assays 1-octanol, 1-dodecanol or 1-octadecanol were repeatedly injected into the peritoneal cavity or implanted in the bladder of mice. No induction of primary lung tumours was recorded, however a low incidence of benign bladder tumours was reported (Stoner, 1973; Bryanet al, 1966). Ando (1972) published a study in which small groups of mice (n = 4-6), implanted intra-peritoneally with Ehrlich ascites tumour cells, were exposed i.p. to different doses of 1-decanol, 1-dodecanol, 1-tetradecanol, 1-hexadecanol and 1-octadecanol once daily for 5 consecutive days. Although a prolongation of survival time was observed, no conclusions can be drawn regarding the carcinogenic potential of these alcohols.

Conclusion.Several members of the category of the long chained alcohols have been tested as control substances in skin painting studies. Even taking into account the limitations of these experiments, the data show that none of aliphatic alcohols tested have a potential to induce local skin tumours upon repeated dermal application at or above the maximum tolerated (irritant) dose. However, these data are unsuitable to assess properties such as co-carcinogenicity or tumour promotion for this category of alcohols. Most of

the study protocols considered here have almost certainly induced considerable local effects, however details of the irritation responses are limited and were reported only in a few cases. Irrespective of the causative agent, irritation at the site of application is a significant confounder in skin painting studies and its role in the tumour development of non-genotoxic chemicals has been well established (for examples see Nesselet al., 1998, 1999; Argyris, 1985).

The genotoxic potential of the long chain alcohols has been well investigated, bothin vitroandin vivoand no concerns were identified for genotoxicity. Furthermore they lack structural elements of concern for interaction with DNA (Ashby and Tenant, 1991). Together with the lack of response upon repeated application the skin painting studies long chained alcohols are regarded to be of little concern regarding carcinogenicty.

There are conclusive but not suffcient data for the classification of substance Alcohols, C16-18 with regard to carcinogenicity.

Carcinogenicity: IARC, NTP, ACGIH and OSHA do not classify this substance or its components as a carcinogen or suspect carcinogen.

REPRODUCTIVE TOXICITY

It is concluded that the substance Alcohols, C16-18 does not meet the criteria to be classified for human health hazards for Reproductive toxicity

Additional information:
Oral exposure

In a reliable study(Hansen, E. 1992), development was assessed as part of a combined repeat dose and reproductive/developmental toxicity study, conducted according to draft OECD guideline 422. The NOAEL for maternal and foetotoxicity in rats was 2000 mg/kg bw/day (highest dose level). There was no evidence of teratogenicity from the limited examination of the pups that was carried out. Octadecan-1-ol (C18) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

NOAELrat = 2000mg/kg bw/day

In a reliable study (Iglesias G, JJ Hlywka, JE Berg, MH Khalil, LE Pope and D Tamarkin,2002), conducted according to a protocol similar to OECD guideline 414, the NOAEL for maternal toxicity, teratogenicity and foetotoxicity in rabbits, was 2000 mg/kg/day (highest dose tested). The study was performed in compliance with GLP. Docosan-1-ol (C22)) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

NOAELrabbit = 2000mg/kg bw/day

In a reliable study (Iglesias G, JJ Hlywka, JE Berg, MH Khalil, LE Pope and D Tamarkin,2002), conducted according to a protocol similar to OECD guideline 414, the NOAEL was 1000 mg/kg/day for maternal toxicity, teratogenicity and foetotoxicity in rats receiving behenyl alcohol by gavage for 15 days premating, during mating and up until gestation day 17. This is based on the absence of adverse effects in any of the parental, reproductive or foetal parameters examined. Docosan-1-ol (C22)) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

NOAELrat = 1000mg/kg bw/day

In a briefly-reported study (Rodwell D E, Mercieca M D, Rusch G M, Tasker E J,1988), an NOAEL of 200 mg/kg bw/day was determined for maternal toxicity and an NOAEL of 1000 mg/kg bw/day for developmental toxicity in the rat after oral administration on days 6 to 15 of gestation. Hexan-1-ol (C6) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

NOAELrat = 1000mg/kg bw/day

Dermal exposure:

The developmental toxicity of 2 -EH following dermal absorption was examined in a OECD TG 414 rat study that was conducted under GLP. 2 -EH was applied to the skin of 25 females at 252, 840, and 2520 mg/kg bw/day under an occlusive dressing during gestational days 6 -15 for 6 hours per day. The dose levels were selected based on the results of a preliminary study (Tyl et al., 1992).

The maternal toxicity was mild. There were no deaths or severe clinical signs of toxicity. A reduced body weight gain in high-dose rats was noted, and local skin irritation in rats at the intermediate and the high dose level.

2 -EH had no adverse effect on the maternal gestational parameters, or maternal organ weights, or on the fetal weight, sex ratio, viability, or the incidence of malformations and variations.

Therefore, the NOAEL for maternal systemic toxicity was 840 mg/kg bw/day, based on the effects on body weight gain; the NOAEL for skin irritation was 252 mg/kg bw/day. The NOAEL for developmental toxicity and teratogenicity was 2520 mg/kg bw/day.

2-ethylhexan-1-ol is a substance supporting the category Long Chain aliphatic Alcohols within a carbon chain length range of C6-C22 and it is considered that read-across is valid.

NOAELMaternal: (840 mg/kg bw d)

NOAEL developmental toxicity and teratogenicity : (2520 mg/kg bw d)

Inhalation exposure:

Groups of approximately 15 sprague-dawley rats were exposed to 7 h/day on gestation days 1-19 to 3500 mg/m3 1-hexanol, which was the highest concentration which could be generated as a vapor. Dams were weighed daily for the first week of exposure and weekly thereafter and were sacrificed on day 20. Fetuses were serially removed, blotted dry, examined for external malformationa, sexed, weighed, fixed, and examined for visceral or skeletal defects.

In a reliable study (Nelson B K, Brightwell W S, Khan A, Krieg E F Jr, Hoberman A M,1989), an NOAEC of 3500 mg/m3 (the highest achievable concentration in the test system) was determined in the rat for maternal toxicity and developmental toxicity after administration by inhalation for 7 hours/day on gestation days 1 to 19.Hexan-1-ol (C6) is closely related to the registered substance, Alcohols, C16-18 and it is considered that read-across is valid.

NOAECrat = 3500mg/m3

Toxicity to reproduction: other studies
Additional information
Docosanol administered by gavage to rats aged 6-7 months for 28 days did not affect bodyweight or the weights of any of the organs weighed other than a statistically significant increase in weight of

the seminal vesicles at the lower dose levels (1 and 10 mg/kg/day). There were no histological differences in the accessory sexual organs.

Docosanol had no effect on the weight or histology of the prostate in intact rats but increased the RNA/DNA quotient in the ventral prostate. Plasma LH and testosterone were reduced. In orchidectomised rats docosanol increased the prostate and adrenal weight but there was no increase in orchidectomised and adrenalectomised rats, a weight reduction being observed. Also docosanol had a thymolytic effect in intact rats but not in adrenalectomised rats where the thymus weight was increased. These results suggest a stimulation of adrenal steroid secretion but this may not be the only effect of docosanol.

Docosanol is closely related to the registered substance, Alcohols, C16-18, and it is considered that read-across is valid.

No NOAEC identified : 100 mg/kg bw d)

TOXICOKINETIC (ADME studies)

Distribution results were reported for lauryl alcohol (98% pure). 95% of the dose adminstered was recovered from the application site at 24 hours after dosing. 0.13% remained in the body while 0.10% was excreted in the urine and faeces. 2.61% was excreted in expired air as CO2. The ratio of the amount of compound excreted via expired air to the amount absorbed is the expiratory excretion rat. It was 91% for lauryl alcohol. The respiratory excretion rates for all the other alcohols investigated were >65% although all the actual data is not reported.

Absorption decreased with increasing carbon chain length. The absorption rate was investigated in different solvents (squalene, castor oil, triethyl citrate (TEC). The percutaneous absorption rate of undiluted n-octanol was 50%, this was increased in squalene but decreased in castor oil or TEC. This was also reported with the other alcohols tested and the tendency was more pronounced at higher concentrations.

The degree of skin irritation was proportionally related to the degree of percutaneous absorption.

Interpretation of results: no bioaccumulation potential based on study results
Following skin application of lauryl alcohol about 2.84 % of the administered dose was absorbed. Of this absorbed dose >90% was excreted in expired air (CO2). A similar trend was observed with the other alcohols tested. Absorption decreased with increasing carbon chain length and was affected by solvent and concentration.

At least 65% of the absorbed dose is excreted as CO2 in the expired air. Absorption decreased with increasing carbon chain length and was affected by solvent and concentration

Additional information:
Oral repeated dose toxicity
The NOAEL for 13 week dietary feeding study in rats is ca 750 mg/kg/day (males 723, females 875) based on reduced weight gain and food consumption. The toxicological significance of observed changes in organ weights, all in the absence of histopathological change, is questionable. Increased liver weights at higher dose levels may be indicative of a mild adaptive effect on the liver.
In view of the structural and chemical similarities, it is considereed that the results of the study can be used for read-across to Alcohols, C16-18.
Dermal repeated dose toxicity
A 90-day dermal toxicity study in rats with fatty alcohol blend (56.7% decanol, 42.7% octanol) at dose levels of 0, 100, 300, or 1,000 mg/kg resulted in severe irritation at the application site. Severe irritation including fissuring of the skin occurred in 40% of the animals at 100 mg/kg/day and 80% of the animals at the limit dose. Slight changes in hematology, clinical chemistry, and organ weights were noted at the limit dose of 1,000 mg/kg/day.
NOAEL has been based on a local irritation effect rather than a systemic effect. Therefore it is proposed (by the author of the EPSR) that on the basis of a lack of systemic effects reported in the study, the NOAEL following dermal administration of fatty alcohol blend for a minimum of 90 days is greater than 1000 mg/kg/day.
Inhalation repeated dose toxicity
Under the conditions of the test no treatment-related toxic effects were found in male and female Wistar rats which were exposed to 2-ethylhexanol vapor up to 120 ppm ie. 638.4 mg/m³ . (Klimisch HJ; Deckardt K; Gembardt C; Hildebrand B,1998).The substance Alcohols, C16-18, the subject of this dossier) is expected to exhibit very similar toxicity due to its close structural similarity to 2-ethylhexanol. Comparable metabolism would occur. Correcting for molecular weight, a conservative NOAEC of 1188.79 mg/m3 can be derived (638.4 x 242.45) / 130.2 =1188.79 mg/m3

PHOTOINDUCED TOXICITY

not phototoxic

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

DATA ON MAN

Alcohols, C16-18 or Cetostearyl alcohol, cetearyl alcohol or cetylstearyl alcohol is a mixture of fatty alcohols, consisting predominantly of cetylandstearyl alcohols and is classified as a fatty alcohol.

It is used as an emulsion stabilizer, opacifying agent, and foam boostingsurfactant, as well as an aqueous and nonaqueous viscosity-increasing agent. It imparts an emollient feel to the skin and can be used in water-in-oil emulsions, oil-in-water emulsions,and anhydrous formulations. It is commonly used in hair conditioners and other hair products

Clinical skin irritation and sensitization studies of product formulations containing 8.4%, 6.36%, 6.0%, 4.0%, 3.3%, 3.25%, 3.0%, 2.85%, 2.0%, and 1.0% Alcohols, C16-18 produced no substantial evidence of irritation or sensitization.

Based on the available data it is concluded that Alcohols, C16-18 or Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol, Myristyl Alcohol, and Behenyl Alcohol are safe as cosmetic ingredients in the present practices of use.

Alcohols, C16-18 do not induce skin sensitization in humans, and there is no conclusive evidence that they induce eczema.

No serious injuries or fatalities have been reported following accidental ingestion of Long Chain aliphatic Alcohols.

In this inter-laboratory assessment of the human patch test hexanol gave responses significantly lower than the positive control and results were similar between laboratories. N-hexanol was therefore not considered as a skin irritant.

Neurotoxicity. There is no evidence in the available toxicity studies or scientific literate to indicate neurotoxic effects of the of Alcohols, C16-18 in humans or laboratory animals. There are conclusive but not suffcient data for the classification of substance Alcohols, C16-18 with regard to Neurotoxicity.

Immunotoxicity. There is no evidence in the available toxicity studies or scientific literate to indicate Immunotoxic effects of the Alcohols, C16-18 in humans or laboratory animals. There are conclusive but not suffcient data for the classification of substance Alcohols, C16-18 with regard to Immunotoxicity.

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- HERA http://www.heraproject.com
- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

CHAMOMILLA RECUTITA FLOWER EXTRACT (CAS: 84082-60-0)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

4000 -- - CIR, https://www.cir-safety.org/sites/default/files/chamomile.pdf

Additional information:
Sprague-Dawley rats of either sex (number not stated; males or females only not specified) were fed increasing doses (1, 2, 4, and 8 g/kg body weight) of chamomilla recutita (matricaria) flower extract (aqueous extract), dissolved in water, for 14 days. Neither signs of toxicity nor mortalities were observed at doses up to 4 g/kg body weight. Information relating to effects of the 8 g/kg dose was not included. All of the animals remained physically active.
Data on repeated dose toxicity were presented in a study on the the effect of chamomile tea on the activity of hepatic phase I and phase II metabolizing enzymes from the rat.40 Chamomile tea is made from the dried flower heads of Chamomilla recutita (matricaria). Five female Wistar rats (8 to 9 weeks old) had free access to Chamomile tea solution (2% w/v in water), whereas the control group had access to water. After 4 weeks of treatment, the animals were killed. Dosing had no significant influence on body weight, and there were no signs of gross pathology of internal organs. Liver weight/body weight ratios of treated rats were not significantly different from control values.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 5 000 mg/kg bw
Additional information:
n an acute oral toxicity study (limit test), ten rats were given a single oral dose of Oil Chamomille at 5000 mg/kg bw. Animals were observed for mortality and clinical signs for 14 days.
No mortality or clinical signs was observed. In this study, the oral LD50 of Oil Chamomille was higher than 5000 mg/kg bw in rats.
Under the experimental conditions of this study, the test substance is not classified according to Regulation (EC) No. 1272/2008 (CLP) and to GHS.

SKIN IRRITATION AND CORROSIVITY

irritant
Additional information:
An in vitro skin irritation study was performed according to the OECD Guideline 439, the EU Method B.46 and in compliance with GLP, using the EPISKINTM reconstructed human epidermis model.
The test item was applied, as supplied, at the dose of 16 µL to 3 living Reconstructed Human epidermis (SkinEthic RHE® model) during 42 minutes. The application was followed by a rinse with 25 mL of DPBS and a 41 hours post-incubation period at 37°C, 5% CO2. Cell viability was then measured by enzymatic conversion of the vital dye MTT into a blue formazan salt that was quantitatively measured after extraction from tissues. Two additional killed control tissues were used for MTT direct interference and two living and two killed tissues for colour interference.
The mean corrected percent viability of the treated tissues was 2.5%, versus 1.2% in the positive control (5% Sodium Dodecyl Sulfate).
The mean OD negative control obtained after a 1:2 dilution of the formazan extracts in isopropanol is include in the acceptability criteria range which is ≥ 0.4 ≤ 1.5.
The mean percent tissue viabilites obtained with the negative control and positive controls are within the range of historical data.
Under the experimental conditions of this study, and with the classification non-corrosive obtained with the in vitro skin corrosion test (HSMC-PH-17/0469), the test item has to be classified in Category 2 "Irritating to skin" according to the Regulation (EC) No.1272/2008 (CLP) and to the GHS.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

irritant
Additional information:
An in vitro skin irritation study was performed according to the OECD Guideline 492 and in compliance with GLP, using the in vitro reconstructed human cornea-like epithelium tissues (EpiOcularTMtissue model).
Test item Camomille HE Egypte BLH (Essential Oil of Blue Chamomilla) was applied as applied at the dose of 50 µL to 2 living DPBS pre-treated RhCE (EpiOcularTM tissue model) during 30 minutes at 37°C, 5% CO2, 95% humidity (standard culture conditions). The exposure period was followed by extensive rinsing with DPBS at room temperature, a 12 minutes post-exposure immersion period at room temperature and a 2 hours post-exposure incubation at standard culture conditions. The tissue viability was measured by performing an MTT assay. Additionally, 2 killed RhCE (EpiOcularTM tissue model) were treated in the same manner in order to generate non-specific MTT reduction. Moreover, 2 living and 2 killed RhCE (EpiOcularTM tissue model) were treated in the same manner but they were incubated in assay medium instead of MTT solution in order to generate non-specific living and killed colour controls.
The mean corrected percent tissue viability of the RhCE replicates treated with test item Camomille HE Egypte BLH (Essential Oil of Blue Chamomilla) was 44.39%, versus 32.69% in the positive control (Methyl acetate).
In conclusion, under the experimental conditions adopted and in accordance with Regulation EC No. 1272/2008, test item Camomille HE Egypte BLH (Essential Oil of Blue Chamomilla) has to be identified as potentially requiring classification and labelling according to UN GHS Category 2 or Category 1.

SKIN SENSITISATION

sensitising
Additional information:
- Patients with dermatitis were treated in different studies (See Section 7.10.4) with a fragrance mixture, essential oils, and individual substances, at 2% in yellow paraffin, to identify the potential skin sensitisers comprised in cosmetics.
German chamomile has shown a skin sensitising potential in all of the three studies.
- A constituants approach was made using the OECD QSAR Toolbox which confirms the skin sensitising potential of the registered substance. Indeed, some of its constituents are classified as skin sensitisers Cat.1B (Bisabolone Oxide A, CAS N° 22567-38-0) and is potentially present above the CLP generic concentration limit of 1% that triggers classification of the mixture.
Conclusion: Skin sensitiser 1B

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
Gene mutation assay:
A bacterial reverse gene mutation assay (Ames test) was performed according to the OECD test guideline No. 471 and in compliance with GLP (Envigo, 2018). Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 and Escherichia coli strain WP2 uvrA were treated with the test item using both the Ames plate incorporation and pre-incubation methods at up to nine dose levels, in triplicate, both with and without the addition of a rat liver homogenate metabolizing system (10% liver S9 in standard co-factors).
The test item precipitated in the overlay agar in the test tubes from 1000 µg/plate up to the highest investigated concentration. Precipitation of the test item in the overlay agar on the incubated agar plates was observed from 2500 µg/plate up to the highest investigated concentration. The undissolved particles had no influence on the data recording.
The plates incubated with the test item showed reduced background growth in strains TA 1537, TA 98, and TA 100.
Toxic effects, evident as a reduction in the number of revertants (below the indication factor of 0.5), were observed in all strains used.
No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with test item at any dose level, neither in the presence nor absence of metabolic activation (S9 mix). There was also no tendency of higher mutation rates with increasing concentrations in the range below the generally acknowledged border of biological relevance.
Appropriate reference mutagens were used as positive controls and showed a distinct increase of induced revertant colonies.
The substance is therefore considered as non-mutagenic according to the Ames Test.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

not bioaccumulative
Using in FOOD and Drug industries.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Sensitisation data
After a first experiment using a perfume mixture (ICDRG) containing 1 essential oil and 7 other fragrance substances, a group of 86 humans were tested with essential oils and 42 with individual ingredients at St John''s Hospital for Diseases of the Skin in London.
Among the 86 positive patients to the perfume mixture, 3 (3.4%) showed a positive response to German chamomile.

Repeated Dose Toxicity
Fourteen health volunteers (7 males, 7 females) were given 200 ml of chamomile tea daily for 2 weeks. None of the subjects reported adverse effects after ingestion of the tea.41
An analysis of urine samples collected before dosing, during the dosing period, and after dosing indicated that depletion of creatinine and the elevation of hippurate and glycine were strongly associated with chamomile tea intake.

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EMA, European Medical Agency

CITRIC ACID (CAS: 77-92-9 / 5949-29-1)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

250 -- European Chemical Agency ECHA.EU https://echa.europa.eu/registration-dossier/-/registered-dossier/15451/7/6/1 There are no reliable 28-day or 90-day studies available, so this endpoint is waived. Numerous studies have been reported in the literature and are discussed below. The most reliable studies are 10-day studies in rats and mice, with the following results:

NOAEL (10 d) 4000 mg/kg bw/day rats (unidentified gender)

LD50 (10 d) 5660 (+/- 0.44) mg/kg bw/day rats (unidentified gender)

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (mouse) 5400 mg/kg bw
LD50 dermal (rat) > 2 000 mg/kg bw
Additional data: Acute intraperitoneal LD50 values of 940 in mice and 725 mg/kg in rats (males only) were determined in a reliable study conducted according to an appropriate test protocol. The study was not conducted according to GLP.

SKIN IRRITATION AND CORROSIVITY

A reliable study conducted largely in accordance with OECD 404 and in compliance with GLP, found the citric acid to be mildly irritating to the skin of rabbits. Current EC criteria would find the material to be non-irritant.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

Category 2 (irritating to eyes) based on GHS criteria
A generally reliable study, apparently conducted according to OECD 405 and GLP, reported that a 30% aqueous solution of the test substance caused well defined to moderate conjunctival irritation that had not fully resolved after 14 days. A 10% solution was associated with weak to moderate conjunctival effects, resolved after 7 days. Given the 30% solution effects would have been allowed to dissipate for 21 days, it is likely the test substance would not be considered irritating to the eyes according to EU criteria (please see attached expert letter as reference).

SKIN SENSITISATION

No data are available which suggest that citric acid should be classified as a skin or respiratory sensitiser according to Regulation (EC) No 1272/2008.

DERMAL/PERCUTANEOUS ABSORPTION

No data

MUTAGENESIS / GENOTOXICITY

Citric acid (CAS number 77-92-9) has been tested in a number of bacterial assays, all of which gave negative results. There is also information from a lower reliability study that citric acid does not cause chromosome aberrations in vitro: this result does not agree with a recently published study. Evidence for genetic toxicity has been described in published results from an in vitro micronucleus study and an in vitro comet assay. An in vivo chromosome aberration study does not support the conclusion of the recently reported in vitro studies in mammalian cells, and an in vivo rodent dominant lethal assay also showed no evidence of chromosome damage.

Citric acid is negative in in vivo genotoxicity testing, although effects have been observed in some in vitro studies. Moreover, it has been used as a food additive over a long period. In addition, citrate plays a central role in cellular metabolism, so it is considered that classification for mutagenicity is not required according to Regulation (EC) No 1272/2008.

CARCINOGENICITY

In a rat feeding study, animals dosed with 5% citric acid in the diet did not show an excess of tumours in comparison with control animals when tested over a period of 2 years (Horn et al., 1957). However, there was limited evidence that high doses of citrate salts increased the incidence of tumours produced by co-administration of known bladder carcinogens (Inouea et al., 1988; Ono et al., 1992; de Camargo et al. 1991; Fukushima et al.1986; Behnke et al., 1964). Where citric acid or citrate salts were administered alone during these studies, no dose-related tumours were noted.

No reliable carcinogenicity studies are available, however, further testing is not considered necessary because:

• The substance is not classified for mutagenicity; and

• There is no evidence from long term human exposure to citric acid that it is a carcinogen.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

REPRODUCTIVE TOXICITY

n accordance with Annex XI, Section 1 of REACH, the evidence based on:

(1) The available developmental toxicity studies. A study by the Food & Drug Research Laboratories (1973) researched the teratogenic effects of citric acid in mice (NAOEL > 241 mg/kg/d), rats (NAOEL > 295 mg/kg/d), rabbits (NAOEL > 425 mg/kg/d), and hamsters (NAOEL > 272 mg/kg/d), There were no reported teratogenic effects in any of the species tested;

(2) A long history of human exposure. For example, Citric Acid is naturally present in common fruit and vegetables. It is also added to processed food and beverages. (HERA 2005). In addition, Citric Acid has well established and documented metabolic pathways in humans. (WHO Food Additives, Series 5, 1973);

is sufficient to fulfil the requirements for this endpoint.

TOXICOKINETIC (ADME studies)

Citric acid is a metabolic intermediate vital to the TCA respiration pathway found in all animal and plant cells. There is little evience that citric acid and the citrate salts have deleterious effects, even in large doses. Indeed there is some support for the fact that citric acid in the human diet is favourable by inhibiting the formation of calcium oxalate kidney and bladder stones. This statement is applicable to the citrate salts since once absorbed citrate salts will dissociate into citric acid and their counter-ion.

PHOTOINDUCED TOXICITY

No data

DATA ON MAN

In a skin prick test which were not conducted according to any guideline and not in compliance to GLP and with very limited provided details, it was observed that the test substance, citric acid, casued positive results in 3 of 91 patients whereof one of the patients also reacted to benzoic and propionic acids.

A study was conducted to evaluate the effect of inspiratory flow rate on the cough response to citric acid (Barros et.al., 1990.) It is considered by the authors that the cough response to citric acid is produced mainly by irritation of the larynx and trachea. Variations in the inspiratory flow rate might lead to changes in deposition of the drug, and consequently in the cough threshold.

The effect of inspiratory flow rate was studied in 11 healthy non-smoking volunteers aged 23 to 29 years (9 male, 2 female). The test substance was administered by inhalation of a nebulised solution via apparatus which limited and measured the inspiratory flow rate to 50, 100 and 150 l/minute of increasing concentrations of citric acid.

The test was finished when a cough was produced after each inhalation at one concentration (cough threshold) or the maximum concentration was reached. Each concentration was given at three different flow rates. The exposures were repeated on 3 days at least 48 hours apart.

The mean cough threshold was determined to be 21 (±9-54) mg/l at an inspiratory flow rate of 50 l/min and 43 (±13-141) mg/l at 150 l/minute. It was concluded that inspiratory flow rate should be controlled when cough challenges with citric acid are performed.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- FOOD AND DRUG ADMINISTRATION FDA

COLLAGEN (CAS: 9007-34-5)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

8600 -- - VKM Report 2016:65, https://vkm.no/download/18.761cd04215dabef8a9e82c2d/1502797650515/Risk%20assessment%20of%20%22other%20substances%22%20%E2%80%93Collagen%20from%20fishskin.pdf

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (mice) 50 ml/kg

SKIN IRRITATION AND CORROSIVITY

no data

MUCOSAE IRRITATION AND CORROSION (eye irritation)

no data

SKIN SENSITISATION

not classified as sensitizer
Additional information:
however, some people may be intolerant, depending on the origin of the collagen itself. Parts of the population that can be especially affected by fish collagen are persons that are allergic to fish. However, no studies were found that investigated the sensitisation in the general population.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not genotoxic / mutagenic
Additional information:
The induction of chromosomal aberrations was studied in CHL/IU cells (a cell line consisting of fibroblasts derived from the lungs of newborn female Chinese hamsters) exposed to fish collagen (produced by solubilized tilapia skin) at concentrations of 1.3, 2.5 and 5 µl/ml for a short treatment (time not indicated) with and without metabolic activation, and for 24 hours without metabolic activation (chromosomal aberration test ISO 10993-3:2003) (Yamamoto et al., 2014). There were no significant differences in structural or numerical chromosomal aberrations between treatment groups and control.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

Collagen and gelatin are proteins of variable solubility that will be partly absorbed from the gastrointestinal tract after digestion. Collagen and gelatin hydrolysate are processed forms, which are more water-soluble. Used as a nutritional supplement, the role of the gelatin will mainly be as a supply of amino acids. Most amino acids in collagen may be used in protein synthesis. This is not the case for hydroxyproline which is a non-proteinogenic amino acid produced from proline after incorporation into a peptide chain by post-translational hydroxylation. Most dietary hydroxyproline appears to be absorbed in small peptides by the so-called IMINO system transporters (Broer et al., 2009). Absorbed hydroxyproline will be oxidized in the body after conversion to glycine and pyruvate (Wu et al., 2011).
No human or animal studies on metabolism and excretion of collagen, gelatin or collagen/gelatin hydrolysates from fish were found. However, as collagen and gelatin are proteins of variable solubility that will be partly absorbed from the gastrointestinal tract, it is anticipated that the absorbed parts will become building blocks of new proteins in the body.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Absorption, distribution, metabolism and excretion (ADME)
To measure the absorption of the collagen hydrolysate from cod skin, the concentration of hydroxyproline-containing peptides in human blood was determined after ingestion of the collagen hydrolysate (Shigemura et al., 2014). Healthy volunteers (two females and two males, average age 27 years) fasted for 12 hours before ingesting 30.8, 153.8 and 384.6 mg/kg bw of collagen hydrolysate dissolved in 100 ml of water (that is 2, 10 and 25 g for a 65 kg person). All four volunteers ingested the three different doses of collagen hydrolysate with a week-long washout between the ingestions. Approximately 10 ml blood was collected from each participant before and 15, 30, 60, 120, 240 and 360 min after ingestion. The hydroxyproline-containing peptide levels in human plasma were measured. A dosedependent increase of free hydroxyproline in plasma was found after ingestion of collagen hydrolysate. The quantity and structures of food-derived gelatin hydrolysates in human blood from three sources of type I collagen were compared by Ohara et al. (2007) in a single-blind crossover study. Five healthy male volunteers ingested type I gelatin hydrolysates from fish scale, fish skin or porcine skin after 12 hours of fasting. Amounts of free form hydroxyproline and hydroxyproline-containing peptide were measured over a period of 24 hours. Hydroxyprolinecontaining peptides comprised approximately 30% of all detected hydroxyproline. For free form hydroxyproline and for hydroxyproline-containing peptide, the AUC0-24 h varied in order of fish scale gelatin hydrolysate ≥ porcine skin gelatin hydrolysate ≥ fish skin gelatin hydrolysate. Proline-hydroxyproline was a major constituent of hydroxyproline-containing peptides. The quantity and structure of hydroxyproline-containing peptides in human blood after oral administration of gelatin hydrolysate depended on the gelatin source.

BIBLIOGRAPHY

- MSDS
-TOXNET database on toxicology

- ECHA database on REACH registered substances
- CIR Cosmetic Ingredients Review
- VKM Report 2016:65

DIMETHICONE (CAS: 63148-62-9 / 9006-65-9 / 9016-00-6)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

1000 -- - CIR, https://www.cir-safety.org/sites/default/files/FAR_Methicones_032022.pdf

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat)> 2000 mg/kg bw
LD50 dermal (rat) > 2008 mg/kg bw
LD50 dermal (rabbit)> 2000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

Slightly irritatant
Additional information:
Three rabbits and 3 guinea pigs were exposed to non-occlusive, daily applications of 0.5 ml of Dimethicone (100 cm2 /s; dynamic viscosity or specific gravity values were not provided) to a 2.5 cm2 patch of closely shaven skin for 10 d. No erythema or signs of skin irritation or inflammation were noted in the animals. In an acute dermal toxicity study, undiluted, Dimethicone (57,000 kg/m□s) was applied to the shaved backs of 5 male and 5 female adult New Zealand White rabbits, under occlusion, for 24 h, at a dose of 2000 mg/kg bw. Erythema was observed at the application site in all 10 rabbits, but resolved by the 7th day of observation.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

mild to minimal irritant
Additional information:
Most ocular irritation studies using rabbits classified Dimethicone, ranging in concentration from 10% to 35%, as a mild to minimal irritant. The most common finding was a conjunctival reaction. However, instillation of 0.005 ml 15% Dimethicone produced minor to moderate conjunctival irritation in all 6 rabbits; the irritation cleared in 5 of the 6 rabbits within 72 h. Additionally, a few studies reported conjunctival reactions, chemosis, and persisting redness, especially when the eyes were unrinsed. Similar to Dimethicone, Methicone and Vinyl Dimethicone also produced conjunctival reactions.

SKIN SENSITISATION

not sensitizer
Additional information:
Dimethicone (tested undiluted and at 79%) was not a sensitizer in 4 assays using mice and guinea pigs. It was not a sensitizer at 5.0% in a clinical HRIPT using 83 subjects

DERMAL/PERCUTANEOUS ABSORPTION

Penetration of Dimethicone (9.5 kg/m□s and 332.5 kg/m□s) was examined in female human abdominal skin and vaginal tissue. Both viscosities were applied in infinite doses for 96 h to the donor side of split-thickness human abdominal skin sections (reference standard) and full-thickness human vaginal tissue mounted in Franz in vitro diffusion cells. (The identification of the vehicle and receptor fluid was not provided.) The dermal flux rate for Dimethicone (332.5 kg/m□s) in abdominal skin was 0.3 ng/cm2/h, compared to 2 ng/cm2/h for vaginal tissue; while the flux rates for Dimethicone (9.5 kg/m□s) in abdominal skin were 0.2 ng/cm2/h and 6 ng/cm2/h for vaginal tissue. The authors concluded that there was a low penetration rate, which occurred more rapidly in vaginal tissue, for both viscosities. In a dermal penetration study, the authors sought to determine if Dimethicone interacts with and alters the stratum corneum lipid microstructure. Excised human stratum corneum tissue samples were obtained from the inner thigh of a healthy 50 yr-old woman and the abdomen of a healthy 26 yr-old man. An in vitro model lipid system containing stratum corneum fatty acids was also used to mimic the skin barrier. These tissue samples were rinsed with 0.001% m/m trypsin inhibitor and stored for 48 h in 76% humidity, at ambient temperature, to achieve an approximately 20% hydration level. The hydrated samples were then treated for 20 min in various viscosities of excess Dimethicone (332.5, 475, 950, or 19,000 kg/m□s) at 37 ºC, removed with a cellulose tissue, and analyzed for change using thermal profile, x-ray diffraction, polarized light microscopy, and transmission electron microscopy. All results indicated that Dimethicone did not disturb or interact with the liquid crystalline structure of the upper layer of the epidermis, and hence is not likely to penetrate the skin barrier.

MUTAGENESIS / GENOTOXICITY

not genototxic / mutagenic
Additional information:
Dimethicone tested negative for genotoxic effects in multiple Ames tests, at up to 5000 µg/plate, bacterial reverse mutation assays, at up to 79% in formulation, micronucleus tests, at up to 5 g/kg, and in mouse cell and Chinese hamster ovary (CHO) assays, at up to 10,000 µg/ml, both with and without metabolic activation.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CARCINOGENICITY

not carcirogenic
Additional information:
Dimethicone was negative for carcinogenicity in both an oral (up to 2.5% Dimethicone in diet for 76 wk) and a dermal carcinogenicity study (lifetime application; 50 µl of the test article (motor oil) that contained an unspecified amount of Dimethicone) using mice. One treated mouse in the dermal study had a palpable skin mass at the application site during wk 65, which regressed by wk 67; no application site dermal neoplasms were microscopically confirmed in either treated or control mice.

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
Dimethicone was tested in numerous oral-dose (using rats) and dermal-dose (using rats, rabbits, monkeys) reproductive and developmental toxicity studies. In an oral study with rats, 3.3 ml/kg/d Dimethicone was administered directly to the stomach for 6 d. Males treated with 1 of 3 Dimethicone samples (no further details provided) had significantly decreased body weight and/or decreased testes or seminal vesicles weights. No treatment-related adverse findings were noted in pregnant females or fetuses, dosed orally, via diet, and dermally. In an intergenerational study, a motor oil containing an unspecified amount of Dimethicone was applied undiluted in doses of 0.1, 0.4, and 1.5 ml/kg, to the shaved backs of the parental (P1) and first generation (F1) of Sprague-Dawley rats, daily for an 8-wk premating period, 3-wk mating period, and throughout gestation and lactation. No statistically significant differences in mortality or survival rates were seen in F1 rats on day 0 (parturition), however, mortality after parturition was significantly decreased in the 0.4 and 1.5-ml/kg groups. Conversely, mortality in the F2 litter was significantly increased in the 0.4 ml/kg group on day 0. Absolute testes weights significantly reduced in the adult F1 male rats of the 1.5 ml/kg group, beginning wk 7, but the relative testes to body weight ratio was not significantly different from controls

TOXICOKINETIC (ADME studies)

Several acute pharmacokinetic studies in dogs, rats, and a monkey reported minimal gastrointestinal absorption of Dimethicone and up to 99.99% recovery of the administered dose via excretion.1 In a dose study, beagle dogs were fed 91% Dimethicone at a dose of 300 mg/kg/d for 120 d in the diet. Although one female showed atrophy of the spleen, and another female had slightly reddened rugae near the stomach and mucus in the intestine, Dimethicone was not detected in any organs or considered absorbed.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

In human studies, absorption was seen in humans following ingestion of a Dimethicone sample containing lowmolecular-weight polymers. Dermal upper back exposure to Dimethicone for 10 d did not increase blood or urine silicone concentrations in men

In a human repeated insult patch test (HRIPT), Dimethicone (11,875 kg/m□s) was tested neat as a negative control, and was used as a vehicle for a 5% (v/v) solution of an unspecified test substance. Sodium lauryl sulfate (0.1% aqueous solution) was used as a positive control. Of the 115 subjects enrolled, 106 completed the study; no subjects withdrew due to adverse reactions to the test substance. Induction consisted of 9 consecutive applications, where 0.2 ml of Dimethicone was applied under a semi-occlusive dressing for 24 h. The test sites were evaluated in the following 48 - 72 h. After the 9th application, there was a 10 to 15-d non-treatment period. Challenge occurred in the sixth week of the study; the substance was applied to an unexposed site for 24 h, and graded after 24 - 48 h. No evidence of sensitization to Dimethicone, as a control or vehicle, was observed.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EMA, European Medical Agency

ETHYLHEXYLGLYCERIN (CAS: 70445-33-9)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

100 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/16725/7/6/2

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 2 000 mg/kg bw
LD50 dermal (rat) > 2 000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

moderate irritant

MUCOSAE IRRITATION AND CORROSION (eye irritation)

According CLP regulation: H318: Causes serious eye damage

SKIN SENSITISATION

not sensitizer

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not genotoxic / mutagenic according in vitro gene mutation study in bacteria: S. typhimurium TA 1535, TA 1537, TA 98 and TA 100

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not toxic reproductive
NOEL 50 mg/kg bw/day

Teratogenecy: not determinable due to absence of adverse toxic effects

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

EUGENIA CARYOPHYLLUS BUD OIL (CAS: 84961-50-2)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

1000 -- - https://pmc.ncbi.nlm.nih.gov/articles/PMC5615916/

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) 5000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

no data

MUCOSAE IRRITATION AND CORROSION (eye irritation)

H319: Causes serious eye irritation.

SKIN SENSITISATION

H317: May cause an allergic skin reaction.

DERMAL/PERCUTANEOUS ABSORPTION

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
Mutagenicity studies employing Salmonella typhimurium strains. Clovinol did not show genotoxicity when tested on TA-98, TA-100 and TA-102 with or without metabolic activation; rather exhibited significant antimutagenic potential against the known mutagens, sodium azide, NPD and tobacco as well as against 2-acetamidoflourene, which needed metabolic activation for mutagenicity.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA European Chemical Agency

EUGENOL (CAS: 97-53-0)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

300 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/13694/7/6/1

Weight-of-evidence NOAEL = 300 mg/kg bw/d (Chronic study, rats, Rel.2)

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (mouse)1,500 - 3,000 mg/kg bw
LC50 inhalation (rat) > 5 mg/L
Additional information:
In a single dose oral toxicity study, groups of five male and five female mice were administered 180 to 3,000 mg/kg body weight of eugenol in 1% solution of carboxymethylcellulose in saline by gavage. One male mouse in the 750 mg/kg body weight dose group died and two of the five male mice and all five female mice in the 3,000 mg/kg body weight dose group died.
The acute toxicity of inhaled eugenol was investigated in groups of five male and five female rats per test concentration of 0, 0.77, 1.37, or 2.58 mg/L for 4 hours in an exposure chamber, followed by 14 days of observation. Control and low dose rats showed no changes. Some intermediate-dose rats showed temporary wet snouts and red-brown staining of the fur immediately after dosing. Temporary, readily reversible signs of toxicity were noted, including irregular breathing (gasping), lethargy, overnight weight loss and overnight reduced food and water intake, after inhalation of eugenol at a concentration of 2.58 mg/L; however, there were no deaths and no evidence of blood in the respiratory tract. The rats were normal in all respects within 48h. Histophathological examination of the lungs after the 14-day observation period was normal. The acute LD50 was reported to be >2.6 mg eugenol/L air. Taken altogether, these findings suggest that eugenol would have a 4-hour LC50 of greater than 5 mg/L.

SKIN IRRITATION AND CORROSIVITY

not classified as skin irritan / corrosive
Additional information:
The potential for skin irritation from dermal exposure to eugenol (4 hours, semi-occluded conditions, undiluted test material) was assessed in female rabbits. The average scores calculated from the numerical values given for the irritation observed at the 24-, 48- and 72-hour observations were 1.9 for erythema and 1.0 for oedema. As the mean value obtained for both erythema and edema was less than two, it was concluded that the test material is considered not to be an irritant.
Based on the results, eugenol has a mean value of <2.3 for erythema or for oedema for all 4 animals from gradings at 24, 48, and 72 hours. While the recovery period did not extend to 14 days, there were signs of recovery after 7 days in 3 out of 4 animals; only 1 out of 4 animals had signs of continued irritation and slight scaling after 7 days. There was no sign of pronounced variability in the response among the animals.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

irritant for eyes Category II
Additional information:
The potential for eye irritation following exposure to eugenol was assessed in 6 female rabbits (0.1 mL of undiluted eugenol). Observations were carried out at regular intervals over 7 days following exposure. Eugenol appeared to affect the rabbit eyes 1 day following application; however, the effects were reversible as the eye irritation grades decreased over the 7-day observation period.
This eye irritation information for eugenol is based on the standard Draize scale which has an overall score based on a 110 point rating scale. This rating scale is not directly compatible with Regulation (EC) No 1272/2008, Annex I section 3.3 classification criteria. However, based on guidance from various agencies, eugenol appears to be severely irritating in the first 24 hours post-exposure, moderately to mildly irritating after 24 and 72 hours post-exposure, and practically non-irritating after 7 days post-exposure.

SKIN SENSITISATION

sensitising
Additional information:
Eugenol demonstrated evidence of skin sensitization potential in mice in a key and supporting local lymph node assay (LLNA) at concentrations of ≥ 10% (Takeyoshi et al., 2004; Lalko and Api, 2006). In addition, a guinea pig maximization test indicated that eugenol was mildly sensitizing at a concentration of 5% (Takeyoshi et al., 2004).

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

no adverse effect observed (negative)
Additional information:
The potential of eugenol to cause genotoxicity was investigated in 3 key studies(1 in vitro and 2 in vivo) including 1 bacterial reverse mutation assays, 1 mammalian chromosome aberration test and 1 mammalian gene mutation assay. These three studies meet the minimum genotoxicity data requirements for this substance. In addition a number of in vitro and in vivo supporting assays are included in the evaluation. All of the key and supporting studies provided negative results. Several in vitro and in vivo studies were evaluated as unreliable and were disregarded; these studies presented a mix of negative and positive results, as claimed by the authors. However, all of these studies suffered from serious technical and reporting deficiencies and in some cases the results and conclusions were clearly contradicted by the more reliable studies.

For Annex VII section 8.4.1, in a key study and two supporting studies eugenol did not increase the reverse mutation rate when tested in various bacterial strains (including, but not limited to, Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 and Escherichia coli strain WP2uvrA) either in the presence and/or absence of an externally-added metabolic activating system (S9).

For Annex VIII section 8.4.2 there is no key study for the in vitro cytogenicity endpoint. The available in vitro studies were considered unreliable, primarily because the dose levels used were too high, which is a major deviation from the relevant test guidelines in terms of dose setting, and caused excessive toxicity, and consequently they were disregarded. However, using a column 2 adaptation the in vitro data are not required if adequate data from an in vivo cytogenicity test are available. In this case there is a key oral gavage micronucleus study that is supported by six other studies of reliability grade 2, all of which provided negative results. These studies include micronucleus studies using the oral gavage, intraperitonel, and oral capsule dose routes, and a chromosome aberration study using oral capsules. A study waiver was included for the genetic toxicity in vitro cytogenicity endpoint.

For Annex VIII section 8.4.3, there is no key study for the in vitro mutagenicity endpoint. However, using a column 2 adaptation the in vitro data are not required if adequate data from an in vivo mutagenicity test are available. In this case there is a key mouse transgenic assay that is supported by a TEGA assay. These studies all provided negative results. A study waiver was included for the genetic toxicity in vitro gene mutation endpoint.
The conclusion regarding the genotoxic potential of eugenol has taken into account that:
-Studies of the metabolism of eugenol indicate rapid metabolism; any formation of putative reactive metabolites would be followed by Phase II conjugation reactions leading to rapid detoxification (JECFA, 2006a, b).
-In vivo studies showed no evidence of DNA binding by eugenol. While study results were mixed, some data suggest that eugenol or the purported eugenol metabolites eugenol quinone methide and hydroxychavicol may bind to DNA in vitro (Bodell et al.,1998; Sakano et al.,2004); however, in vivo mouse studies all produced negative results (Phillips et al.,1984; Phillips, 1990). Moreover, while O-demethylation has been reported in rats (Sutton et al.,1985), the metabolism of eugenol does not result in the formation of the

hydroxychavicol metabolite and in vivo studies in humans have indicated that the methoxy group of eugenol is resistant to cleavage in man (Fischer et al.,1990). The lack of adduct detection in the in vivo test systems is likely due to the presence of detoxification processes (i.e.,glutathione conjugation), which are likely not present to a significant extent in the in vitro test systems. These processes either conjugate parent eugenol or neutralize the oxidative metabolites that may be generated by microsomal metabolism.
-Eugenol shows no structural alerts for genotoxicity.
-Structural analogues of eugenol have also provided some data erroneously reported as positive. For example, Isoeugenol is reported as negative in the Ames bacterial mutation assay, negative in the CHO chromosome aberration test in vitro, negative in male mice in a micronucleus test but positive in female mice of the same study. However, it is clear from the data that this is a statistical correlation only, caused by a particularly low value in the female vehicle control group. When historical control data are included in the evaluation of the result then the study is clearly negative in both sexes. (NTP technical Report 551, 2010). It is considered therefore, that the data for eugenol are most relevant in the evaluation of the genotoxic potential of this substance and reference to any of the analogues raises questions about the reliability of the studies on those analogues. In particular it is considered that methyl eugenol is not a relevant analogue because of the difference in its metabolic pathway.
In summary, all of the reliable and relevant in vitro and in vivo genotoxicity studies show no evidence of genotoxic potential for eugenol.
The lack of genotoxicity is consistent with the finding of no substantive carcinogenic activity in mouse and rat oral bioassays, as reported by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2006b) and the European Food Safety Authority (EFSA, 2009).

CARCINOGENICITY

not carcirogenic
Additional information:
The carcinogenic potential of eugenol was evaluated in key studies in male and female B6C3F1 mice and male and female F344/N rats (NTP, 1983) and in a supporting study in female CD-1 mice (Miller et al., 1983). In rats, there was no evidence of carcinogenicity in either male or females compared to Controls. In the key mouse study, dietary eugenol at concentrations of 0 (control), 3,000, or 6,000 ppm for 103 weeks resulted in a dose-dependent increase in the incidence of hepatocellular adenomas and carcinomas (combined; statistically significant at the high-dose in females); however, eugenol is concluded not to be carcinogenic in mice, based on a number of considerations including a lack of a dose-response relationship in the increase in hepatocellular tumours in male mice and high and variable incidences of adenomas or carcinomas (combined) within the historical range for B6C3F1 mice. In the key rat study, dietary administration of eugenol at concentrations of 0 (control), 3,000, or 6,000 ppm in males and 0 (control), 6,000, or 12,500 ppm in females did not result in an increase in tumour incidence in either males or females. In the supporting mouse study, dietary administration of 0.5% eugenol did not result in an increase in the incidence of hepatic tumors through the 20-month dosing period.
IARC Monographs, Volume 36, reports that no cell transformation data are available on eugenol.
No inhalation or dermal carcinogenicity studies have been conducted.

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
2-generation study on Isoeugenol (similar to OECD 416, GLP, Rel. 2, K):
- NOAEL fertility ≥ 700 mg/kg bw/day.
- NOAEL development ≥ 230 mg/kg bw/day / LOAEL = 700 mg/kg bw/day, as a worst-case based on decreased male and female F2 pup weights.
- LOAEL parental toxicity ≤ 70 mg/kg bw/day, based on decreased body weight gains at all dose-levels, although probably linked to the bolus effect.
Developmental toxicity study on Isoeugenol (similar to OECD 414, GLP, Rel. 2, K):
- LOAEL maternal toxicity = 250 mg/kg bw/day, based on dose-dependent reduced body weight gain.
- NOAEL developmental toxicity = 500 mg/ kg bw/day, based on intra-uterine growth retardations mildly delayed skeletal ossification observed at 1000 mg/kg bw/day. However, this finding is likely secondary to maternal toxicity and not indicative of a teratogenic effect.

TOXICOKINETIC (ADME studies)

Eugenol is expected to be absorbed via the oral, dermal, and inhalation routes; eugenol is rapidly distributed to various organs including (but not limited to) the small and large intestines, kidneys, liver, adrenal gland, stomach, and brain. Eugenol is rapidly metabolised primarily via phase-II conjugation, to form glucuronide and sulphate conjugates. The major route of elimination is the urine.
no bioaccumulation potential

Specific investigations: other studies
A computational network model that integrates 18 in vitro, high-throughput screening assays measuring estrogen receptor (ER) binding, dimerization, chromatin binding, transcriptional activation, and ER-dependent cell proliferation. The network model uses activity patterns across the in vitro assays to predict whether a chemical is an ER agonist or antagonist, or is otherwise influencing the assays through a manner dependent on the physics and chemistry of the technology platform (“assay interference”).
The chemical structure of eugenol was investigated in the Derek Nexus (Q)SAR system for potential structural alerts for oestrogenicity and thyroid toxicity. In both cases the prediction was negative and it is concluded that eugenol does not have a potential for endocrine disruption.
A validated (standardized) estrogen receptor (ER) competitive-binding assay was used to determine the ER affinity for Eugenol. Uteri from ovariectomized Sprague-Dawley rats were the ER source for the competitive-binding assay. Eugenol was demonstrated to have no binding affinity for the estrogen receptor.
A two-generation reproductive toxicity study on a read-across substance (isoeugenol) showed no effects on any other reproductive parameters throughout both generations. Sperm parameters and vaginal cytology were unchanged in the F0 and F1 generations.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

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RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

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RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

EUGENYL ACETATE (CAS: 93-28-7)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

230 -- - NOAEL for reproductive was considered to be 230 mg/kg/day, based on a decreased number of male pups per litter during the F0 cohabitation and decreased male and female pup weights during the F1 cohabitation among high-dose group animals (NTP, 2002; Layton et al., 2001).

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) 1670 mg/kg bw
LD50 dermal (rabbit) > 5 000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

Under the experimental conditions of this study, the test substance is not classified for skin irritation according to Regulation (EC) No. 1272/2008 (CLP) and to the GHS.
Additional information:
An in vitro skin irritation study was performed according to the OECD Guideline 439 and in compliance with GLP, using the EPISKINTM reconstructed human epidermis model.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

Under the test conditions, no prediction can be made for the test substance according to the Annex VI of Regulation (EC) No. 1272/2008 (CLP) and to the GHS.
Additional information:
An in vitro eye irritation study was performed according to the OECD Guideline 438 and in compliance with GLP to evaluate the possible ocular corrosive or severe irritating effects of the test item after administration on enucleated chicken eyes.
This study is considered as acceptable and satisfies the requirement for in vitro eye irritation endpoint.

SKIN SENSITISATION

Sensitizer
Additional information:
In vivo: skin sensitizer Cat. 1B (WoE - LLNA, OECD 429, GLP, Rel. 2)
QSAR: Skin sensitiser Cat. 1B (WoE - QSAR models, rel.2)

DERMAL/PERCUTANEOUS ABSORPTION

Under the test condition, penetration of test material through excised human epidermis after 72 h was found to be 0.092 ± 0.017 %. Also, high correlation between water solubility and percentage penetration through human epidermis of test material was observed. However due to significant methodological deficiencies, it is considered that the absolute penetration level may not be accurate.

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
- Ames Test (OECD 471, GLP, K, rel. 1): non mutagenic up to limit concentration in S. typhimurium TA 1535, TA 1537, TA 98, TA 100 & E.coli WP2uvrA.
- Unscheduled DNA synthesis assay (OECD 482, GLP, K, rel.2) : no induction of UDS in rats hepatocytes.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not classified as toxic to reproductive
Additional information:
NOAEL for reproductive was considered to be 230 mg/kg/day, based on a decreased number of male pups per litter during the F0 cohabitation and decreased male and female pup weights during the F1 cohabitation among high-dose group animals (NTP, 2002; Layton et al., 2001).

TOXICOKINETIC (ADME studies)

A study was performed to quantify the rate of hydrolysis of eugenyl acetate in rat skin cytosol, rat skin microsomes, rat hepatic S-9, rat hepatic microsomes and human microsomes (male and female). Eugenyl acetate (500 µM) was incubated with microsomal protein (0.0125 mg/mL for microsomes and 0.1 mg/mL for S-9 fraction for 3 minutes) and skin protein (0.0375 mg/mL for microsomes and 0.1 mg/mL for cytosol for 15 minutes) at 37 °C. Kinetic constants Vmax, Km and CLint (defined as the Vmax/Km ratio) were determined by HPLC.
Incubation of isoeugenyl acetate (500 µM) with microsomal protein (0.0125 mg/mL) revealed that hydrolysis was complete within approximately 20 minutes of incubation. Kinetic analysis of the hydrolytic reaction in hepatic microsomes (39 -970 µM, 3 minutes incubation) yielded Vmax (nmol/minute/mg of protein): 3829 (rat), 3656 (human male) and 2748 (human female); Km (µM): 97 (rat), 89 (human male) and 52 (human female); and CLint (mL/minute): 39.6 (rat), 41.3 (human male) and 52.9 (human female). Preliminary results demonstrated that rat plasma and preparations of rat skin also readily hydrolyse eugenyl acetate into eugenol. Kinetic analysis of the hydrolytic reaction in rat skin microsomes and cytosol (39 -970 µM, 15 minutes incubation) yielded Vmax (nmol/minute/mg of protein): 114 (skin cytosol) and 505 (skin microsomes); Km (µM): 216 (skin cytosol) and 223 (skin microsomes) and CLint (mL/minute): 0.5 (skin cytosol) and 2.9 (skin microsomes). Kinetic analysis of the hydrolytic reaction in rat hepatic S-9 fraction (39 -970 µM, 3 minutes incubation) yielded Vmax = 60 nmol/minute/mg of protein, Km: 173 µM and CLint = 0.4 mL/minute.
Under the test conditions, eugenyl acetate was rapidly hydrolysed by liver, plasma and skin esterases to the corresponding alcohol, eugenol. The most extensive activity of the esterases was observed in the hepatic microsomal fraction. There was stoichiometric conversion to eugenol of hepatic, blood and skin preparations incubated with the test material. The most extensive activity was observed in the hepatic microsomal fraction. Slow rate of hydrolysis of esters in skin correlates with their decreased sensitization potential. Under the conditions of this study, test material absorption into the systemic circulation would be minimal following dermal or oral exposure. Rapid hydrolytic conversion by enzymes in the liver, blood and skin, as well as in the intestinal fluid and intestinal cells, would limit systemic exposure to the parent molecules.

PHOTOINDUCED TOXICITY

not induce photo toxicity
Additional information:
Based on available UV/Vis spectra, eugenyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity. UV/Vis absorption spectra (OECD TG 101) for eugenyl acetate were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol− 1 · cm− 1 (Henry et al., 2009).

DATA ON MAN

no data

BIBLIOGRAPHY

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- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
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GLUCOSAMINE SULFATE (CAS: 29031-19-4)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

2149 -- - https://cot.food.gov.uk/sites/default/files/cot/tox200826.pdf

Additional information:
A NOAEL of 2700 mg/kw bw was reported in rats given glucosamine sulphate for 52 weeks. The NOAEL in dogs given glucosamine for 26 weeks was 2149 mg/kg bw/day (Setnikar et al, 1991).

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 8000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

not classified as skin irritant

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not classified as eye irritant

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

Skin permeation of Glucosamine Sulfate was evaluated in Sprague-Dawley full-thickness rat skin. Freshly excised rat skin was mounted between the donor and receptor cell (area of diffusion was 2.14 cm2). Donor cells, facing the stratum corneum surface, contained 5% Glucosamine Sulfate aqueous solution (3 ml). Receptor cells, which faced the dermis side, were filled with normal saline solution (12 ml). At predetermined time intervals, 0.5 mL of the receptor solution was withdrawn and refilled with the same volume of fresh receptor solution. Samples were analyzed by HPLC. The skin permeation rate (amount recovered in receptor fluid) was determined to be 13.27 µg/cm2 /h.

MUTAGENESIS / GENOTOXICITY

no data

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

Blood levels, tissue distribution, and excretion patterns of radioactivity were studied in Sprague-Dawley rats (44 rats/ sex) after oral administration of Glucosamine HCl diluted with unlabeled Glucosamine Sulfate (dose not reported). Plasma, urine, feces, blood, and organs/tissues were evaluated for radiolabel concentrations. At 1 - 2 h after administration, Glucosamine radioactivity was bound to or incorporated into plasma proteins. After peaking at 2 - 4 h, radioactivity declined from plasma at a slower rate (t1/2 = 46 h). Approximately half of the radioactivity was excreted as [14C]carbon dioxide, and 40% of the radioactivity was excreted in the urine. Only 2% of the administered dose was excreted in feces. Radioactivity analysis in tissues and organs revealed that the from the labeled Glucosamine quickly entered into all tissues, included cartilage, reaching a maximum at 8 h.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

The penetration
The penetration of a 10% Glucosamine Sulfate cream into the synovial fluid of patients with knee osteoarthritis (134 subjects/group) was evalauted. For treated groups, cream (2 g) was placed on the knee, for 1-3 h, followed by synovial fluid collection. A control group was not subjected to any treatment, but their synovial fluid was collected. Synovial fluid from both treated and control groups was evaluated for Glucosamine concentrations via HPLC. The mean Glucosamine concentrations in treated and control patients were 100.56 ng/ml and 17.83 ng/ml, respectively ($p < 0.0001$).
ADME
The pharmacokinetics of Glucosamine after oral administration of crystalline Glucosamine Sulfate and Glucosamine HCl were evaluated in 12 healthy volunteers (5 male and 7 female). 25 Volunteers received once-daily, oral administrations of crystalline Glucosamine Sulfate soluble powder at a dose of 1500 mg, or Glucosamine HCl capsules at a dose of 500 mg, for 3 consecutive days, alone, or in combination with chondroitin sulfate (400 mg). Glucosamine was determined at steady state in plasma collected up to 48 h after the last dose by a validated LC-MS/MS method. After Glucosamine Sulfate administration, peak concentrations (Css, max) and extent of exposure (AUCss) averaged 9.1 ± 6.3 μM and 76.5 ± 23.0 μM/h, respectively. Significantly lower plasma concentrations ($p \leq 0.005$) were determined after the administration of Glucosamine HCl alone (Css, max and AUCss averaged 4.5 ± 1.8 μM and 21.4 ± 7.6 μM/h, respectively), or in combination with chondroitin sulfate (Css, max and AUCss averaged 3.3 ± 1.0 μM and 13.8 ± 5.4 μM/h, respectively).
CLINICAL STUDIES Case Reports
A 76-yr-old woman with arterial hypertension and osteoarthritis was referred for evaluation after an episode of urticaria after drug intake. The patient was prescribed Glucosamine Sulfate for osteoarthritis, and suffered from erythematous lesions and facial swelling within several hours after Glucosamine Sulfate intake. The following day, 5 min after a new dose, the patient developed tongue, facial, and throat swelling with facial erythema. She was treated in the emergency department with antihistamines and corticosteroids. Symptoms resolved within 4 h. After a washout period, a skin prick test and intradermal test with Glucosamine Sulfate was performed. The skin prick test yielded negative results, however, the intradermal test (concentration of 1.5 mg/ml) yielded positive results with a papule of 35 mm2 . The intradermal test in 10 healthy volunteers was negative.
RISK ASSESSMENT Glucosamine Sulfate:
The Norwegian Food Safety Authority calculated margin of safety (MoS) values for the use of 10% Glucosamine Sulfate in a body lotion, leg cream, and face cream, and from overall exposure from cosmetics. These values were calculated assuming 100% dermal absorption, a NOAEL value of 430 mg/kg/d, and a calculated relative daily exposure of 123.20, 43.50, and 24.13 mg/kg bw/d, for the body lotion, leg cream, and face cream, respectively.

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EFSA, European Food Safety Agency

GLYCERIN (CAS: 56-81-5)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

10000 -- - European Chemical Agency ECHA.EU https://echa.europa.eu/registration-dossier/-/registered-dossier/14481/7/6/1

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

LD50 (oral) rat 27,200 mg/kg
Results for natural and synthetic glycerine were comparable with an oral LD50 of 27,200 mg/kg.
LC50 (inhalation) rat 5.85 mg/L
LD50 (dermal) guinea pigs 56,750 mg/kg

SKIN IRRITATION AND CORROSIVITY

A round-robin testing program was conducted in 14 laboratories. The dermal irritation potential was examined. Glycerin was considered to be non irritating to the skin in rabbit irritation studies in 14 testing laboratories.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

A round-robin testing program was conducted in 20 laboratories. The eye irritation potential was examined.

Based on the results obtained from 20 different testing laboratories, glycerin was considered to be nonirritating in 19 laboratories and of questionable irritation in one laboratory.

SKIN SENSITISATION

Glycerol failed to provoke an SI of 3 or more at any test concentration examined, despite employing relatively high doses of material (maximum concentration 100%) and is thus considered to be non-sensitising.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

In the available evaluations performed by official bodies (OECD 2002, EFSA 2017) a number of additional genotoxicity toxicity studies were evaluated and summarised. The overall conclusion was that there is no in-vitro or in-vivo data that indicates glycerol to have a genotoxic potential.

EFSA conclusion: Glycerol did not show any genotoxic activity in different in vitro assays, which include negative results in the bacterial reverse mutation assay (Ames test), in chromosome aberration assays and in studies on DNA damage in mammalian cells. Questionable results obtained in a HGPRT gene mutation assay did not show a dose–response effect and were therefore judged of no biological significance. A lack of valid in vivo genotoxicity data was not of concern since clear negative findings were observed in in vitro assays. On this basis, the Panel considered that glycerol as a food additive did not raise concern with respect to genotoxicity.

OECD conclusion: There are no structural alerts (expert judgement) which raise concern for the inherent mutagenic potential of glycerol. In vitro, glycerol was negative (with and without metabolic activation) in Ames tests and did not induce chromosomal effects in mammalian cells. The responses seen in a limited gene mutation study in mammalian cells are of uncertain biological relevance as the doses were not maximised. Only two in vivo studies are available. A negative result was observed in a chromosome aberration test, and an increase (not statistically significant) in post implantation loss was seen in a rat dominant lethal assay. However, for both assays, the limited details reported and absence of a positive control, mean no reliable conclusions can be drawn from the in vivo data.

Thus, overall, there is no in vitro or in vivo data that indicates glycerol to have a genotoxic potential.

CARCINOGENICITY

There was no indication of a carcinogenic response in rats fed 8000 mg/kg/day glycerol in the diet for 2 years.

REPRODUCTIVE TOXICITY

The study has limitations but there was no evidence of any adverse effects on reproductive parameters.
NOAEL (chronic) rat 2 000 mg/kg bw/day
There is no evidence of a developmental toxicity effect in rats, mice and rabbits. The highest dose levels ranged from 1180 mg/kg/day in rabbits to 1310 mg/kg/day in rats.

TOXICOKINETIC (ADME studies)

Glycerol is considered a primordial biomolecule found in all species of living organisms. It is a building block for lipid synthesis and one of the end products of lipid metabolism. Glycerol is also one of the degradation products of glucose metabolism.
Reliable information about toxicokinetics is available from literature and was evaluated and summarised by the OECD (SIDS Initial Assessment Report 2002) and EFSA (Re-evaluation of glycerol (E 422) as a food additive 2017). There was no new relevant information identified up to and including 2021 (most recent literature research).

PHOTOINDUCED TOXICITY

not phototoxic

DATA ON MAN

In a study of 420 patients with eczema, 419 showed no irritation or sensitization when tested with a 50% solution in water. One individual reportedly was sensitized but the study design does not prove that.
The dermal irritation potential was examined in 33 humans, 30 female and 3 male. Under the conditions of the study, Glycerine USP (25% concentration) exhibited no clinical irritation when tested in humans.

BIBLIOGRAPHY

- European Chemical Agency ECHA.
- FOOD AND DRUG ADMINISTRATION FDA
- Cosmetic Ingredient Review CIR
- Worth Publishers, Inc., 70 Fifth Avenue, New York, NY, 1970

GLYCERYL STEARATE SE (CAS: 11099-07-3)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

1000 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/2133/7/6/1
Additional information:
All available subacute, subchronic and chronic repeated dose toxicity studies resulted in NOAELs ≥ 1000 mg/kg bw/day.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 5 000 mg/kg bw
LD50 dermal (ratl) > 2 000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

not irritating
All available studies on skin and eye irritation showed no irritating potential of the category members.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritating
All available studies on skin and eye irritation showed no irritating potential of the category members.

SKIN SENSITISATION

not sensitising
All available studies showed no skin sensitisation potential of the category members.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
In none of these studies mutagenicity in bacteria could be observed.
In none of these studies clastogenic effects in mammalian cells could be observed.
In none of these studies mutagenicity in mammalian cells could be observed.

CARCINOGENICITY

not carcinogenic
Additional information:
Based on expert judgment, there is no evidence that members of the Glycerides category cause carcinogenicity.

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
Based on the results of the study, the NOAEL for developmental toxicity in male and female rats of the F1 and F2 generation was 1342 and 2262 mg/kg bw/day, respectively. These doses corresponded to a concentration of 25000 ppm of the test substance in the diet.
Overall conclusion fordevelopmental toxicity/teratogenicity
The available data on the developmental toxicity/teratogenicity of Glycerides comprise reproductive/developmental toxicity screening studies (see Toxicity to reproduction) as well as (pre-natal) developmental toxicity studies with category members. Only one study reported foetal effects in rabbits given 4280 mg/kg bw/day of Medium Chain Triglycerides, attributable to maternal toxicity. The substance did not produce any effects in rats at the same dose level and in rabbits given 1000 mg/kg bw/day.
Altogether, no effects on (pre-natal) development were observed in any of studies in rats, rabbits and mice. NOAEL values for (pre-natal) developmental toxicity were all at or well above the currently applied limit dose value of 1000 mg/kg bw/day. Thus, no hazard was identified.
Based on the available data and following the category approach, all members of the Glycerides category are considered to have no toxic effects on intrauterine development.

TOXICOKINETIC (ADME studies)

Bioaccumulation of fatty acids takes place, if their intake exceeds the caloric requirements of the organism.
In the study by St-Pierre (2004) with 12-[1-14C]acetoxy-octadecanoic acid-2,3-diacetoxy-propyl ester (surrogate of Glycerides, castor-oil-mono, hydrogenated, acetates (CAS 736150-63-3), systemic distribution of the radiolabelled material was confirmed in rats. Radioactivity was detected in all tissues and organs sampled (adipose tissue, gastrointestinal tract and content, kidneys and adrenals, liver, thymus and the remaining carcass) with highest levels recovered in the gastrointestinal tract, liver and the remaining carcass. Due to excretion and absorption of the radiolabelled material, the radioactivity content in the gastrointestinal tract decreased rapidly over the course of the study (168 h). This was similar for the radioactivity recovered in liver, whereas the radioactivity found in the carcasses was nearly constant at the selected time points, indicating that the radiolabelled material may have been distributed to other tissues than the ones selected for analyses. Based on the results of this study, no bioaccumulation potential was observed for 12-acetoxy-octadecanoic acid-2,3-diacetoxy-propyl ester.
Metabolism
Glycerol can be metabolised to dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, which can then be incorporated in the standard metabolic pathways of glycolysis and gluconeogenesis. Fatty acids are degraded by mitochondrial β-oxidation which takes place in the most animal tissues and uses an enzyme complex for a series of oxidation and hydration reactions resulting in the cleavage of acetate groups in form of acetyl CoA. The alkyl chain length is thus reduced by 2 carbon atoms in each β-oxidation cycle. The complete oxidation of unsaturated fatty acids such as oleic acid requires an additional isomerisation step. Alternative pathways for oxidation can be found in the liver (ω-oxidation) and the brain (α-oxidation). Thus iso-fatty acids such as isooctadecanoic acid have been found to be activated by acyl coenzyme A synthetase of rat liver homogenates and to be metabolised to a large extent by ω-oxidation. Each two-carbon unit resulting from β-oxidation enters the citric acid cycle as acetyl CoA, through which they are completely oxidized to CO2. Acetate, resulting from hydrolysis of acetylated Glycerides, is readily absorbed and feeds naturally into physiological pathways of the body and can be utilized in oxidative metabolism or in anabolic syntheses (CIR, 1983, 1987; IOM, 2005; Lehninger, 1998; Lippel, 1973; Stryer, 1996; WHO, 1967, 1974, 1975, 2001; Adolph, 1999).
Excretion
As far as Glycerides are not hydrolysed in the gastrointestinal tract, they are excreted in the faeces.
In general, the hydrolysis products glycerol and fatty acids are catabolised entirely by oxidative physiologic pathways ultimately leading to the production of carbon dioxide and water. Glycerol, being a polar molecule can readily be excreted in the urine. Small amounts of ketone bodies resulting from the oxidation of fatty acids are excreted via the urine (Lehninger, 1998; IOM, 2005; Stryer, 1996).
In rats given a single dose of 12-[1-14C]acetoxy-octadecanoic acid-2,3-diacetoxy-propyl ester at 5000 mg/kg bw, the mean total recovery of radioactivity in the excreta of the 72 h period post-dose was 108.5% of the dose (urine, 6.5%; faeces, 24.5%; CO2, 77%; and cage wash, 0.5%). Most of the recovered radioactivity (97.5%) was excreted by 24 h post dose (St-Pierre, 2004). The results thus confirm that Glycerides are mainly excreted as CO2 in the expired air as a result of metabolism.
A detailed reference list is provided in the technical dossier (see IUCLID, section 13) and within the CSR.

PHOTOINDUCED TOXICITY

not phototoxic

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

DATA ON MAN

Medium chain and long chain triglycerides are used in humans for parenteral nutrition.
Well tolerated intravenous concentrations during a 12 hour infusion were found to be 100 mg triglycerides/kg bw/h.

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

HELIANTHUS ANNUUS SEED OIL (CAS: 84776-03-4 / 8001-21-6/ 164250-88-8)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

9250 -- - ECHA, European Chemical Agency. This NOAEL data of Soybean oil, deodorizer distillate which is closest in chemical composition, production technology and properties.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

Not expected to be acutely toxic. Ingestion of a single dose is unlikely to cause harm.

SKIN IRRITATION AND CORROSIVITY

Not expected to be classified as corrosive/irritant to skin

MUCOSAE IRRITATION AND CORROSION (eye irritation)

Not classified as an eye irritant or considered seriously damaging to the eye.

SKIN SENSITISATION

Not expected to be classified as a respiratory sensitizer. Does not demonstrate potential for skin sensitization.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

Not expected to be classified as germ cell mutagenic, carcinogenic nor as a reproductive toxicant. This substance or mixture is not found on the following international and US lists: NTP, IARC, and OSHA.

CARCINOGENICITY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Not expected to be classified as germ cell mutagenic, carcinogenic nor as a reproductive toxicant. This substance or mixture is not found on the following international and US lists: NTP, IARC, and OSHA.

REPRODUCTIVE TOXICITY

Not expected to be classified as germ cell mutagenic, carcinogenic nor as a reproductive toxicant. This substance or mixture is not found on the following international and US lists: NTP, IARC, and OSHA.

TOXICOKINETIC (ADME studies)

SPECIFIC TARGET ORGAN TOXICITY (SINGLE EXPOSURE): Not expected to be classified as a specific target organ toxicant (single exposure). SPECIFIC TARGET ORGAN TOXICITY (REPEATED EXPOSURE): Not expected to be classified as a specific target organ toxicant (repeated exposure). ASPIRATION HAZARD: Not expected to be classified as presenting an aspiration hazard.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

According data of CIR experts HELIANTHUS ANNUUS SEED OIL using on human''s body is safe

BIBLIOGRAPHY

- MSDS
- ECHA, European Chemical Agency
- FDA, Food and Drug Administration
- CIR, Cosmetic Ingredient Review

HIPPOPHAE RHAMNOIDES OIL (CAS: 225234-03-7 / 90106-68-6)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

9220 -- - Regulatory Toxicology and Pharmacology, Volume 91, December 2017, Pages 50-57
Additionl information:
Seabuckthorn (Hippophae rhamnoides L.) has been traditionally used as medicine and nutritional supplement for a long period of time. However, information on the systemic toxicity and safety evaluation of seabuckthorn and its extracts is still scarce. The purpose of this study was to evaluate the potential toxicity of seabuckthorn oil by an acute oral toxicity study in mice and a 90-day repeated oral toxicity study in rats. No mortality or signs of toxicity was observed in mice treated with 20 mL/kg body weight seabuckthorn oil in the acute toxicity study. In the subchronic toxicity study, 80 Sprague-Dawley rats (10 animals per sex per treatment group) were administrated with 10, 5, 2.5 and 0 (control) mL/kg body weight of seabuckthorn oil daily for 90 days by gavage. There were no signs of toxicity and treatment-related changes in rats treated with seabuckthorn oil on mortality, body and organ weights, food consumption, blood biochemistry and hematology, gross necropsy and histopathological examinations. Based on the finding of this study, the maximum tolerated dose of seabuckthorn oil was >20 mL/kg for mice for acute toxicity study, and the no-observed-adverse-effect level was 10 mL/kg body weight for both male and female rats for 90-day toxicity study.
In source NOAEL were done by volume, take to account density which is 0,922 g/cm3, calculation made to mass: m = Vd = 0,922 g/cm3*10 ml = 9,22 g = 9220 mg/kg bw.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

During the 14 day single dose acute toxicity study, no adverse effects were observed in mice treated with 20 mL/kg body weight of seabuckthorn oil.

SKIN IRRITATION AND CORROSIVITY

not irritant
Additional information:
In an acute dermal study albino rabbit were treated by 0,5 ml Hippophae rhamnoides oil for 4 h, after cleaned, no dermal irritation were observed.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritant

SKIN SENSITISATION

not sensitizer

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genototxic

CARCINOGENICITY

not carcirogenic

REPRODUCTIVE TOXICITY

not toxic to reproductive

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

TOXICOKINETIC (ADME studies)

not bioaccumulative
Additional infromation:
Seabuckthorn (Hippophae rhamnoides L.) has been traditionally used as medicine and nutritional supplement for a long period of time.

PHOTOINDUCED TOXICITY

not induce photo toxicity

DATA ON MAN

Seabuckthorn (Hippophae rhamnoides L.) has been traditionally used as medicine and nutritional supplement for a long period of time.

BIBLIOGRAPHY

- Regulatory Toxicology and Pharmacology, Volume 91, December 2017, Pages 50-57
- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

HYDROLYZED COMARUM PALUSTRE ROOT/STEM EXTRACT (CAS:)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

300 -- - Lund and Rimpler, 1985. Earlier studies: Rodewald, 1950

Additional information:
Only few studies have addressed potential toxicity of Potentilla species and their extracts. No signs of acute toxicity could be observed after intraperitoneal and oral application of a Potentilla erecta rhizome extract (prepared with a water–acetone mixture) in doses up to 200 and 300 mg/kg body weight, respectively.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

no data

SKIN IRRITATION AND CORROSIVITY

no data

MUCOSAE IRRITATION AND CORROSION (eye irritation)

no data

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

no data

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EMA, European medical agency
- Journal of Ethnopharmacology: https://hortus-medicus.ch/wp-content/uploads/Potentilla_Rev.pdf

INULA HELENIUM EXTRACT (CAS: 84012-20-4)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

83 -- - ScienceDirect, 2025. https://www.sciencedirect.com/topics/medicine-and-dentistry/elecampane

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

no data

SKIN IRRITATION AND CORROSIVITY

no data

MUCOSAE IRRITATION AND CORROSION (eye irritation)

no data

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

no data

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- ScienceDirect, 2025. https://www.sciencedirect.com/topics/medicine-and-dentistry/elecampane

ISOPROPYL MYRISTATE (CAS: 110-27-0)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

1000 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/16077/7/6/1
Additional information:
Based on a weight of evidence approach, all available subacute and subchronic repeated dose toxicity studies resulted in NOAELs of 1000 mg/kg bw/day or greater.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 2 000 mg/kg bw
Additional information:
In summary, several studies are available studying the acute oral toxicity of SCAE C2-C8 Category members resulting in oral LD50 values greater than 2000 mg/kg bw. For acute inhalation toxicity three studies are available within the SCAE C2-C8 Category. From these studies a LC50 value of > 5 mg/L was determined. Acute dermal toxicity data from two category members consistently showed no effects at the limit dose of 2000 mg/kg bw.
Thus, the available data indicate a very low level of acute toxicity for the category members and thus no hazard for acute oral, inhalative and dermal toxicity was identified.

SKIN IRRITATION AND CORROSIVITY

not irritating
Additional information:
Based on the results of the available animal studies as well as according to the results on human skin, none of the substances within the fatty acid C2-8 ester category is considered skin irritating. Therefore, based on a weight of evidence approach, no classification for skin irritation for all substances within the fatty acid C2-8 esters category is required.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritating
Additional information:
A primary eye irritation study was conducted equivalent to EU Method B.5 with 3 New Zealand White rabbits. One eye of the rabbits was exposed to 0.1 mL test substance for 24 h and subsequently scored for reactions.
The readings revealed no indications for a eye irritating potential of isopropyl myristate.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

SKIN SENSITISATION

not sensitising
Additional information:
Taken together, all available data for assessment of the skin sensitising potential indicate that members of the category Fatty acid C2-8 esters have no skin sensitisation potential and classificationaccording to EU classification criteria for skin sensitisation is not required.
Based on a weight of evidence approach, SCAE C2-C8 have no sensitsing potential.

DERMAL/PERCUTANEOUS ABSORPTION

Dermal absorption of isopropyl myristate was predicted to be 0.00020 mg/cm2/event (very low).

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
In none of these studies mutagenicity in bacteria could be observed.
In none of these studies clastogenic effects in mammalian cells could be observed.
In none of these studies mutagenicity in mammalian cells could be observed.

CARCINOGENICITY

not classified as carcirogenic
Additional information:
Based on expert judgment, there is no evidence that members of the SCAE C2-8 cause carcinogenicity.

REPRODUCTIVE TOXICITY

not classified as toxic to reproductive
Additional information:
Studies on reproduction toxicity/fertility were available for the following category members (CAS#): 111-62-6 and 123-95-5.
For ethyl oleate and butyl stearate a 90-day subchronic NOAEL for fertility was found to be 5500 and 6000 mg/kg bw/d in rats.
The NOAEL for maternal and developmental toxicity for 2-ethylhexylstearate (CAS# 91031-48-0) and for 2-ethyl hexyl stearate (CAS# 22047-49-0) was found to be 1000 mg/kg bw/day.

TOXICOKINETIC (ADME studies)

The log Pow of 5 to 11 indicates that the substances are highly lipophilic and may have the ability to pass through biological membranes and some of the category members with very high log Pow may even have the ability to accumulate in the body.

Absorption

All available studies of all category members on the acute oral toxicity resulted in acute oral LD50 > 2000 mg/kg bw in rodents. This suggests that the SCAE C2-C8 members are either of low toxicity or there is little absorption of the substances following oral ingestion. It is possible that absorption through the gastrointestinal tract could occur by micecullar solubilisation, as this mechanism is of importance for highly lipophilic substances, particularly those who are poorly soluble in water (1mg/L or less). The rate at which SCAE C2-C8 molecules diffuse across membranes could limit their distribution.

QSAR based dermal permeability regarding molecular weight, log Pow and water solubility, calculated a dermal absorption of 0.892 – 39.9 cm/ h (DERMWIN v2.00, 2009) for the SCAE C2-C8 category members. This value is considered as an indicator that the substances in the SCAE C2-C8 category have low potential for dermal absorption.

For the SCAE C2-C8 category members with log Pow above 4, the rate of penetration may be limited by the rate of transfer between the stratum corneum and the epidermis, but uptake into the stratum corneum will be high. And those with log Pow above 6, the rate of transfer between the stratum corneum and the epidermis will be slow and will limit absorption across the skin. Uptake into the stratum corneum itself may be slow. The substance must be sufficiently soluble in water to partition from the stratum corneum into the epidermis.

Therefore the water solubility of less than 1 mg/L for the SCAE C2-C8 suggests that dermal uptake is likely to be low. Overall the calculated low dermal absorption potential, low water solubility, high molecular weight (>100) and the high log Pow value suggests that dermal uptake of SCAE C2-C8 in humans is considered as very limited and the dermal exposition is considered negligible for hazard assessment.

SCAE C2-C8 category members all have low vapour pressure of ≤ 0.357 Pa at 25°C (QSAR); therefore indicating that inhalation as a vapour will be minimal. Also, butyl stearate: (CAS No: 123-95-5) is a waxy solid, therefore the particles paste together and thus the risk of forming respirable dust is minimal.

Highly lipophilic substances will tend to concentrate in adipose tissue and depending on the conditions of exposure may accumulate. Although there is no direct correlation between the lipophilicity of a substance and its biological half-life, it is generally the case that substances with high log Pow values have long biological half-lives. The high log Pow of 6 to 11 of some of the substances indicates that some SCAE C2-C8 may have the potential to accumulate in adipose tissue.

Metabolism

The Fatty Acid SCAE Et-, Bu, Prop- and EtHe esters (SCAE C2-C8) are likely to be metabolised like any other dietary fats. High molecular weight aliphatic esters are readily hydrolysed to the corresponding alcohol and acid and then generally oxidised to carbon dioxide and water via well known metabolism of breakdown into two-carbon fragments which are used by the body for energy and building blocks for synthesis. During digestion, they are hydrolysed to the free fatty acids for absorption from the intestine into the blood stream aided by lipase enzymes and bile salts as demonstrated in the rat by Mattson et al. (IUCLID section 7.1.1, Mattson and Volpenhain, 1972). Once formed the free fatty acid is metabolised by known oxidative processes or they are reconstituted into glyceride esters and stored in the fat depots in the body.

The liver will be the primary site of metabolism of ethanol, butanol, isopropanol and ethylhexanol, where it will undergo phase I and phase II metabolism. Through a series of oxidative steps the alcohols will be oxidised to the corresponding aldehyde and acid and finally detoxified to carbon dioxide.

Studies on genotoxicity (Ames-Test, gene mutation in mammalian cells in-vitro, cytogenicity tests in vitro and micronucleus assay in-vivo) were negative, i.e. there is no indication of a reactivity of SCAE C2-C8 or its metabolites under the test conditions.

Excretion

The main route of excretion is expected to by expired air as CO2. The second route of excretion is expected to be by biliary excretion and the feces.

Exemplarily, experimental data of ethyl oleate (is the ethyl ester of oleic acid) provided this assumption: 14C-labeled carbon of 5 mL/kg of ethyl oleate (CAS No. 111-62-6) was rapidly excreted in respiration CO2 (approximately 70%), faeces (7 -10%), and urine (1-2%), with essentially complete elimination by 72 hours after administration (IUCLID section 7.1.1, Bookstaff, 2003).

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Sensitisation data
In a study with human volunteers the test substance did not show a skin sensitisation potential.

Exposure related observations in humans: other data:
This study showed that there were no clinically significant negative effects from consuming ethyl oleate at levels up to 16 g/day (approximately 200 mg/kg bw) for 12 weeks.

BIBLIOGRAPHY

- HERA http://www.heraproject.com
- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

JUNIPERUS COMMUNIS FRUIT EXTRACT (CAS: 84603-69-0)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

120 -- - Data were taken from Committee on Herbal Medicinal Products (HMPC): Assessment report on Juniperus communis L., pseudofructus (galbulus), 20 July 2022
EMA/HMPC/241319/2021

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 5 000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

Category 2 (irritant) based on GHS criteria

MUCOSAE IRRITATION AND CORROSION (eye irritation)

Category 2 (irritating to eyes) based on GHS criteria

SKIN SENSITISATION

Skin sensitisation: skin sensitizer, based on available human data and the presence of classified ingredients.

DERMAL/PERCUTANEOUS ABSORPTION

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
A Bacterial Reverse mutation Assay (Ames test) was performed according to OECD test guideline No 471 with Juniper oil. No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose, either in the presence or absence of metabolic activation. Juniper oil does not induce gene mutations in bacteria under the test conditions whereas the positive control chemical (with and without metabolic activation) induced significant increase of colonies. Juniper oil is therefore considered as non-mutagenic according to the Ames test.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information: The antifertility and abortifacient activitiesofJuniperusCom- munis Extract (ethanolic extract) were evaluated using groups of 10 colony-bred, female Swiss albino rats (weights D 140– 180 g). Two additional experiments were also conducted to con- rm suspected abortifacient activity. Females were mated with mature males (three females per male) of proven fertility. After mating, two groups of female rats received oral doses of 300 and 500 mg/kg body weight, respectively, on days 1 to 7 of pregnancy. Each dose of the testsubstance was prepared with an equal amount of gum acacia, thoroughly mixed and suspended in distilled water. The 10 control rats were dosed with gum acacia suspension according to the same procedure. On day 10 of preg- nancy, the rats were laparotomized under light ether anesthesia to determine the presence of implantation sites in both uterine horns. Wounds were sutured and, on days 14, 15, and 16, the same doses were administered only to rats with implantation sites. Rats were laparotomized on day 18 to determine abortifa- cient activity, and sutured rats were allowed to deliver. On day 10 of pregnancy, no implantation sites were present in 5 of 10 rats dosed with 300 mg/kg and in 8 of 10 rats dosed with 500 mg/kg. Implantation sites were observed in all control rats. Compared to controls, the average number of embryos was signi cantly re- duced in the group dosed with 500 mg/kg. Following the administration of doses(days 14, 15, and 16) to the remaining rats with implantation sites, only three of ve rats dosed with 300 mg/kg and neither of the two rats dosed with 500 mg/kg had implants on day 18. These results for rats with implantation sites were indicative of early abortions. For rats in which pregnancies continued, delivery was not possible; thus, the remaining embryos were aborted later (Agrawal, Bharadwaj, and Mathur 1980). A second experiment evaluating the abortifacient activity of Juniperus Communis Extract was conducted according to the procedure in the preceding paragraph, with the exception that doses(300 or 500 mg/kg)were administered to groups of ve rats only on days 14, 15, and 16 of pregnancy. Following parturition, the number of litters delivered was determined. In both dose groups, early or late abortions resulted and no pups were born. All control rats had implantation sites on day 18, and the average number of pups delivered was 9.5 § 1.8. Neither body weight loss nor side effects was/were noted in this experiment or the preceding experiment (Agrawal, Bharadwaj, and Mathur 1980). In a third set of experiments, three of the rats without implants on day 10 were allowed to mate with males after 2 months of rest. Although the matings were successful, no implantations were reported (Agrawal, Bharadwaj, and Mathur 1980). Based on the results of the preceding three experiments, the investigators concluded that Juniperus Communis Extract had antifertility and abortifacient effects in rats, but was not teratogenic.

TOXICOKINETIC (ADME studies)

no data

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

PHOTOINDUCED TOXICITY

not induce photo toxicity
Additional information see DATA ON THE MAN
The phototoxicity of undiluted Juniper Berry Oil was evalu- ated using hairless mice and swine. No phototoxic effects were reported (Research Institute for Fragrance Materials 1976)

DATA ON MAN

Sensitisation data (human)
Two hundred consecutive patients and 50 subjects positive to balsams were tested with the 35 essential oils including Juniper berries.
Of the 20 patients positive to balsam of Peru and negative to other balsams, one patient showed positive reactions to Juniper. Of the 23 patients positive to turpentine and negative to other balsams, one patient showed positive reactions to Juniper. Of the 31 patients positive to turpentine, one patient showed positive reactions to Juniper. Of the 31 patients positive to balsam of Peru, one patient showed positive reactions to Juniper.
Under the test conditions, Juniper oil induced skin sensitization in human.

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EMA, European Medical Agency
- Final Report on the Safety Assessment of Juniperus Communis Extract, Juniperus Oxycedrus Extract, Juniperus Oxycedrus Tar, Juniperus Phoenicea Extract, and Juniperus Virginiana Extract- Committee on Herbal Medicinal Products (HMPC)

MEDICAGO SATIVA EXTRACT (CAS: 84082-36-0)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

166 -- - EFSA, https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2009.997

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 3 000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

non-irritant
Additional information:
The Reconstructed Human Epidermis test, conducted according to OECD test guideline 439 and to GLP, was performed to evaluate skin irritation potential of Alfalfa, ext.
After 60-minute exposure on the surface of the EpiDerm constructed epidermis, and 42 ± 4 hours post exposure incubation time, viability of the tissue was assessed and compared to the negative (DPBS) and positive control (SDS). The percentage of viability obtained was 95.3% and therefore, Alfalfa, ext. was classified as non-irritant to the skin.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not classified as eye irritant
Additional information:
The Bovine Corneal Opacity and Permeability (BCOP) test, conducted according to OECD test guideline 437 and to GLP, was performed to evaluate the eye hazard potential of Alfalfa, ext.
The undiluted test item was applied for 10 minutes then rinsed followed by an incubation period of 120 minutes. Negative and positive control items were tested concurrently. The two endpoints, decreased light transmission through the cornea (opacity) and increased passage of sodium fluorescein dye through the cornea (permeability) were combined in an empirically derived formula to generate an In Vitro Irritancy Score.
The In Vitro Irritancy Score for Alfalfa, ext. was determined at 5.9; therefore, no prediction of eye irritation can be made.

SKIN SENSITISATION

not sensitising
Additional information:
In an in vitro KeratinoSens test (key event 2), conducted according to OECD test guideline 442D and to GLP, the skin sensitisation potential of Alfalfa, ext. was determined negative. In an in vitro Human Cell Line Activation test (key event 3), conducted according to OECD test guideline 442E and to GLP, the skin sensitisation potential of Alfalfa, ext. was determined positive.
In the murine Local Lymph Node Assay (key event 4), conducted according to OECD test guideline 429 and to GLP, Alfalfa, ext. was not considered as a skin sensitizer.
Based on the available in vitro and in vivo data, Alfalfa, ext. is not classified as a skin sensitizer according to criteria set out in the Regulation (EC) No 1272/2008.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
Bacterial Reverse Mutation assay conducted according to OECD test guideline 471 and to GLP was performed to determine mutagenic potential of Alfalfa, ext.
In the dose-range finding study, the test item was initially tested up to concentrations of 5000 µg/plate in the strains TA100 and WP2uvrA in the direct plate assay. The bacterial background lawn was not reduced at any of the concentrations tested and no biologically relevant decrease in the number of revertants was observed. Results of this dose-range finding test were reported as part of the first mutation assay.
In the first mutation experiment, the test item was tested at a concentration range of 52 to 5000 µg/plate in the strains TA1535, TA1537, TA98 and TA102. The test item did not precipitate on the plates at these dose levels. The bacterial background lawn was not reduced at any of the concentrations tested and no biologically relevant decrease in the number of revertants was observed.
In the second mutation experiment, the test item was tested at a concentration range of 52 to 5000 µg/plate in the tester strains TA1535, TA1537, TA98, TA100 and TA102 in the pre-incubation assay. The bacterial background lawn was not reduced at any of the concentrations tested and no biologically relevant decrease in the number of revertants was observed.
The test item did not induce any increase in the number of revertant (His+) colonies in any of the five Salmonella tester strains and in the number of revertant (Trp+) colonies in E. coli tester strain WP2uvrA both in the absence and presence of S9-metabolic activation.
The acetone extract of alfalfa was tested in the Ames assay in two Salmonella strains, TA98 and TA100 with and without metabolic activation (S9). It did not increase the number of revertants in either Salmonella strain.
A phyto-preparation derived from alfalfa extract was tested in the Ames assay in TA98, TA100 and TA1537 strains with and without metabolic activation (S9) at concentrations up to 50’000 µg/plate. It did not increase the number of revertants in the presence and absence of metabolic activation.
SOS chromotest in the Escherichia coli PQ37 test strain was performed to determine the DNA-damaging potential of the phyto-preparation derived from alfalfa extract applied at 20 different concentrations (0.0734 to 38 500 µg/ml). Under the test conditions, the phyto-preparation did not to induce the SOS functions in Escherichia coli, indicating that it has no DNA-damaging potential.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EFSA, European Food Safety Agency

MENTHOL (CAS: 1490-04-6 / 2216-51-5 / 89-78-1 / 15356-60-2)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

188 -- - ECHA https://echa.europa.eu/. Additional information: In a valid 2 years oral feed study in rats the NOAELs were 375 mg/kg bw/d for male rats and 667 mg/kg bw/d for male and female mice. For female rats the NOAEL is 188 mg/kg based on slightly reduced body weight at 375 mg/kg bw. For repeated dermal and inhalative toxicity no valid studies are available.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 (oral) rat 3180 mg/kg bw
LD50 (dermal) rabbit >5000 mg/kg
LC50 (inhalation) rat 5289 mg/m3
NO(A)EL rat: Males&females: <4225 mg/m³
Acute Toxicity: other routes: LD50 of menthols from natural sources and synthetically produced was 1000 to 2500 mg/kg bw in rats.
In the reliable acute oral toxicity study demonstrated a low systemic toxicity with a LD50 higher than 2000 mg/kg bw.

In the acute inhalation study a LC50 > 5000 mg/m³ was (rat, aerosol, 4 h) was determined.

According to CLP classification criteria (Regulation (EC) No 1272/2008) a classification is therefore not justified.

SKIN IRRITATION AND CORROSIVITY

According CLP: H315: Causes skin irritation.
Specific concentration limits:
Concentration range (%): > 25
Hazard categories:
Skin Irrit. 2
Additional data:The day before the experiment was started the rabbits were weighed and an area of 10 x 10 cm on the back was clipped as closely as possible with an electric clipper.
On the experimental day the rabbits were physically restrained on a test table, and the backs were treated on six different fields: Two anterior treatment sites, two centrally located test sites and two posterior treatment sites. To each of the fields about 0.5 ml of one of the test concentrations was applied and covered with gauze packs, 2.5 x 2.5 cm. The gauze packs were secured with a cross of 1 cm wide adhesive tape and fixed with Scanpor tape, 7.5 cm width, loosely wound round the trunk. Five test concentrations were used: 100%, 50%, 25%, 5%, or 1%. After an exposure time of 4 hours the tape and packs were remoced and the treated skin was cleaned with soap and lukewarm water. The skin reactions were read.
With the undiluted test substance menthol was irritating to the skin (erythema sore: 3 and and edema score: 3). The undiluted compounds were irritating to the skin. Dilution of the compounds led to a pronounced decrease in the irritating properties of the compounds. No skin reaction at all were observed for D-menthol and menthol liquid at 5 % dilution and for L- and D/L-menthol at 1 % dilution.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

According CLP: H319: Causes serious eye irritation.
Specific concentration limits:
Concentration range (%): > 25
Hazard categories:
Eye Irrit. 2
Additional data: About 0.1 ml of the test article solution or vehicle was placed in the left or right eye, respectively, of each rabbit by gently pulling the lower lid away from the eyeball to form a cup into which the test substance was dropped. The lids were then gently held together for about one second. The eyes were examined and the grade of ocular reaction was recorded 1 hour later. 24 hours later an examination was performed before and after installation of oculoguttae flouresceini. After the examination the eyes were rinsed with 20 ml of a 0.9% sodium chloride solution. The eyes were also examined 48 and 72 hours after the treatment, as well as on day 7.
Based on the cornea score = 2.1 a classification as Cat.2, H319 is adequate. However, considering the cornea score = 1.9 of the solvent a classification is not necessary, but taken into account the hole database, a classifiaction as Eye Irrit. 2; : C>25% seems adequate.

SKIN SENSITISATION

not considered to have sensitizing properties
This is in agreement with the OECD SIDS initial assessment that concluded: All studied isomers of menthol are moderately irritating to the skin and slightly irritating to the eye. The skin sensitization potency of menthol isomers in animals and humans is low.(OECD SIDS 2003).
Additional information: The sensitisation potential of L-menthol (CAS 2216-51-5) was investigated by means of the Buehler Test for sensitisation in guinea pigs. The test procedure followed the OECD guideline 406. A concentration of 25% w/v of the test substance in ethanol:DEP (1:1) was selected for induction and challenge and no sensitization potential was identified (Cutbert 1991). A LLNA with L-menthol (CAS 2216-51-5) is available as a secondary source evaluated within the OECD SIDS initial assessment on the menthols and showed also no skin sensitization potential. In addition a limited skin sensitisation study using a modified Draize procedure reported no sensitization potential for brasilian methol (racemic, l-enthol, d-menthol) (Hopf, 1974). The OECD SIDS Initial Assessment Report 2003 evaluated L, D, and racemic L/D menthols together and gives the rational for a menthol category as follows: "Category Rationale: The menthols category is comprised of the isomers L-menthol, D-menthol, the racemate and menthol (unspecified isomers). The menthols can be considered as a category because of their similarity in physico-chemical, toxicological, ecotoxicological and environmental fate properties….In summary, the available toxicity data indicate very similar toxicity profiles for all of the menthol isomers investigated." The category justification is documented in a comprehensive 15 page annex to the SIDS Assessment report (Annex 1: Menthols Category Justification). The annex is attached to the study record entry on the OECD SIDS evaluation in the chapter “Toxicokinetics) as attached background material.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information: Menthol was investigated in the Salmonella/microsome test (Ames test). Result: negative, no evidence of mutagenic activity of menthol was seen (with and without mutagenic activation). Additional, menthol was evaluated as negative in a cytogenetic assay and also in a CHO/HGPRT test. In an in-vivo micronucleus assay no indication for a mutagenic effect was found.
In all relevant (key-studies) in vitro genetic toxicity assays (Ames test, cytogenetic test, CHO/HGPRT test) and the in-vivo micronucleus test, menthol was negative.

CARCINOGENICITY

Not carcinogenic
A bioassay of dl-menthol for possible carcinogenicity was conducted by administrating the test chemical in feed to Fisher 344 rats and B6C3F1 mice.
No carcinogenic effects were observed at the highest applied doses.
Additional information: In male and female rats the survival rate was not affected by treatment and no carcinogenic effects of D/L-menthol were found in any organ.

In mice of either sex, no tumors occurred in dosed groups at incidences that were significantly different from those for corresponding control groups.

From the available studies a classification according to CLP classification criteria (Regulation (EC) No 1272/2008) is not justified.

REPRODUCTIVE TOXICITY

Not toxic to reproductive
Additional information
Development toxicity/teratogenicity studies on rats, rabbits, mice and hamsters revealed no evidence of teratogenic effects of menthol.
NOEAL (rat): 218 mg/kg bw/day
Fertility study:

In the EOGRTS study according OECD 443, the NOAEL for systemic toxicity in the F0 and F1 adult animals was concluded to be the intermediate dose of 419-499 mg/kg/day for males and 455-594 mg/kg/day for females, based upon the impaired body weight gain at the high dose level.

Based on the results obtained in this study it was concluded that the No-Observed-Effect-Level (NOEL) for reproductive performance of the F0 and F1 Cohort 1B animals was the intermediate dose of 419-499 mg/kg/day for males and 455-594 mg/kg/day for females due to lower litter size observed in both generations at the high dose level, a level which was associated with reduced food consumption and body weight gain in the parental animals of both generations.

The NOEL for the F1 and F2 offspring up to weaning was concluded to be the intermediate dose of 512-611 mg/kg/day due to reduced pre-weaning growth in both generations.

Developmental toxicity/teratogenicity studies:

The administration of up to 218 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.
The administration of up to 185 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

The administration of up to 405 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

The administration of up to 425 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly
discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

Based on the results of the EOGRTSand the developmental toxicity studies a classification according to CLP classification criteria (Regulation (EC) No 1272/2008) is not justified.

TOXICOKINETIC (ADME studies)

The OECD SIDS Initial Assessment Report concludes on toxicokinetics, metabolism and distriburion:

"L-, D/L- and the unspecified menthol isomer are well absorbed by the oral route of exposure and are mainly excreted as glucuronides. In rats an extensive enterohepatic circulation additionally leads to various hydroxylated degradation products. Glucuronides and degradation products are eliminated mainly via urine, minor quantities via the faeces."

IDS Initial Assessment Report 2003 evaluated L, D, and racemic L/D mentols together and gives the rational for a menthol category as follows:

"Category Rationale: The menthols category is comprised of the isomers L-menthol, D-menthol, the racemate and menthol (unspecified isomers). The menthols can be considered as a category because of their similarity in physico-chemical, toxicological, ecotoxicological and environmental fate properties.

Additional information: The category justification is documented in a comprehensive 15 page annex to the SIDS Assessment report (Annex 1: Menthols Category JustificationCategory Justification). The annex is attached to this study entry as attached background material. The main information of the Annex 1 is also copied below:

"As structural isomers, the members of the menthol category share the same molecular weight. Of particular importance to environmental effects are the values for partition coefficient (log Kow), vapour pressure and water solubility.

The enantiomeric menthols have identical physical properties (apart from their specific rotation), but the racemates differ from the optically active forms in, for example, their melting points. The slight differences are within the range of uncertainty range of laboratory tests.

The water solubility was determined for three products. Due to the similar molecular structures, no significant differences in the solubility are expected. The vapour pressure at environmental relevant temperatures was determined for L-menthol and an unspecified isomer mixture. As well as for the parameters above, similar values are expected for D-menthol and the racemate.

Investigations on toxicokinetics show that L-, D/L- and the unspecified menthol are well absorbed via the oral route. For all of the isomers, elimination is rapid and mainly occurs as glucuronic acid conjugates via urine, minor amounts via faeces. Significant differences in toxicokinetic properties of menthol isomers were not reported.

The available toxicity data indicate very similar toxicity profiles for D -, L-, D/L-menthol and the unspecified menthol isomer mixture. In mammalian species the low toxicity is manifested in LD50 values generally greater than 2000 mg/kg bw in acute studies, limited toxicity in repeated dose studie s, and no effects in teratology evaluations. Irritation to skin and eyes was slight to moderate. The low hazard potential is not unexpected, since the FDA regulates menthol as a GRAS (generally recognized as safe) component and an acceptable daily intake (ADI) of 0-4 mg/kg bw for L- menthol and D/L-menthol was adopted in 1999 by the Joint FAO/WHO Committee.

All of the products have been tested for acute oral toxicity, skin and eye irritation in rodents, often following identical test protocols.

Data for sensitization, repeated dose toxicity, genetic toxicity, fertility, and carcinogenicity are available for D/L-menthol and mostly for L-menthol as well.

D/L-menthol is a racemic mixture of the D- and L- isomers and contains both isomers in equal proportion. Data gaps for D-menthol and the unspecified isomer mixture can therefore be filled by the respective results with the racemic mixture and the doses for each isomer might be equivalent to half of the total tested D/L -dose.

L-menthol showed no embryotoxic or teratogenic properties at not maternally toxic dose levels (maternally toxic dose levels were not tested). No experimental data with the other menthol isomers is available with regard to developmental toxicity. Since there is no indication of a relevant difference between the isomers in their toxicokinetics and metabolism, and since this is further supported by all other available toxicological data, which do not show any evident differences in the respective toxicological profiles, there is no reason to assume that the stereoisomeric properties may affect the toxicological properties of the menthol isomers. Hence, a similar result in developmental toxicity studies would reasonably be expected from studies with D-menthol, the racemate or the unspecified menthol isomer.

Because of the low hazard potential of the chemicals in the menthols category, no further toxicity tests are recommended."

(OECD SIDS Assessment Report, Annex 1: Menthols Category JustificationCategory Justification).

The OECD SIDS Initial Assessment Report concludes on toxicokinetics, metabolism and distriburion:

"L-, D/L- and the unspecified menthol isomer are well absorbed by the oral route of exposure and are mainly excreted as glucuronides. In rats an extensive enterohepatic circulation additionally leads to various hydroxylated degradation products. Glucuronides and degradation products are eliminated mainly via urine, minor quantities via the faeces."

Additional toxicological data:
in vitro test:
when haemolysates of infantile erythrocytes were mixed with 50, 100, 200 and 500 gamma menthol, the
methaemoglobin content rose by up to 100 %, namely from 0.7 to 1.5%; these values are absolutely within physiological limits and this effect could be neutralized with vitamin C
(test substance: unspecified isomer)

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

In an in vitro study with human liver samples menthol (isomer unspec.) inhibited the glucuronidation of 7 -hydroxy-4 -methylcoumarin (45% inhibition).

Allergic hypersensitivity was investigated in a group of 228 selected dermatologic patients by patch tests with menthol 1 % in petrolatum; incidence of pronounced sensitization: 1.3 %.

menthol racemic (8% in petrolatum) produced no irritation after a 48 h closed-patch test in human subjects

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

PARAFFINUM LIQUIDUM (CAS: 8012-95-1 / 8042-47-5)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

1624 -- - ECHA, European Chemical Agency. Additional information:Subchronic Exposure (up to 90 days/ 13 weeks):
LOAEL (subchronic, oral, CRL:CD female rats) = 20000 ppm (1624 mg/kg bw/day) –slightly increased incidence of minimal multifocal chronic inflammation in liver.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

No mortality or clinical signs of toxicity were observed
LD0 (oral, rat) =5000 mg/kg bw;
LD50 (oral, rat) >5000 mg/kg bw.
No mortality or clinical signs of toxicity were observed.
LC0 (inhalation, rat) =210 mg/m3.
No mortality or clinical signs of toxicity were observed
LD0 (rabbit, dermal) = 2000 mg/kg bw;
LD50 (rabbit, dermal) > 2000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

not irritant for skin
additional information:
Study results:
No signs of skin irritation were observed
Conclusions:
Mineral Paraffin Oil is a liquid substance, not soluble in water, with very low vapour pressure. The data from animal studies report no skin irritation effects.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

irritant
additional information:
Study results:
Mild, reversible within 72 hours eye irritation was observed in tested animals.
Conclusions:
mild, reversible ocular irritation effect was reported

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

SKIN SENSITISATION

not sensitizer
additional information:
Skin sensitisation:
In accordance with the CLP criteria, skin sensitizer is defined as “a substance that will lead to an allergic response following skin contact”. To be classified as a skin sensitiser (Category 1) there must be evidence of chemicals’s sensitizing effects observed in substantial number of people.
No data on skin sensitisation potential ofMineral Paraffin Oilin humans were located. In addition, no alerts for sensitising properties ofMineral Paraffin Oil components were identified with the applicable QSAR models.
Based on the data summarized here and taking into account that there have been no reports of skin sensitization caused byMineral Paraffin Oil, it is not considered to be a skin sensitizer.
Respiratory sensitisation:
In accordance with the CLP criteria, respiratory sensitizer is defined as “a substance that will lead to hypersensitivity of the airways following inhalation of the substance”.
Generally, a substance is classified as respiratory sensitizer if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or if there are positive results from an appropriate animal test.
Currently, no recognized animal models for the testing of respiratory hypersensitivity are available. Therefore, evidence that a substance can induce specific respiratory hypersensitivity will normally be based on human experience.
However, no hypersensitivity reactions associated with exposure toMineral Paraffin Oilwere reported in humans. Therefore,Mineral Paraffin Oilis not considered to be a respiratory sensitizer.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

Hightly refined paraffinum liquidum not mutagenic / genotoxic
additional information:Screening of Mineral Paraffin Oil hydrocarbon components for mutegenicity/genotoxicity using several available QSAR models provide negative prediction results for this endpoint.
Epidemiology studies provide some evidence of mutagenic effects in occupationaly exposed to mineral oil mists workers, including increase in the frequency of chromosomal aberrations in the peripheral blood lymphocytes (glass workers) and mutagenic effect of urine in the Ames assay toS. typhimuriumin the presence of exogenous metabolic system (cold-rolling steel plant workers). However, because workplace exposures are of complex nature, involving many other chemicals, possibly including high concentration of PAH in mineral oil products, the clear cause-effect relationship is not possible to establish.
In general, mutagenicity/genotoxicity properties reported for Mineral Oils are attributed to PAH content of these products. Thus, highly or severely refined Mineral Oils are not considered as being mutagenic/ genotoxic. The IP346 assay is used by mineral-oil producers to define if a mineral oil is highly or severely refined. The IP346 assay measures the amount of material extractable in dimethyl sulfoxide (DMSO): mineral oils with a DMSO-extractable content < 3% are considered as highly or severely refined.

CARCINOGENICITY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Hightly refined paraffinum liquidum not carcinogen.
Additional information:
Cancer Hazard
* While Mineral Oil has been tested, it is not classifiable as to its potential to cause cancer.
NEW JERSEY DEPARTMENT OF HEALTH AND SENIOR SERVICES: Right to Know Program, PO Box 368, Trenton, NJ 08625-0368, (609) 984-2202

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
The data on toxicokinetics of Mineral Paraffin Oil confirm that long-chain aliphatic hydrocarbons have only limited absorption potential after inhalation, oral and ingestion exposure routes. Thus, animal studies show that up to 95 -99% of ingested food-grade mineral oil leaves the body unchanged with the faeces, and only up to 5% being absorbed via the intestinal mucosa. The absorbed Mineral Paraffin Oil is distributed to the liver and fatty tissues. Aliphatic hydrocarbons in this fraction are not expected to undergo extensive metabolism in animals or humans.
Moreover, Mineral Paraffin Oils have been used as solvent controls in a number of reproductive and developmental studies and have consistently shown no evidence of reproductive or developmental effects in rats (EU EFSA, 2009).
Based on the information summarised here, reproductive or developmental toxicity is not likely to be associated with exposure to Mineral Paraffin Oils.

TOXICOKINETIC (ADME studies)

Discussion on bioaccumulation potential result:
The data on toxicokinetics of Mineral Paraffin Oil suggest that long-chain aliphatic hydrocarbons have only limited absorption potential after inhalation, oral and ingestion exposure routes. Thus, animal studies show that up to 95 -99% of ingested food-grade mineral oil leaves the body unchanged with the faeces, and only up to 5% being absorbed via the intestinal mucosa. The absorbed Mineral Paraffin Oil is distributed to the liver and fatty tissues. Aliphatic hydrocarbons in this fraction are not expected to undergo extensive metabolism in animals or humans.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA European Chemical Agency
- Tsitou P, Heneweer M, Boogaard PJ. Toxicogenomics in vitro as an alternative tool for safety evaluation of petroleum substances and PAHs with regard to prenatal developmental toxicity. Toxicol in vitro 2015;29:299-307

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

PHENOXYETHANOL (CAS: 122-99-6)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

500 -- - European Chemical Agency ECHA.EU https://echa.europa.eu/registration-dossier/-/registered-dossier/15160/7/6/1 Several repeated oral dose toxicity studies were available. The benchmark dose method was used to derive a BMDL10. The most critical effect was determined to be the renal hyperplasia in male rats. Combining the subchronic and chronic studies in rats a BMDL10 of 369 mg/kg bw/day has been derived.
In a 90-day repeated-dose dermal toxicity study in white rabbits toxicologically non relevant effects were observed. Therefore the highest dose tested (500 mg/kg bw/day) was designated as the NOAEL for systemic toxicity.
In a 14-day inhalation study with rats pathological examinations revealed no treatment-related changes in either males or females. Morphological changes indicating irritation were found in nasal cavity, larynx and lung of male and female mid- and high-concentration animals. A NOAEC of 48.2mg/m³ was determined.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50oral (rat) 1 840 mg/kg bw
LD50 dermal (rabbit) > 2 214 mg/kg bw
LC50 inhalation (rat) > 1 000 mg/m³ air (nominal)
Acute oral toxicity:

CLP: Cat. 4 / EU: Xn R22

Acute dermal toxicity:

CLP: not classified / EU: not classified

Acute inhalation toxicity: (testing up to 1000 mg/m3 displayed no effects)

CLP: not classified / EU: not classified

Clinical signs: Apathy, prone position, narcotic state, morphine tail, opisthotonos, secretion of the conjunctiva, anaesthesia-like state and delayed mortality were observed (no further details).

LD50 ca. 300 microliters/kg (original finding, corresponding to approx. 333 mg/kg bw)

SKIN IRRITATION AND CORROSIVITY

2-Phenoxyethanol is not irritating to rabbit skin
A mild primary irritation was observed in one rabbit 1 hour after application, which was reversible within 24 hours (BASF AG, 1983). Although the test conditions were not in full accordance with OECD guideline 404, the results should be considered representative for the toxicological properties of 2-phenoxyethanol. 2-Phenoxyethanol was not an irritant to rabbit skin.

According to OECD 404, the skin irritation potential of 2-phenoxyethanol was determined (Sasol, 1983).The test substance was applied to the intact skin of rabbits for 4 hours under occlusive conditions. After removal of the test substance, no oedema, but very slight erythema were noted in 2 of 6 animals. All erythema were reversible within 48 hours. Under the test conditions, 2-Phenoxyethanol was not irritating to the skin.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

Eye irritation: The single application of 0.1 mL unchanged test material in the eye of each of 3 rabbits clearly induced signs of irritation in all 3 animals; the signs were of maximal severity between 48 and 72 hours following application (BASF AG, 1983). Thereafter, a tendency to reversibility was observed and after 15 days, only one animal still displayed slight corneal opacity affecting less than ¼ of the corneal area of the treated eye. The test substance 2-phenoxyethanol is therefore considered an eye irritant.

Effects on eye irritation: irritating

Effect level: empty Endpoint conclusion: Adverse effect observed

Justification for classification or non-classification
Skin irritation: not irritating to skin.

Eye Irritation:

EU: Xi R36

CLP: Cat. 2

SKIN SENSITISATION

Animal data

In the guinea pig maximisation test, undiluted 2-phenoxyethanol was used for the challenge after intradermal and epicutaneous induction (BASF AG, 2002). The observations at 24 h and 48 h after challenge exposition revealed no reactions in any animal.
2-Phenoxyethanol was not sensitizing to the skin of guinea pigs in the maximization test.

no adverse effect observed (not sensitising)

DERMAL/PERCUTANEOUS ABSORPTION

2-Phenoxyethanol was rapidly absorbed through rat skin mounted in both the static and flow-through diffusion cell with either aqueous ethanol or MEM as receptor fluid. The stratum corneum did not appear to be a good barrier to 2-phenoxyethanol penetration. Occlusion increased the permeability coefficient of 2-phenoxyethhanol in the static cell. The permeability profile and amount absorbed were similar for human and rat skin in the flow-through system with tissue culture medium. The mass balance recovery of 2-phenoxyethanol in the unocccluded studies was low; static diffusion 68% and flow-through diffusion cell 51% at 24 hr, due to the high evaporation, as confirmed by only 7.5% remaining on the aluminium foil at 24 hr. The losses from the skin decreased proportionally throughout the experiment due to the penetration of 2-phenoxyethanol into the skin and receptor fluid.

MUTAGENESIS / GENOTOXICITY

2 -Phenoxyethanol was tested for genotoxic potential in an adequate battery of in vitro and in vivo tests with various end points.

In vitro: 2-Phenoxyethanol was not a point mutagen in studies on bacteria at concentrations up to 5000 µg/plate with and without metabolic activation (BASF AG, 2002; Sasol, 1994; Nipa Laboratories, 1982). Further tests on point mutations on the HGPRT locus in eukaryotic cells yielded also negative results (BASF AG, 2002, The Dow Chemical Company, 1987).
In vitro testing on chromosome-damaging effects in Chinese hamster cell cultures indicated no effects with and without metabolic activation (BASF AG, 2002; Unilever, 1985).

The available data indicate that 2 -phenoxyethanol was neither an in vitro cell mutagen nor a clastogen.

In vivo: The in vivo assays also showed no mutagenic effects with 2-phenoxyethanol treatment.
No chromosome-damaging effects were observed and testing on DNA damage in vivo via the UDS test in Wistar rat also failed to show mutagenic effects. (BASF, 2002, Nipa Laboratories, 1982; BASF AG, 2002; The Dow Chemical Company, 1988)

The available data indicate that 2-phenoxyethanol was not an in vivo cell mutagen or clastogen.

Overall, 2-phenoxyethanol is unlikely to pose a genotoxic hazard to man.

The available data indicate that 2-phenoxyethanol is not genotoxic.
Negative in the Ames test, negative results in mammalian chromosomal aberration and gene mutation tests.

CARCINOGENICITY

NOAEL 249 mg/kg bw/day
Two carcinogenicity (104 weeks) OECD 451 and GLP compliant studies are available. A drinking water study was conducted with F344/DuCrlCrlj rats. 50 rats per sex were exposed to nominal concentration of 0, 2500, 5000, and 10000 mg/L. Analytical concentrations in drinking water were determined with HPLC. Based on chemical intake data the mean intake of test substance across the duration of the study was estimated to be 124, 249, and 510 mg/kg/day in males and 191, 380, and 795 mg/kg/day in females. Mortality and clinical signs were investigated. Food intake, water intake and body weight were determined weekly during the first 13 weeks followed by measurements once every 4 weeks until study termination. After 104 weeks urinalysis, haematology, blood chemistry, gross pathology, organ weights and histopathology (both non-neoplastic and neoplastic lesions) were examined. No neoplastic lesions were found in either sex. Additionally, a drinking water study with B6D2F1/Crlj mice was conducted. The study design and examination/observations were similar to the study in rats. However, the dose levels differed and were 0, 5000, 10000 and 20000 mg/L. Based on chemical intake data the mean intake of test substance across the duration of the study was estimated to be 468, 898, and 1701 mg/kg/day for males and 586, 1072, and 2058 mg/kg/day for females. After 104 weeks repeated dosing, no treatment related neoplastic lesions were found in either sex. Based on both rat and mice studies, there is no evidence of carcinogenic activity of the test substance in male or female rat and mice.

For DNEL derivation, the benchmark dose method was used to derive a BMDL10 on basis of repeated dose toxicity studies. BMDL10 = 369 mg/kg bw/day.

Based on the assessment of all available data classification in accordance with EU Directive 67/548/EEC (DSD) and EU Classification, Labeling and Packaging of Substances and Mixtures (CLP) Regulation No. 1272/2008 is not warranted

REPRODUCTIVE TOXICITY

In a multi-generation study, fertility was minimally decreased at a dose that caused neonatal toxicity. The NOAEL for parental and neonatal toxicity was 375 mg 2-phenoxyethanol/kg bw/day.

In prenatal developmental toxicity studies, no effects on the developing foetus were seen in rats and rabbits (BASF AG, 2006 and Dow Chemical USA, 1985 and 1987).

In rats, oral administration of 2-phenoxyethanol elicited distinct signs of maternal toxicity at a dose level of 1,000 mg/kg bw/day (BASF AG, 2006). The test compound had no influence on gestational parameters and induced no signs of developmental toxicity up to and including the highest test dose of 1,000 mg/kg bw/day. In particular, there were no indications of teratogenic effects, which were causally related to the test substance. The NOAEL for maternal toxicity is 300 mg/kg bw/day. The NOAEL for prenatal developmental toxicity was 1,000 mg/kg bw/day.

In rabbits, dermal administration of 600 and 1000 mg/kg bw/day resulted in intravascular red blood cell haemolysis and death of some dams (Dow Chemical USA, 1985 and 1987). No treatment-related malformations occurred. Also fetuses from animals treated with 1000 mg/kg bw/day which survived to day 28 did not exhibit external, visceral or skeletal alterations. The NOAEL for teratogenicity and embryotoxicity was >600 mg/kg bw/day and for maternal toxicity was 300 mg/kg bw/day.

TOXICOKINETIC (ADME studies)

According to OECD 417, biokinetic data of 2-phenoxyethanol were studied in male and female rats after single oral administration (BASF AG, 2007).In rats exposed to14C-2-phenoxyethanol, the test substance was rapidly and almost completely absorbed from the gastrointestinal tract with the highest plasma concentrations present 1-2 hours post-dosing.

After absorption, the radioactive material was distributed in different organs and tissues (GI tract, kidney, liver, pancreas, brain, muscle, heart, uterus, skin, bone marrow, and bone), tissue radioactivity concentrations generally declined with time parallel to plasma concentrations. In exhaled air, no relevant amounts of the administered radioactivity were detected as CO2. The excretory investigations indicated a rapid excretion and showed that recovered radioactivity was predominantly excreted via urine (urine: 92-94%; faeces: 1.9-2.9%). Furthermore the results demonstrated that there were no gender differences in the excretion pattern, irrespectively of the dose.

The bioavailability of the test substance was generally > 90% of the applied dose. The plasmakinetic data indicated that an increase of the dose resulted in a disproportional increase of the AUC-values, demonstrating a saturation of excretion with increasing dose.

In a second study according to OECD 417 (BASF AG, 2007),the investigation of the metabolism of 2-phenoxyethanol in excreta, bile and plasma samples of female rats after oral administration of14C-2-phenoxyethanol was carried out. The results of this study confirmed the biokinetic data of BASF AG(2007). Overall, the elimination of the test compound was fast with up to approximately 70% of the dose being excreted within the first 6 hours (urine and faeces).

The authors observed that 2-phenoxyethanol was nearly completely metabolised. In urine and bile, less than 0.7% of the dose had been assigned to the parent compound. The parent compound was mainly metabolised to phenoxyacetic acid (PAA) by oxidation of the terminal hydroxyl group to carboxylic acid(up to 64% of the dose). Seven further metabolites were identified with up to < 10% of the applied dose. The other metabolic changes of14C-phenoxyethanol were either ring sulfation after hydroxylation or conjugation with glucuronic acid at the side chain. In a further step, these metabolites were mainly hydroxylated at the ring and in one case the terminal hydroxyl group was oxidised to carboxylic acid. In another study, The Dow Chemical Company (1986) identified also only small amounts of the parent compound and increased amounts of the metabolite PAA in serum samples of rabbits. This finding is further supported by a publication of Lappin et al. (2002). In this study oral administration of 4-chloro-2-methylphenoxyacetic acid (MCPA), a phenoxy herbicide, to the dog resulted in a significantly different pharmacokinetic profile to that observed in the rat. Excretion was much less rapid and metabolism more extensive in the dog and faecal elimination was an important route, particularly at higher doses. For the same dose levels area under the plasma curve (AUC) in dogs was up to one order of magnitude higher than in rats. These differences reflect the well-established low renal clearance of certain organic acids by dogs. Metabolic profiles from human volunteer studies, and indirect evidence from poisoning cases, suggest that in the case of MCPA (and the phenoxy herbicides in general) the rat is the more relevant model for human exposure.

BASF AG (2007) evaluated the relative rates of 2-phenoxyethanol metabolism in different species in vitro using liver S9 fractions. Since the haemolytic effects of 2-phenoxyethanol have been shown to be due to the intact parent compound (see chapter 7.9.3: BASF AG, 2007), any species differences in the overall metabolic fate of this compound could be useful in estimating interspecies variations in sensitivity to haemolysis.
The results indicated that the in vitro metabolism of 2-phenoxyethanol was primarily NADPH dependent, producing PAA as the major metabolite. The following species differences in the rate of PAA formation were found (from the highest to the lowest rate): human > rat > mouse > rabbit. With the exception of the rabbit data, these results were consistent with the in vitro relative sensitivity of these species to the haemolytic effects of 2-phenoxyethanol (see section 7.9.3: BASF AG, 2007).

These data suggest that metabolism of 2-phenoxyethanol to PAA is likely a detoxification pathway that limits haemolysis. In conclusion, human blood cells appeared to be more resistant to 2-phenoxyethanol-induced haemolysis than rat or rabbit blood cells and human liver tissue appeared to more rapidly metabolise 2-phenoxyethanol than either rat or

rabbit liver.

The dermal absorption of 2-phenoxyethanol through rat and human skin under static and flow-through conditions was investigated in in vitro studies by Roper et al. (1997). 2-Phenoxyethanol was rapidly absorbed through rat skin mounted in both the static and flow-through diffusion cell with either aqueous ethanol or modified Earle's medium (MEM) as receptor fluid. The stratum corneum did not appear to be a good barrier to 2-phenoxyethanol penetration. Covering increased the permeability coefficient of 2-phenoxyethanol in the static cell. The permeability profile and amount absorbed were similar for human and rat skin in the flow-through system with tissue culture medium. The mass balance recovery of 2-phenoxyethanol in the uncovered studies was low; static diffusion 68% and flow-through diffusion cell 51% at 24 h, due to the high evaporation. Percutaneous absorption values were determined as follows:

Rat: static (uncovered skin, 24 h): 64 ± 4%; static (covered skin, 24 h): 98.8 ± 7.0%; flow-through (uncovered skin, 24 h): 43 ± 3.7%

Human: flow-through (uncovered skin, 6 h): 59.3 ± 7.0%

Taking into account all metabolism/biokinetic data, there is no potential for bioaccumulation of 2-phenoxyethanol.

The physiologically-based pharmacokinetic (PBPK) model of Troutman et al (2015) was developed in order to reduce uncertainty associated with interspecies extrapolation and to derive margins of safety that can be used for risk assessment of phenoxyethanol, particularly after oral and dermal exposure. The total uncertainty factor for extrapolation of animal data to humans could be reduced from 100 to 25, i.e. if the margin of exposure is >25 the use of phenoxyethanol can be considered as safe.

References:

Lappin, G. J. et al. (2002). Absorption, metabolism and excretion of 4-chloro-2-methylphenoxyacetic acid (MCPA) in rat and dog. Xenobitika, Vol.32, No2, 153-163

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Human data

Skin sensitisation to 2-phenoxyethanol should be considered a very rare cause of adverse reactions in humans using cosmetics and topical antiseptics containing 2-phenoxyethanol. Extensive case histories and volunteer studies exist and these consistently report very low incidence rates of the order of 1 to 3 per 1000 individuals exposed. Such rates would certainly not justify classification for this effect.

Only 15 patients developed a positive reaction to Euxyl K400 (consisting of MDGN and 2 -Phenoxyethanol in a proportion of 1 to 4). Of these, 11 were positive to MDGN and 2 to phenoxyethanol. Sensitisation was more common in men. The agreement between sensitisation to Euxyl K400 and MDGN was good (Kp = 0.68), whereas agreement between Euxyl K400 and phenoxyethanol was poor (Kp = 0.23).

- Urine analysis: In 89 % of the samples 2-phenoxyethanol was detected (>= 0.1 mg/l, Cmax= 151 mg/l). In the rotation printing area significantly elevated 2-phenoxyethanol levels were detected compared to the delivery area.

Prick test with the body lotion gave +++ reaction (histamine ++). In an open application test the single ingredients of the body lotion for 30 minutes resulted in strong wheal reaction with pseudopods to phenoxyethanol (PE). Tests with all other ingredients were negative. The prick test with Euxyl K 400 1% petrolatum and with a dilution series of PE resulted in ++ reaction to Euxyl K 400 in a ++ reaction to Euxyl K 400 and in a + reaction to 1.0 % PE, * to 5.0 % PE, and ++ to 10 % PE. The same test in 2 control persons gave negative results.
The single components of the lotion (except PE) were negative also in the patch test. A serum sample from the patient was tested for IgE antibodies against PE with experimental prototype reagents. The test could not confirm the presence of IgE against PE. Total IgE were slightly elevated at 75.10 kU/l.An immediate reaction to PE with contact urticaria reaction to the body lotion was observed (1.0 % PE).
The strong +++ wheal reaction to the body lotion is not completely consistent with the results of the dilution series with PE. The reason for this difference might be the vehicle. The dilution series were performed in an aqueous solution, by which the percutaneous penetration and absorption might have been lowered.

Skin prick test with phenoxyethanol (10 %, 5.0 %, and 1.0 % in petrolatum) was positive in the patient, and negative in the two controls. IgE antibodies were negative. Total IgE was slightly elevated.

Twelve panelists had reactions of varying duration following irradiation. Five had readily visible but mild reactions (a score of 1) at 1 hour, three panelists had scores of 1 at 24 hours, and one had a score of 1 at both 1 and 72 hour. All of these reactions had subsided by the next evaluation. The final two panelists had reactions at 1, 24 and 48 hours, and at 1, 48 and 72 hours, respectively. All of these reactions were readily visible but mild. One panelist also had a mild reaction at 72 hours at the unexposed patch site. This panelist had no reactions at the irradiated site. It was concluded that phenoxyethanol was not phototoxic under the conditions of the study. Occasional incidence of slight erythema were observed at the irradiation site, but these were not considered significant since erythema was occasionally observed at both non irradiated sites and blank control patch sites.

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

- Safety Data Sheets
- European Chemical Agency ECHA
- Cosmetic Ingredient Review CIR
- Food and drug administration FDA

PROPOLIS EXTRACT (CAS: 85665-41-4)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

1400 -- - oral 90 day treatment. Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). Food Chem Toxicol. 1998 Apr;36(4):347-63 usual daily recommendation in dietary supplements: 0.25-0.50 g/day Shaw D, Leon C, Kolev S, Murray V. Traditional remedies and food supplements. A 5-year toxicological study (1991-1995). Drug Saf. 1997 Nov; 17(5): 342- 56.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50(oral) rat 12600 mg/kg To investigate the safety of propolis granule, the acute toxicity of the propolis granule produced from the propolis obtained from the Nan province was investigated. After feeding the rats with the propolis granule of 500 mg/kg BW, 1,000 mg/kg BW, 2,500 mg/kg BW, and 5,000 mg/kg BW, the normal behavior and physiological appearance during the period of the experiment were observed. It was observed that one rat, which had received the propolis granule of 5,000 mg/kg BW, died immediately after feeding. From the investigation, it was seen that propolis granule at doses up to 5,000 mg/kg BW is safe for administration to Wistar rats.

SKIN IRRITATION AND CORROSIVITY

not irritant

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritant

SKIN SENSITISATION

not sensitizer

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic

CARCINOGENICITY

not carcinogenic

REPRODUCTIVE TOXICITY

not toxic to reproductive

TOXICOKINETIC (ADME studies)

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

This finding concludes that propolis granule does not present any toxicity or abnormal symptoms on acute or subchronic administration to rats. In addition, no remarkable hematological or biochemical parameters or histopathology of the liver and the kidney were observed in rats after receiving propolis. Thus, this information on the toxicity of propolis granule can be used for application as pharmaceutical evidence for consumption of supplementary diet prepared from propolis as possessing no possibility of any toxic effects.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

- msds
- Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). Food Chem Toxicol. 1998 Apr;36(4):347-63
- Shaw D, Leon C, Kolev S, Murray V. Traditional remedies and food supplements. A 5-year toxicological study (1991-1995). Drug Saf. 1997 Nov; 17(5): 342-56.
- Evaluation of the Stability of Propolis Granule and Toxicity Study in Wistar Rats, Chiang Mai J. Sci. 2018; 45(1) : 162-176

PROPYLENE GLYCOL (CAS: 57-55-6)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

5300 -- https://cfpub.epa.gov/ncea/pprtv/documents/PropyleneGlycol.pdf

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

NON-TOXIC
LD50 20800 mg/kg RAT ORAL AND CUTANEOUS
LC50 FISH > 5500 mg/l
INHALATION TOXICITY: 31704 mg/m3
DDVELOPMENTAL NOAEL MATERNAL: 52 mg/kg
NOAEL FETAL: 10000 mg/kg
DERMAL TOXICITY: NOEL: 246720 mg/m2

SKIN IRRITATION AND CORROSIVITY

NOT IRRITANT

MUCOSAE IRRITATION AND CORROSION (eye irritation)

NON CORROSIVE

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

SKIN SENSITISATION

NOT SENSITIZING

DERMAL/PERCUTANEOUS ABSORPTION

Following the application of 1200 microlitres/cm2, the % absorbed was 0.14%. It was also recorded that the stratum corneum was damaged by continuous exposure to propylene glycol.

MUTAGENESIS / GENOTOXICITY

Not genotoxic / mutagenic

CARCINOGENICITY

Not carcirogenic

REPRODUCTIVE TOXICITY

NEGATIVE

NOAEL: 10100 mg/kg

TOXICOKINETIC (ADME studies)

Propylene glycol is rapidly absorbed following oral administration. About 10% of the substance is distributed in the tissues, mostly in the liver and kidneys. The main route of excretion is urine.

PHOTOINDUCED TOXICITY

Not phototoxic or photoallergenic

DATA ON MAN

No data

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EPA, United States Environmental Protection Agency.

RETINYL PALMITATE (CAS: 79-81-2)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

7,71 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/13687/7/6/1

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 2 000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

not skin irritant
Additional information:
In the key study for skin irritation according to the OECD guideline 404 (deviation from current guideline: occlusive application, observation period), retinyl acetate (860 mg/g test substance or 86% in the test substance) induced mean scores for erythema of 2.3 and edema of 1.0 (24, 48 and 72 hours, 6 animals) in Vienna White rabbits (BASF 82/202-205). Erythema were found to be not fully reversible in 5/6 animals until the end of the observation period (8 days), whereas edema fully reversed within 8 days. Scaling was observed in 6/6 animals at the end of the study.
Althought the present key study on retinyl palmitate does not meet the criteria for classification as a skin irritant according to directive 67/548/EEC, the supportive study and the findings from structurally similar substances, i.e retinyl acetate and retinyl propionate, provide evidence for dermal irritative potential of this substance group, warranting a respective classification. However, the dermal irritative potential of retinyl palmitate appears to be lower than for retinyl acetate and retinyl propionate on the basis of the present data.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not eye irritant
Additional information:
The key study for eye irritation was performed according to GLP and OECD guideline 405, using New Zealand White Rabbits and undiluted test substance (approx. 95% retinyl palmitate; DSM 221016). For eye irritation the mean irritation score (24 and 48 and 72 hrs) for conjuctival redness was 0.3, in 1/3 animals. No effects on corneal opacity, iris lesion or chemosis of the conjuctivae were noted. No adverse effects on the eye was noted after administration of the test substance when diluted (30%). The test substance was not an eye irritant under the conditions of the study.

SKIN SENSITISATION

not skin irritant
Additional information:
A reliable skin sensitisation GLP guideline (OECD 406) study (GPMT) was performed in guinea pigs: 4/20 animals after 24 hours, 2/20 animals after 48 hours showed dermal reaction after challenge. No skin reactions were noted at challenge in control groups and at re-challenge in treatment/control groups.

DERMAL/PERCUTANEOUS ABSORPTION

A higher recovery was found, i.e 106.2% (Gel, 24h), when charcoal filter paper was placed on top of the protective patch around the edges of the dosing area for 1h after test substance application, indicating evaporation of retinol from the dosing site.

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
In the key study for bacterial mutagenicity similar to OECD TG 471, no mutagenic effects were noted in Salmonella typhimurium strains (TA 1535, TA 1537, TA 1538, TA 98, TA 100)

CARCINOGENICITY

not classified as carcirogenic
Additional information:
No key study addressing carcinogenicity according to current standard protocols are available for retinyl palmitate. However, retinol and respective ester have been reported in literature and reviewed in the context of their putative potential to exert cancer preventive activity (IARC 1998). A limited evidence for cancer preventive activity has been noted in animal studies on the basis of consistent inhibitory effects in rat mammary cancer models and equivocal effects in mouse mammary cancer models. A limited number of animal studies showed increased tumor incidences, i.e. mammary adenocarcinomas, benign/malignant phaeochromocytomas after long term maintenance with retinyl palmitiate and/or retinyl acetate.
On the basis of human studies, evidences suggest a lack of cancer preventive activity for cancers at the aero-digestive tract, lung, breast, colorectal, bladder, prostate and stomach. However, according to observational epidemiological studies, no consistent evidence for a relation between dietary retinol and increased cancer rates was shown.
On the basis of all available information on genotoxicity of retinyl palmitate and relevant studies on its respective structural and metabolic analoges retinol and retinyl acetate, retinyl palmitate is defined to be non-genotoxic in a weight of evidence.
Taken together, no indication is given for further testing retinyl palmitate in a carcinogenicity study.

REPRODUCTIVE TOXICITY

not classified as reproductive toxic
Additional information:
Developmental studies with retinyl palmitate was performed, in cynomolgus monkeys (Hendrickx 2000):
NOAEL developmental = 4.1 mg/kg bw/d
NOAEL maternal = 11 mg/kg bw/d.

TOXICOKINETIC (ADME studies)

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Basic toxicokinetics:
Vitamin A is a micronutrient essential for most mammalian species and is one of three fat soluble Vitamins. The term “Vitamin A” is used as a generic descriptor for compounds that exhibit the biological properties of retinol or other closely related naturally occurring derivatives. Vitamin A occurs in nature primarily as retinyl ester and retinol. It is an essential factor for the growth and maintenance of higher organisms. It is required for visual function, epithelial cell differentiation and reproduction.
Dietary Vitamin A, which is mostly in the form of retinyl esters, is absorbed in the upper part of the small intestine by mechanisms similar to those for lipid absorption. The esters undergo hydrolysis to release retinol, which is incorporated into mixed micelles and absorbed by enterocytes, where it is bound to an intra-cellular protein called CRBPII (cellular retinol binding protein II). It is then re-esterified to form retinyl esters. The esters are incorporated into chylomicrons and are hydrolyzed in the general circulation. Chylomicron remnants are taken up by tissues, particularly the liver. Remnants are degraded within the hepatocytes, and the released retinol is transferred to stellate cells for storage after re-esterification.
In the present study on basic toxicokinetics, the exposure to retinyl palmitate and its main metabolites in plasma was examined within the framework of prenatal developmental toxicity studies in cynomolgus monkeys (Hendrickx 2000). Retinyl palmitate was administered daily to female monkeys by nasogastric intubation at dose levels of approx. 4.1, 11, 22, 44 mg/kg (7500, 20000, 40000, 80000 IU/kg) during early pregnancy (i. e. between gestational days 16 and 27). Control monkeys were administered the vehicle (physiological saline or distilled water). Retinol, retinyl esters and the metabolites were determined using a reversed-phase HPLC assay.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Direct observations: clinical cases, poisoning incidents and other
Single oral application of 10000 IU or 30000 IU retinyl palmitate, corresponding to the maximum allowed daily dose and of Vitamin A during pregnancy (and its 3 fold increased dose, respectively) produced
significant increases in plasma retinyl esters and RAs. In contrast, no siginficant changes in REL, retinyl esters and RAs levels were observed after daily dermal application for 21 days of the same doses.

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

RHUS GLABRA EXTRACT (CAS: 90106-33-5)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

5000 -- - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC8229005/

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

ACUTE TOXICITY (Oral, dermal, inhalation, ..)
LD50 oral (rat) > 5000 mg/kg bw
SKIN IRRITATION AND CORROSIVITY
no data
MUCOSAE IRRITATION AND CORROSION (eye irritation)
no data
SKIN SENSITISATION
no data
DERMAL/PERCUTANEOUS ABSORPTION
no data
MUTAGENESIS / GENOTOXICITY
no data
CARCINOGENICITY
no data
REPRODUCTIVE TOXICITY
no data
TOXICOKINETIC (ADME studies)
no data
PHOTOINDUCED TOXICITY
no data
DATA ON MAN
no data
BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- NIH, National Libraty of Medicine

RIBES NIGRUM SEED OIL (CAS: 68606-81-5 / 97676-19-2)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

10000 -- - EMA, https://www.fitoterapia.net/archivos/201712/wc500240199.pdf?1
Additional information:
Feeding mice with a daily dose of 3 g/kg of dried leaves during 6 months did not reveal any toxicity (Hänsel et al., 1994).

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) 49 g/kg

SKIN IRRITATION AND CORROSIVITY

No data

MUCOSAE IRRITATION AND CORROSION (eye irritation)

No data

SKIN SENSITISATION

No data

DERMAL/PERCUTANEOUS ABSORPTION

No data

MUTAGENESIS / GENOTOXICITY

No data

CARCINOGENICITY

No data

REPRODUCTIVE TOXICITY

No data

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

TOXICOKINETIC (ADME studies)

No data

PHOTOINDUCED TOXICITY

No data

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA European Chemical Agency
- EMA, European Medical Agency

SODIUM CHONDROITIN SULFATE (CAS: 9007-28-7 / 9082-07-9)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

1000 -- - FDA, https://www.fda.gov/files/food/published/GRAS-Notice-000666---Chondroitin-sodium-sulfate.pdf

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) >10000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

irritant

MUCOSAE IRRITATION AND CORROSION (eye irritation)

irritant

SKIN SENSITISATION

not skin sensitizer
Additional information:
As part of the above described subchronic toxicity study, additional investigations were performed to determine potential allergenicity, if any, of chondroitin sulfate sodium (Masiello and Oberto, 2013). For this, immunoglobulin IgG, IgA and IgE in serum from rats treated repeatedly with chondroitin sulfate sodium for 13 weeks by the oral route (dose levels: control, 250, 500 and 1000 mg/kg bw/day) were measured. No significant differences between pre-test and Week 13 data, nor between control and treated groups data were observed, with the exception oflgG in females dosed with 1000 mg/kg bw/day. In these animals, IgG from Week 13 samples were significantly lower at statistical analysis than controls at 13 weeks. In general the direction of this finding is not considered a concern. In addition, most of the IgG from pre-test phase samples were similar to those recorded during Week 13, therefore the decrease of IgG was considered irrelevant. IgG values in females dosed with 1000 mg/kg bw/day after 13 weeks of treatment in fact, were no significantly different from pre-dose values in the same group of animals and their values are considered to be normal values in the population of rats. The investigators concluded that no inflammation or immunological processes occurred following chondroitin sulfate sodium administration. The findings from this study corroborate the safety of chondroitin sulfate sodium.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not genotoxic / mutagenic
Additional information:
In three separate studies, the mutagenic effects of non-animal chondroitin sulfate sodium, the subject of this GRAS assessment, were investigated (Miraglia et al., 2016). These methods included a bacterial reverse mutation test (Ames test) using Salmonella typhimurium strains and Escherichia coli WP2 strains, an in vitro mammalian chromosomal aberration study in Chinese Hamster Ovary Cells (CHO), and a mutation in mouse lymphoma cell assay (Fluctuation Method). The results of these experiments indicate that chondroitin sulfate sodium is unlikely to be genotoxic. These studies support the safety of chondroitin sulfate sodium.
In Ames test:
Chondroitin sulfate
sodium was assayed in the toxicity test at a maximum concentration of 5000 !lg/plate and at four lower concentrations spaced at approximately half-log intervals: 1580, 500, 158 and 50.0 !lg/plate. No toxicity was observed with any tester strain at any dose level, in the absence or presence of S9 metabolism. Chondroitin sulfate sodium did not induce two-fold increases in the number of revertant colonies in the plate incorporation or pre-incubation assay, at any dose level, in any tester strain, in the absence or presence of S9 metabolism. It is concluded that chondroitin sulfate sodium does not induce reverse mutation in S. typhimurium or E. coli in the absence or presence ofS9 metabolism (Miraglia et al., 2016; Bisini and Oberto, 2011).

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

In a study in rats and dogs, Conte et al. (1995) investigated biochemical and pharmacokinetics aspects of chondroitin sulfate following oral treatment. Chondroitin sulfate was found to be partially absorbed from the gut, both as intact chondroitin sulfate and as lower molecular weight fractions of depolymerised material. In another study with radio-labelled chondroitin sulfate, Palmeri et al. (1991) reported that following ingestion, chondroitin is found in the plasma and in tissues such as the liver, kidneys and cartilage. Partially depolymerised chondroitin sulfate was found to be excreted in the urine (Conte et al., 1991). In a study in six subjects, Baici et al. (1992) reported that oral consumption of 2 g of chondroitin sulfate (64% chondroitin sulfate A and 32% chondroitin sulfate C) by 18 subjects did not produce measurable changes in the total serum concentration of glycosaminoglycans, suggesting that chondroitin sulfate is not absorbed. The possibility that low molecular weight, desulfated oligomers and monomers may be produced and absorbed could not be ruled out. Baici et al. (1992) described the results of studies conducted by other investigators including Palmieri et al. (1990), Conte et al. (1991), and others. Palmeieri et al (1990) reported that over 70% of the radioactivity administered orally to rats and dogs is absorbed. Conte et al. (1991) reported that the absolute bioavailability of the glycosaminoglycan was 13.2% of the administered dose of chondroitin sulfate. In another study described by Biaci et al. (1992), it was reported that following administration of 35S04-chondroitin sulfate orally to rats only a small portion of the radioactivity was absorbed. The remaining radioactivity was excreted in the feces. When 35S04¬ chondroitin sulfate was administered orally to rats pretreated with antibiotics to depress the bacterial flora, almost all the radioactivity was found in the feces. It was concluded that sulfatases present in the intestinal bacterial flora were responsible for sulfate splitting from the chondroitin sulfate chain, and that no intact chondroitin sulfate can be absorbed through the intestinal wall. Palmieri et al. (1990) dosed Wistar rats and dogs orally with 16 mg/kg bw of a mixture of tritiated chondroitin sulfate A and C (MW 14,000 D). More than 70% of the radioactivity was absorbed. Plasma levels showed a rapid increase after oral administration, followed by a large plateau with a maximum at the 14th and 28th h in the rat and in the dog, respectively. Radioactivity was found in tissues, and urine was the main route of excretion. However, the known lability of tritium coupled with the use of a chromatographic gel size that could not distinguish compounds in the molecular weight range of concern raise doubts that the measured radioactivity can be equated to chondroitin sulfate. However, as summarized in a review article by Bali et al. (200 1), other studies support that chondroitin sulfate is absorbed in the intestinal tract. In general, oral administration of 2 or 3 g of chondroitin sulfate to humans produced an increase in the concentration of chondroitin sulfates in the blood after 3-6 hours.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Specific Human Bioavailability Study
In summary, the results of this comparative pharmacokinetic study showed that the bioavailability of chondroitin sulfate, ~Di-4S and ~Di-OS in extent of absorption (AUC) was significantly higher after the test formulation as compared to the reference formulation. The difference in rate of absorption (Cmax) was less marked, while no significant difference in tmax was noted between the formulations. The test formulation, administered in single dose, is able to yield an increase in plasma chondroitin sulfate and deriving disaccharides whose bioavailability is higher than that of the reference formulation (higher extent of absorption). The safety and tolerability of a single dose of both products was excellent.
The safety assessment during this study showed 5 adverse events that occurred to 4 subjects (16.7%). These adverse events included cases of headache, abdominal discomfort, diarrhea, Presyncope, and neck pain. All the adverse events occurred after administration of the reference formulation, while no adverse event was reported after administration of the test formulation (chondroitin sulfate sodium). The reported events were not judged to be related to the intake of the chondroitin sulfate on the basis of the physician evaluation. No serious adverse events occurred during the study and no subject discontinued the study due to adverse events or other safety concerns. Similarly, no clinically meaningful effect on vital signs, body weight or laboratory parameters were observed. The results of this study suggest that microbial derived chondroitin sulfate sodium behaves similar to that of animal derived chrondroitin sulfate. These findings also indicate the safety studies of animal derived chrondroitin sulfate are applicable to microbial derived chondroitin sulfate sodium.
Human Observations
In a number of clinical studies, the effects of chondroitin sulfate alone or in combination with glucosamine on osteoarthritis and certain other health endpoints has been extensively .investigated. These studies did not reveal adverse effects. While these studies were not specifically designed to assess toxicity, the absence of adverse effects provides support for the safety. In these studies, use levels of chondroitin sulfate primarily ranged from 800 to 1200 mg/day.

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- EMA, European medical agency
- FDA, Food and Drug Administration

SYMPHYTUM OFFICINALE ROOT EXTRACT (CAS: 84696-05-9)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

100 -- - R I S K P R O F I L E Symphytum officinale extracts, Date of reporting 11.03.2013 - EMA, European Medical Agency. The therapeutic application of comfrey is overshadowed by the well-recognised toxicity of pyrrolizidine alkaloids (Barnes et al., 2007). There are no studies on single or repeated dose toxicity with Symphytum preparations available, neither for PA-containing preparations nor for PA-reduced preparations. It is often reported that acute/chronic ingestion of the (PA-containing) plant material is toxic due to its pyrrolizidine alkaloids content.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

no data

SKIN IRRITATION AND CORROSIVITY

Not classified accroding CLP regulation 1272/2008

MUCOSAE IRRITATION AND CORROSION (eye irritation)

Not classified accroding CLP regulation 1272/2008

SKIN SENSITISATION

No data

DERMAL/PERCUTANEOUS ABSORPTION

Low percutaneous absorption according EMA, European Medical Agency, due this properties percutaneous preparations with SYMPHYTUM OFFICINALE ROOT EXTRACT are safe for use. According worst case scenario dermal absorption Pyrrolizidine Alkaloids up to 4,9%. Usually this data much less than 0,02 - 0,4%

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
Comfrey root liquid extract (liquid extract from fresh Symphytum officinale root; extraction solvent: ethanol 60% (V/V), DER 1:2, pyrrolizidine alkaloid content <1 ppm) was investigated for its ability to induce gene mutations in the bacterial reverse mutation assay (Ames test) in Salmonella typhimurium strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 with and without metabolic activation using the mammalian microsomal fraction S9 mix (liver microsomal fraction derived from male Wistar rats) and plated on selective medium according to the direct plate incorporation and the pre-incubation method. Reference mutagens (4-NOPD, 2-AA, NaN3, MMS) were used to check the validity of the experiments. Comfrey root fluid extract showed no biologically relevant increases in revertant colony numbers of any of the five tester strains in 6 different concentrations (0.0306-5 µl/plate), neither in the presence nor in the absence of metabolic activation. The reference mutagens induced a distinct increase of revertant colonies indicating the validity of the experiments. In conclusion, the comfrey root fluid extract was not mutagenic in the bacterial reverse mutation assay (Benedek et al., 2010). According CoA, max. contain of Pyrrolizidine Alkaloids <0,2%

CARCINOGENICITY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

No data
Additional information:
Due to the availability of Pyrrolizidine Alkaloids Genotoxic/Carcinogenic Activities Can Also Be Found. According CoA, max. contain of Pyrrolizidine Alkaloids <0,2%

REPRODUCTIVE TOXICITY

no data
Additional information:
Due to the availability of Pyrrolizidine Alkaloids Genotoxic/Carcinogenic Activities Can Also Be Found. According CoA, max. contain of Pyrrolizidine Alkaloids <0,2%

TOXICOKINETIC (ADME studies)

Data on absorption of pyrrolizidine alkalaoids are limited and different values are found. The absorption of pyrrolizidine alkaloids through skin in the form of free base may amount to 5% compared to after oral intake (Council of Europe 2008). In an animal study, topical application of an extract resulted in very low absorption of pyrrolizidine alkaloids and 0.1-0.4% was recovered in the urine over the next 24 hours (Sigma-Aldrich). Pyrrolizidine alkaloids are metabolised in the liver and converted to necines and other metabolites. Depending on the structure of the original pyrrolizidine alkaloids, this may eventually lead to end product s which can cause alkylation of DNA (Council of Europe 2008). Absorption In ex vivo experiments, permeation of rosmarinic acid across excised rat skin was about 8 times higher from alcoholic solution than from water, indicating that ethanol may act as a sorption promoter. The flux from water or alcoholic solution was 4.4 or 10 µg/cm2 /h, and the lag time (tlag) was 7.8 or 3.7 h, respectively. Upon topical administration of rosmarinic acid in form of a W/O (water in oil) ointment (25 mg/kg, 50 cm2), the absolute bioavailability was 60% (Ritschel et al., 1989). For available pharmacokinetic data concerning pyrrolizidine alkaloids it is referred to the “Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs)” (EMA/HMPC/893108/2011). Rats suckled by mothers fed lasiocarpine, a pyrrolizidine alkaloid found in comfrey, developed liver damage (Cupp, 2000). After oral administration of tritiated senecionine and seneciphylline to lactating rats, radioactivity was excreted into the milk with concentrations 50% less compared to the blood concentrations. After 6 h 83% of the radioactive necine bases remaining in the blood were not dialyzables, indicating a tight (possibly covalent) binding to macromolecules, such as albumin. Six hours after administration of the pyrrolizidine alkaloids the highest concentrations were detected in the liver and lungs of the rats (De Smet et al., 1992). A study performed with lactating mice, using the same pyrrolizidine alkaloids but 14C-labeled and injected via the intraperitoneal route, showed that 66- 75% of the radioactivity was excreted in the urine, 14-18% in the faeces, 1.14% in the milk of the animals, and 0.2-0.5% was expired as CO2. The highest concentrations of radioactivity were found in the liver (De Smet et al., 1992)

PHOTOINDUCED TOXICITY

No data

DATA ON MAN

no data

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

- R I S K P R O F I L E Symphytum officinale extracts, Date of reporting 11.03.2013
- EMA, European Medical Agency.
- ECHA, European Chemical Agecy

TAMUS COMMUNIS EXTRACT (CAS: 84961-63-7)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

2500 -- - WHO, https://econtent.hogrefe.com/doi/10.1024/0300-9831.71.3.149
additional information:
Various studies have demonstrated that the nutrient and non-nutrient substances present in vegetables and fruit (V&F) are most likely to be responsible for the beneficial effect of the increased V&F consumption. Urged by scientific evidence, current dietary guidelines strongly recommend the consumption of V&F in substantial amounts. In a recent paper (Brit. J. Nutr. 2000; 84, 549-556) V&F availability in 10 European countries was compared with the WHO recommendations (minimum combined V&F intake of about 400 g/day/person), as well as with guidelines of a minimum daily intake of three portions of vegetables (approx. 250 g/person) and two portions of fruit (approx. 150 g/person). All countries, excluding Greece, had a vegetable intake below the recommended minimum. Moreover, in all countries, the percentages of low vegetable consumers were significantly higher than those of low fruit consumers, suggesting that there is considerable room for improvement in the intake of vegetables, an important source of antioxidants. Wild edible greens are among the vegetables commonly consumed in Greece. These greens have a high flavonoid content, which in several cases substantially exceeds the respective values in foods and beverages, such as onions, black tea and red wine (Food Chemistry 2000; 70, 319-323). The high flavonoid content of edible wild greens requires consideration of their role in contemporary diet, as a possible mean for increasing vegetable consumption.

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

no data

SKIN IRRITATION AND CORROSIVITY

no data

MUCOSAE IRRITATION AND CORROSION (eye irritation)

no data

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

no data

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- WHO, World Healt Organisation

TOCOPHEROL (CAS: 54-28-4 (gamma)/ 16698-35-4(beta) / 10191-41-0(DL) / 119-13-1 / 1406-18-4 / 1406-66-2 / 2074-53-5 (DL) / 59-02-9 (D)/7616-22-0)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

500 -- - ECHA, European Chemical Agency. Additional information: Repeated oral dose toxicity:
- subchronic (90-day), rat (oral, gavage), NOAEL = 500 mg/kg bw
- subacute (28-day), rat (oral, feeding), NOAEL ca. 1111 mg/kg bw
- subacute (28-day), dog (oral, feeding), NOAEL >= 360 mg/kg bw

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 rat (Oral): >15.000 mg/kg (OECD Guid. 401)
LD50 rat (Dermal): > 5000 mg/kg (OECD Guid. 402)

Additional information:
The acute oral median lethal dose (LD50) of the test item in the rat was estimated to be greater than 15000 mg/kg bw. According to the a.i. concentration the LD50 of the a.i. (CAS: 1406-66-2) is calculated to be greater than 7500 mg/kg bw.

The acute dermal mediam lethal dose (LD50) of the test item in the rabbit was estimated to be greater than 5000 mg/kg body weight.

SKIN IRRITATION AND CORROSIVITY

slightly irritating
Additional information:
The purpose of this study was to evaluate the degree of irritation produced by the test article, DL-a-Tocopherol, when applied to the intact skin of the albino rabbit. The procedures used were in accordance with those described in OECD Guideline for the Testing of Chemicals, No. 404 (adopted 17th July 1992).
A 0.5 ml aliquot of the test article was spread evenly over a 2.5 cm square of surgical lint and applied over a previously clipped area of the dorsal skin of 3 albino rabbits. The test article was held in contact with the skin, under a semi-occlusive patch assembly, for a 4 hour period. At the end of this period, the patches were removed and the treated skin site on each animal gently cleansed with water. Reaction to treatment, i.e. erythema and eschar as well as oedema formation was assessed 1, 24, 48 and 72 hours and, for 2 animals, also 7 and 14 days after patch removal.
There were no apparent signs of irritation at the treated skin site of the animal used in the preliminary screen throughout the 72 hour observation period.
In 1 of the 2 remaining animals, erythema appeared to increase throughout the initial observation period and at the 72 hour examination it was noted to be moderate to severe. Barely perceptible oedema was also visible 48 and 72 hours after patch removal at the treated skin site of this animal. In a second animal, irritation was evident from 72 hours after patch removal and consisted of barely perceptible erythema and oedema at the treated skin site. Signs of irritation were still evident in both animals at day 7 but subsided completely by day 14.
The Primary Irritation Index for the three animals was calculated to be 1.2.
Under the conditions of this study, the test article, DL-a-Tocopherol as such, may be considered as a slight irritant to the skin of the albino rabbit.
It can be assumed accordingly, that cutaneous exposure to DL-a-Tocopherol such as may potentially give rise to an irritant skin reaction in humans.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritating
Additional information:
The eyes of six animals were not washed out after instillation of the test article. The eyes of 3 animals were washed out, approximately 4 seconds after instillation of the test article, by flushing with physiological saline until all visible test article was removed.
Single application of the test item in the eyes of 9 rabbits was well-tolerated (primary irritation score = 0.0). Based on this result it can be expected that the test item is not irritating to eyes.

SKIN SENSITISATION

not sensitizer
Additional information:
The evaluation of the skin sensitizing potential of RRR-(alpha-, beta-, gamma-, delta)-tocopherol is based on one in-vivo study with the test substance and three in-vivo studies with the a close homolog (RRR-alpha-tocopherol) and a reliable publication.
The skin sensitising potential of the test item was assessed using the Guinea pig maximization test. The assays are done according to the OECD guideline 406.
Key Study:
The test substance, RRR-(alpha-, beta-, gamma-, delta)-tocopherol, was tested for its sensitisation potential in guinea pigs, using the method of B. Magnusson and A. M. Kligman, J. Invest. Dermatol. 52, 268 -276 (1969). The test substance was applied in oily dilutions. 24 and 48 hours after removing of the patches of the challenge application no skin reactions were observed on the test animals as well as on the control animals. According to these test results the test substance can be regarded as a "non-sensitiser" for albino guinea pigs.
Supporting Study:
The study is done with a close homolog of the test substance, RRR-alpha-tocopherol.
For the GPMT 20 female test animals and 20 controls, Pirbright white strain, were used. For the dilution of the test concentration of the intracutaneous test soybean oil and for the epicutaneous application paraffinum album were used.
24 and 48 hours after the removing of the patches of the challenge application neither the test nor the control animals showed any skin reactions on the treated skin areas.
According to these test results the test item can be classified as "no skin sensitizer" in the Magnusson-Kligman test on guinea pigs.
Supporting Study:
The second supporting study was done with a close homolog of the test substance, RRR-alpha-tocopherol, according to the key study. 24 and 48 hours after the removing of the patches of the challenge application neither the test nor the control animals showed any skin reactions on the treated skin areas.
According to these test results the test item can be classified as "no skin sensitizer" in the Magnusson-Kligman test on guinea pigs.
Supporting Study:
This study was also done with a close homolog of the test substance, RRR-alpha-tocopherol.
The sensitising properties of RRR-alpha-tocopherol (Purity 87%) were evaluated in the guinea pig maximization test.
20 guinea pigs were used for the test group and 19 guinea pigs were used for the control group.
Sensitisation rates were 0/20 and 0/19 in the test and control group, respectively. The test substance was not a sensitiser under the conditions of this study.
The information available on the skin sensitizing potential of the test item show no need for a classification of the test item concerning skin sensitization.
Migrated from Short description of key information:
Skin sensitisation:
Key: not sensitising (GPMT)
Supporting: RA: 59-02-9, not sensitising (GPMT)
Supporting study: RA: 59-02-9, not sensitising (GPMT)
Supporting study: RA: 59-02-9, not sensitising (GPMT, publication)
Justification for selection of skin sensitisation endpoint:
Most reliable guideline study was choosen for classification

DERMAL/PERCUTANEOUS ABSORPTION

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Skin permeation studies were conducted using modified Franz diffusion cells and human cadaver skin as the membrane. Specifically, 5% (w/w) alpha--tocopherol acetate was formulated in ethanol, isopropyl myristate, light mineral oil, 1% Klucel® (hydroxypropyl cellulose) gel in ethanol, and 3% Klucel® gel in ethanol (w/w). Samples from the receiver were collected at 2, 4, 6, 8, 12, 24, 30, 36, and 48 hours and analyzed by HPLC for concentrations of alpha-tocopherol acetate and alpha-tocopherol. The permeabilities through human cadaver skin were 1.0 x 10-4 , 1.1 x 10-2 , 1.4 x 10-4 , 2.1 x 10-4 , and 4.7 x 10-4 cm/h for the ethanol solution, isopropyl myristate solution, light mineral oil solution, 1% Klucel® gel, and 3% Klucel® gel, respectively (Mahamongkol et al., 2005).
In an in vitro skin absorption test (similar to OECD 428, non-GLP), it is concluded that DL-alpha-tocopheryl acetate-3H penetrates into and through intact and stripped pig skin (Csato and Klecak, 1995). The total skin penetration rates of DL-alpha tocopheryl acetate 3H from 3 alpha-hydroxy-acid creams were time-, formulation type- and skin condition-dependent, although being not significantly different. The percutaneous absorption observed was in the range of 1.1 – 4.2 %, tested at 1h, 6h and 18h exposure with 3 different formulations (nominal dose 5%).
From this experiment, the dermal absorption rate of RRR-(alpha-, beta-, gamma-, delta)-tocopherol in humans is therefore estimated to be 5%.

MUTAGENESIS / GENOTOXICITY

not genotoxic / mutagenic
Additional information:
In-vitro: Bacterial reverse mutation assay:
- RA: 7695-91-2, Ames test, negative
- RA: 10191-41-0, Ames test, negative
In vitro, cytogenetics:
- RA: 59-02-9, chromosome aberration, negative
- RA: vitamin E, chromosome aberration, negative
In vitro mammalian cell gene mutation:
- RA: 7616-22-0, negative
- RA, in vivo chromosome aberration, negative
Endpoint Conclusion: No adverse effect observed (negative)

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
No apparent differences in reproductive indices were seen between controls and treated groups of parents. Mean gestation period, litter size, sex ratio, and mortality of pups and parents were unaffected by the test substance.
Hematology and clinical chemistry done after 255 days of treatment revealed no toxicologic differences between control and high dose group. None of the organ weights (neither absolute nor relative) of the treated groups were significantly different from control. Microscopic examination of tissues of high dose and control F0 and F1b animals revealed no morphological changes that were attributable to ingestion of the test substance.
Ingestion of the test substance had no effect on body weight gain of the pups.
Based on default values in the REACH guidance Chapter R.8: Characterisation of dose [concentration]-response for human health (Table R8 -17); using the daily intake of 20 gram/day: and the average body weight of the rats of 0.5 kg (data of the 90 day study), the NOAEL of 2% is converted to 800 mg/kg bw/day.

The administration of up to 1600 mg/kg bw of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of-abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

Based on the available data, vitamin E does not need to be classified for effects on fertility and developmental toxicity according to Annex I of Directive 67/548/EEC and according to EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008.

TOXICOKINETIC (ADME studies)

No information from guideline studies for RRR-(alpha-, beta-, gamma-, delta)-tocopherol per se is available.
For the assessment of the toxicokinetic properties, data on the structural analogs alpha-tocopheryl acetate and DL-alpha-tocopherol were taken into account as the Vitamin E ester is rapidly hydrolysed by esterases to alpha-tocopherol under physiological conditions as shown in numerous in vitro and in vivo studies. See read-across hypothesis and justification.
General remarks on absorption and metabolism of Vitamin E (EFSA, 2006 and 2010):
The bioavailability of vitamin E and its esters is related to the efficiency of absorption. Intestinal absorption of lipids and fat-soluble vitamins depends on pancreatic function, biliary secretion to form micelles with the hydrolysed fat, and transfer across intestinal membranes. Nearly all of the vitamin E absorbed across the intestinal mucosa is free tocopherol. In vivo and in vitro studies suggest that the rate of uptake of vitamin E is controlled by passive diffusion. Absorption of tocopherols is incomplete; the extent of absorption is dependent on intake and varies between 20-80%. The proportion absorbed decreases with increasing amount added to experimental diets; the average absorption is about 40-60% while pharmacological doses of 200 mg and more are absorbed to the extent of <10%. Cannulation studies indicate that there is no difference in absorption between alpha-tocopherol and alpha-tocopheryl acetate at physiological doses. At high levels of intake, (> 400 IU/day) a higher degree of absorption was obtained with free tocopherol than tocopheryl esters. About 90% of the free alpha-tocopherol is transported via the lymphatic system into the bloodstream, where it is distributed into lipoproteins on passage into the liver. Tocopherol is excreted as a water-soluble conjugated compound resulting from different oxidation steps.
Oral and intravenous studies:
After oral administration of DL-alpha-tocopheryl acetate (4 ml emulsion with 2 mg DL-alpha-tocopheryl acetate and 50 µC of DL-alpha -tocopheryl-1',2'-3H2-acetate to rats alpha-tocopheryl acetate is extensively metabolised by rat tissues. The adrenals, ovaries, adipose tissue and heart appeared to extract vitamin E from the blood for up to 48 hours after absorption. The metabolite most abundantly occurring under these conditions was alpha-tocopheryl quinone. In the adrenal glands, however, the most highly labeled compound was unesterified tocopherol. The authors concluded that the adrenal tissue played a definite role in the metabolism of vitamin E. (Gallo-Torres, 1971). From these data on oral uptake, theoral absorption is set at 100% (regardless the vehicle).
Thirty minutes after intravenous administration of DL-alpha-tocopheryl acetate (1 ml emulsion with 136 IU unlabeled DL-alpha-tocopheryl acetate and 25 µC of DL-alpha-tocopheryl-1',2'-3H2 –acetate) to rats, 96% of the chromatographed radioactivity was due to unchanged alpha-tocopheryl acetate. Forty eight hours after injection, only 8% of the chromotographed radioactivity found in plasma corresponded to alpha-tocopheryl acetate as such. At this period 16% was metabolised to "free" tocopherol and 64% to tocopheryl quinone. Most of the radioactivity accumulated in the liver. In the liver, alpha-tocopheryl acetate, is rapidly and extensively hydrolysed: 48 hours after injection only 2.8% of the chromatographed radioactivity was due to the injected alpha-tocopheryl acetate. Also the spleen and lung tissues metabolized alpha-tocopheryl acetate extensively. The uptake of the brain and pituitary was very slow compared to the skeletal muscle, adipose tissue, small intestine, adrenals and ovaries which showed a gradual increase in radioactivity in time. After i.v. administration only traces of alpha-tocopheryl acetate in the small intestine were observed. The authors conclude that the intestine of the rat is able to hydrolyze alpha-tocopheryl acetate almost completely (Gallo-Torres, 1971).
Dermal studies:
After dermal application an in vitro study has demonstrated the metabolism of alpha-tocopheryl acetate to alpha-tocopherol in viable pig skin. Topically applied alpha-tocopheryl acetate was bioconverted to the active molecule and free radical scavenger alpha-tocopherol within the skin tissue. No metabolism was detectable in the stratum corneum. This study has also elucidated the kinetics of metabolism of alpha-tocopheryl acetate. The extent of metabolism was highest at 6-12 hours after application. Longer time periods failed to produce a higher extent of metabolism, probably due to the saturation of the hydrolytic pathway (Rangarajan and Zatz, 2001).

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Direct observations: clinical cases, poisoning incidents and other
Subjects:
- Number of subjects exposed: 5
- Known diseases: healthy

Route of exposure: dermal
Details on exposure: 70 µl of the test item was applied on the upper arm (Large Finn chamber) and left theier for 24 h under occlusive conditions.Erythema and edema scores were noted after 1, 24, 48, 72 and 144 h after removal of test item.

Examinations: Erythema, edema
Clinical signs: Only one volunteer showed erythema and edema. The reactions were located in the area of the patch but not where the test item was applied.

Executive summary:
The toxic-irritative effect of the test item was investigated in the modified During-chamber test in five volunteers. No reactions were observed (erythema-edema). The test item is considered to be tolerated well on human skin.

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

TOCOPHERYL ACETATE (CAS: 7695-91-2 / 58-95-7)

NOAEL or SUBCHRONIC TOXICITY (90 days) or SUB-ACUTE TOXICITY (28 days) + DATA SOURCE

500 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/13377/7/6/1

Additional information:
The NOAEL of 500 mg/kg bw/day was based on a well conducted 90-day study in rat comparable to OECD guideline 408 (Abdo, 1986).

ACUTE TOXICITY (Oral, dermal, inhalation, ..)

LD50 oral (rat) > 10 000 mg/kg bw
LD50 dermal (rat) > 3000 mg/kg bw
Additional information:
The acute oral toxicity of Vitamin E acetate was determined for Sprague-Dawley rats. The test material was applied as a 50% solution in olive oil. The animals received a single application of 10000 mg/kg bw by gavage. The median lethal dose (LD50) was >10000 mg/kg bw for males and females.
D, L- alpha-Tocopheryl acetate, which is a derivative of Vitamine E, has been tested in an acute dermal toxicity test (similar to OECD 402, test system: Rat).
A maximum dosis of 3000 mg/kg was applied as the pure substance, which is a viscous oil. A low dosis of 1000 mg/kg was a mixture of the substance with a vegetable oil. This same oil was applied in control groupsNo dermal LD50 could be achieved up to 3000 mg/kg, since no mortality occured.
The test substance causes only slight local erythemas which appear 24 - 48 hours after application. Only few animals showed signs of local abrasion. Female animals are slightly more sensitive to treatment than male animals. Bodyweights were reduced in all groups after the initial 24 h application period. In male groups further weight development was normal. For treated females a slight retardation of weight gain was evident during the first week of the observation period. Final autopsies showed no abnormalities that could be related to treatment.

SKIN IRRITATION AND CORROSIVITY

not irritating
Additional information:
Three Vienna White rabbits were applied the undiluted test substance for 4 hours in accordance with OECD guideline 404. The test substance was not a skin irritant.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritating
Additional information:
The undiluted test substance was instilled into the right eye of each of three rabbits. The left eyes remained untreated and served as control. The eyes were scored at 1, 24, 48, and 72 hours after instillation. Slight irritation was noted at 1-48 h; the eyes were normal at 72 h.

SKIN SENSITISATION

not sensitising
Additional information:
DL-Alpha -Tocopheryl acetate is not a sensitiser as tested in a photoallergic test in Guinea pigs, and with the method of Draize in 203 human volunteers.

DERMAL/PERCUTANEOUS ABSORPTION

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

This study was set up to test the penetrating ability of vitamin-E-acetate (activity: 20 uCi/g) in AHA (alpha-hydroxy-acid) creams into and through explanted domestic pig skin.
The penetration into the stratum corneum and into the living layers of the intact pig skin was time-, and formulation type-dependent. After 6 hours of exposure the mean penetration rates into the horny and living skin layers were: 11.32 ug/cm2 (formulation A), 12.19 ug/cm2 (formulation B) and 7.84 ug/cm2 (formulation H).
Penetration into the stratum corneum was higher than absorption into the living skin layers.
No significant further increase of the total pentration rates occurred by increasing the exposure time up to 18 hours.
In general, removal of the stratum corneum by stripping resulted in non significant increase of the penetration rate, a property likely to be accounted for by the lipophilic nature of the compound.
Based on these experimental data, it is concluded that Vitamin-E-Acetate3H penetrates into and through the intact and stripped pig skin from the 3 formulations tested.

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
No effects were noted in
-an Ames test, OECD 471, GLP (DSM (E.Gocke), 1999)
-an in vitro chromosome aberration test in human lymphocytes, OECD 473, GLP (DSM (A.Chetelat), 1999)
- an in vitro chromosome aberration test in CHL cells, near-guideline and non-GLP with structural analogue alpha-tocopherol (Ishidate, 1984)
-an in vitro gene mutation test in CHO cells, near guideline and non-GLP with structural analogue gamma-tocopherol (Cornwell, 2002)
-an in vivo micronucleus test, similar to OECD 474, non-GLP (Umegaki, 1997).
Thus, DL-Alpha-Tocopheryl acetate is not considered to be genotoxic.

CARCINOGENICITY

not carcirogenic
Additional information:
In a feed study DL-Alpha-Tocopheryl acetate was given to rats at 500, 1000 and 2000 mg/kg bw for 104 weeks (Wheldon, 1978). From this study it was concluded that the test substance has no carcinogenic effects.

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
In a one-generation reproduction rat toxicity study (comparable to OECD 415), the reproductive indices of the treated groups were unaffected and the offspring developed normally. The NOAEL was 800 mg/kg (corresponding to 2%).
In a teratogenicity study with rats and rabbits (equivalent or similar to OECD Guideline 414, pre-GLP), no significant difference in malformations between the control and the treated groups. The NOAEL is >1600 mg/kg bw/day for both species.

TOXICOKINETIC (ADME studies)

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

After oral administration of DL-Alpha-Tocopheryl acetate (4 ml emulsion with 2 mg DL-Alpha-Tocopheryl acetate and 50 µC of d, l-α-tocopheryl-1',2'-3H2-acetate) to rats. DL-Alpha-Tocopheryl acetate is extensively metabolised by rat tissues.
The adrenals, ovaries, adipose tissue and heart appeared to extract vitamin E from the blood for up to 48 hours postabsorptively. The metabolite most abundantly occurring under these conditions was alpha-tocopheryl quinone. In the adrenal glands, however, the most highly labeled compound was unesterified tocopherol. The authors concluded that the adrenal tissue played a definite role in the metabolism of vitamin E. (Gallo-Torres, 1971). From these data on oral uptake, the oral absorption is set at 100% (regardless the vehicle).
Thirty minutes after intravenous administration of DL-Alpha-Tocopheryl acetate
(1 ml emulsion with 136 I. U. unlabeled DL-Alpha-Tocopheryl acetate and 25 µC of DL-Alpha-Tocopheryl-1',2'-3H2-acetate) to rats, 96% of the chromatographed radioactivity was due to unchanged DL-Alpha-Tocopheryl acetate. Forty eight hours after injection, only 8% of the chromotographed radioactivity found in plasma corresponded to DL-Alpha-Tocopheryl acetate as such. At this period 16% was due to unesterified tocopherol and 64% to tocopheryl quinone. Most of the radioactivity accumulated in the liver. In the liver, DL-Alpha-Tocopheryl acetate, is rapidly and extensively hydrolysed: 48 hours after injection only 2.8% of the chromatographed radioactivity was due to the injected DL-Alpha-Tocopheryl acetate. Also the spleen and lung tissues metabolized DL-Alpha-Tocopheryl acetate extensively. Whereas the skeletal muscle, adipose tissue, small intestine, adrenals and ovaries showed a gradual increase in radioactivity in time, the uptake of the brain and pituitary was very slow compared to that of other organs. After i. v. administration only traces of DL-Alpha-Tocopheryl acetate in the small intestine were observed. The authors conclude that the intestine of the rat is able to hydrolyze DL-Alpha-Tocopheryl acetate almost completely (Gallo-Torres, 1971)
Dermal absorption
In an in vitro skin absorption test (similar to OECD 428, non-GLP) , it is concluded that Vitamin-E-Acetate-3H penetrates into and through intact and stripped pig skin (Csato and Klecak, 1995). The total skin penetration rates of Vitamin E acetate 3H from 3 alpha-hydroxy-acid creams were time-, formulation type- and skin condition-dependent, although not significantly different. The percutaneous absorption observed was in the range of 1.1 – 4.2 %, tested at 1h, 6h and 18h exposure with 3 different formulations (nominal dose 5%). The dermal absorption is set at 5%.

PHOTOINDUCED TOXICITY

not induce photo toxicity
Additional information:
DL-Alpha -Tocopheryl acetate is not a sensitiser as tested in a photoallergic test in Guinea pigs, and with the method of Draize in 203 human volunteers.

DATA ON MAN

phototoxicity
DL-Alpha -Tocopheryl acetate is not a sensitiser as tested in a photoallergic test in with the method of Draize in 203 human volunteers.

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/

Part 2A
Adverse Effects and Serious Adverse Effects

CPSR: Part A - Cosmetic Product Safety Information - Annex A9

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

This product is adult use. Undesirable effects of ingredients are described in paragraph 8 but end-product undesirable effects are not detected or recorded. The product is manufactured in compliance with GMP practise.

Historical data about any undesirable effects from the use of the product:

DATE	REPORTED EFFECTS	Notes	Pcs Sold

Part 2A
Information Regarding Cosmetic Product

CPSR: Part A - Cosmetic Product Safety Information - Annex A10

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

Patch Tests have not been carried out on the product under analysis, as they have already been carried out on other similar products, with the same formulation. In no case were any episodes of skin irritation recorded.

Part 2B
Assessment Conclusion

CPSR: Part A - Cosmetic Product Safety Information - Annex B1

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

The assessment conclusion is a statement on the safety of the cosmetic product in relation to the safety requirement of Article 3 of Regulation (EC) No 1223/2009: taking into account all the information contained in the previous pages, in particular the physical - chemical and safety information of the raw materials and of the product itself, the examination of the formula, the exposure expected for the consumer, the warnings and the manner in which they are used, it is considered that, in the current state of knowledge, the product concerned is not harmful to human health if applied under normal or reasonably foreseeable conditions of use. However, any undesirable effects which, in particular cases only, may occur at the expense of the user, cannot be excluded.
The level of purity of the raw materials used is guaranteed by the supplying companies, which are required to release further information through the data sheets, safety data sheets or information sheets.
If significant adverse reactions caused to consumers by this product are reported (for example an abnormal number of undesirable effects), the person responsible for this assessment shall be informed and a reassessment shall be considered.

Head of the safety evaluation **VOROBJOV DMITRI**

Part 2B
Warnings and Instructions for Use on the Label

CPSR: Part A - Cosmetic Product Safety Information - Annex B2

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

This product's presentation is in accordance with a Regulation no 1223/2009 of the European Parliament and of the Council about the labelling of cosmetic product. Restricted ingredients are properly listed on the package. Instruction of use: Apply the cream to the body in light circular movements 3 - 5 minutes until complete absorption 2 - 3 times a day. Cream is designed for daily use. All use instructions are written on the label.

Part 2B
Reasoning

CPSR: Part A - Cosmetic Product Safety Information - Annex B3

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

This assessment is based on:
- The chemical and physical specification of the ingredients
- The general toxicological profile of the ingredients
- The level of exposure of the ingredients
- The specific exposure characteristics of the areas to which the cosmetic product will be applied
- Margin of Safety calculations if available
- The specific exposure characteristics of the population for which the cosmetic product is intended

This assessment is conducted in accordance with the Regulation no 1223/2009 of the European Parliament and of the Council. All the ingredients in the formulation are either commonly used in leave-on products with low toxicity or within the recommended limit as suggested by SCCS and Cosmetic Ingredient Review (CIR).
Provided manufacturer's instructions are followed.
The potential interactions between ingredients have been considered. The submitted test results indicate the product will be safe for intended use concerning the impurity, stability and microbiological quality.

Part 2B
Assessor's Credentials and Approval of Part B

CPSR: Part A - Cosmetic Product Safety Information - Annex B4

Formula Code -

Commercial Name CONCENTRATED CREAM BALM MUMIJO 12 HERBS

SAFETY ASSESSOR

Name and Surname: VOROBJOV DMITRI

Born In: TALLINN **Date** 8/20/1984

Resident In: ESTONIA

Degree In: NATURAL SCIENCE

Date passing state exam for professional qualification: 4/15/2021

Session Year: 2021 **Session Number:** 1

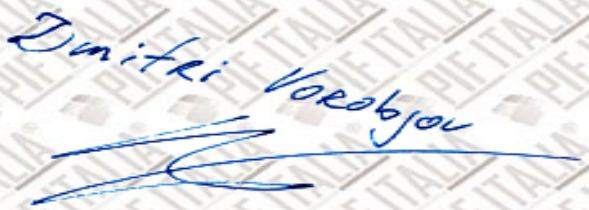
Inclusion on the: 15.04.2021 **N** .

County of: BRUSSEL

DATE

20.02.2025

SIGNATURE



Part 3
Description of the manufacturing method in accordance with good manufacturing practice (GMP)

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

The product is manufactured following the harmonised standards whose references have been published in the Official Journal of the European Union (GMP, Good Manufacturing Practices) to ensure a high level of consumer safety.

Part 4
Evidence of the effects attributed to the product, if necessary

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

The information on the ingredients on the label comes from public sources, and references to properties and effects come from aromatherapy, folk medicine, CosIng, SpecialChem cosmetic and so on. The given information is publicly known and does not require an additional test. All claims on the label should be in compliance with (EC) Regulation 655/2013 and the guidelines to this Regulation.

Parte 5
Information on any animal testing

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

No animal tests have been carried out for finished product. All ingredient TDS and MSDS are availbale by customer with their chemical and physical characteristics.

BIBLIOGRAPHY

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

-Safety Data Sheets and Raw Materials Techniques
-Toxnet (Toxicology database)
-ECHA (European Chemicals Agency) Registered substances database REACH
- Regulation 1223/2009 articles and annexes
-Cosmetics Ingradients cosmetics database
- Opinions of the SCCS
- CIR Cosmetic Ingredients Review
- Book, Абрамзон А.А., Зайченко Л.П., Файнгольд С.И. Поверхностно-активные вещества. Синтез, анализ, свойства, применение. 1988. Ленинград.
- EFSA, European Food Safe Agency
- EMA, European Medical Agency

List of documents attached to the PIF

Formula Code	-
Commercial Name	CONCENTRATED CREAM BALM MUMIJO 12 HERBS

- A1 Formula Finished product
- TDS Finished product
- Impurities Raw Materials
- A7 Product exposure
- A8 INCI toxicology