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 GEL BALM HORSE CHESTNUT TROXERUTIN

Product Category

q. skin care liquid

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

VITATEKA

First Printing Date	Last Checking
06.02.2025	20.02.2025

Table of contents

PART 1 - Description of Cosmetic Product

Formula Code -

Commercial Name

CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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

CPNP reference product:

First Printing Date 06.02.2025 **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 ()

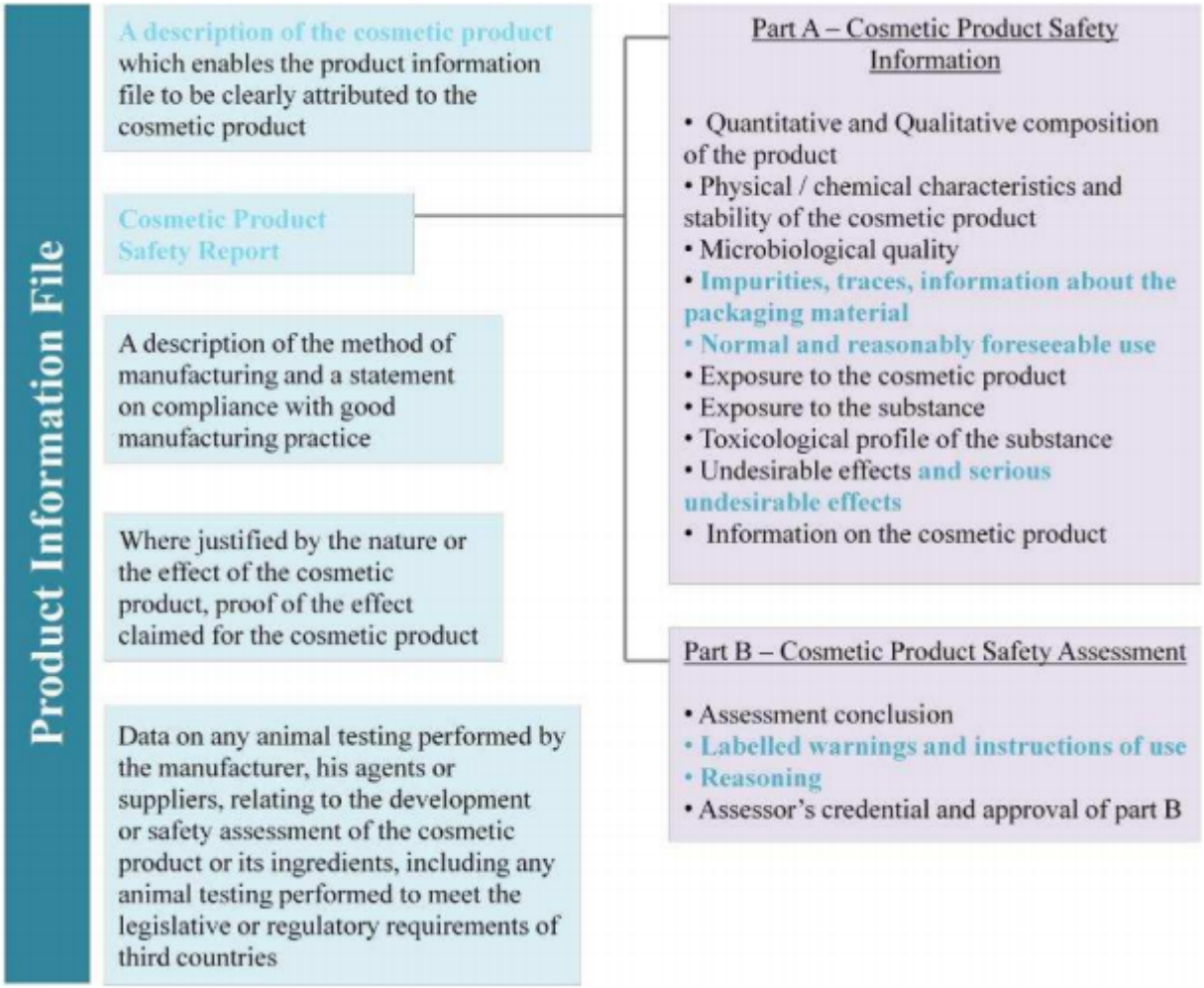
Phone N.

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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	86.300000	AQUA		100.0000	7732-18-5	231-791-2	SOLVENT
2	Propylene glycole	10.000000	PROPYLENE GLYCOL		100.0000	57-55-6	200-338-0	FRAGRANCE, HUMECTANT, SKIN CONDITIONING - HUMECTANT, SKIN CONDITIONING - MISCELLANEOUS, SOLVENT, VISCOSITY CONTROLLING
3	Euxyl PE 9010	1.000000	PHENOXYETHANOL	*	91.5000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
4			ETHYLHEXYLGLYCERIN		8.5000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
5	AESCULUS HIPPOCASTANUM FLOWER EXTRACT	0.500000	AQUA		79.5000	7732-18-5	231-791-2	SOLVENT
6			AESCULUS HIPPOCASTANUM FLOWER EXTRACT		20.0000	8053-39-2	232-497-7	SKIN CONDITIONING
7			PHENOXYETHANOL	*	0.4500	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
8			ETHYLHEXYLGLYCERIN		0.0500	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
9	Carbomer	0.500000	CARBOMER		100.0000	9007-20-9 / 9003-01-4 / 76050-42-5 / 9062-04-8 / 9007-16-3 / 9007-17-4		EMULSION STABILISING, GEL FORMING, VISCOSITY CONTROLLING
10	D-PANTHENOL 75 W	0.500000	PANTHENOL		75.0000	81-13-0 / 16485-10-2	201-327-3	ANTISTATIC, HAIR CONDITIONING, SKIN CONDITIONING
11			AQUA		24.9900	7732-18-5	231-791-2	SOLVENT
12			CITRIC ACID		0.0100	77-92-9 / 5949-29-1	201-069-1	BUFFERING, CHELATING, FRAGRANCE

* 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 GEL BALM HORSE CHESTNUT TROXERUTIN

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

13	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
14	Triethanolamine pure	0.500000	TRIETHANOLAMINE	*	100.0000	102-71-6	203-049-8	BUFFERING, FRAGRANCE, SURFACTANT - CLEANSING, SURFACTANT - EMULSIFYING
15			AQUA		0.0000	7732-18-5	231-791-2	SOLVENT
16	DIOSMINE	0.100000	DIOSMINE		100.0000	520-27-4	208-289-7	ANTIOXIDANT
17	TROXERUTIN	0.100000	TROXERUTIN		100.0000	7085-55-4 / 31511-30-5	230-389-4	SKIN CONDITIONING

* 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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

First Printing Date . . **Last Checking** N° 0 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 PROPYLENE GLYCOL PHENOXYETHANOL CARBOMER MENTHOL TRIETHANOLAMINE PANTHENOL AESCULUS HIPPOCASTANUM FLOWER EXTRACT DIOSMINE TROXERUTIN ETHYLHEXYLGLYCERIN CITRIC ACID

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.

PACKAGING

Formula Code -

CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

First Printing Date . . **Last Checking** N° 0 on 20.02.2025

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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	DIOSMINE	0.100000	Isorhoifin	520-27-4	208-289-7	0.02	2E-05

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	HPLC	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			Acetoisovanillone	6100-74-9	-	0.06	6E-05

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	HPLC	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			6-Iododiosmin	1431536-92-3	-	0.2	0.0002

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	HPLC	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
4			Linarin	480-36-4	207-547-6	0.84	0.00084

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	HPLC	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
5			Diosmetin	520-34-3	208-291-8	1.04	0.00104

Raw Materials Impurities List

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	HPLC	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
6	DIOSMINE	0.100000	Hesperidine	520-26-3	208-288-1	2.2	0.0022

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	HPLC	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
7	Triethanolamine pure	0.500000	Diethanolamine	111-42-2		0.3	0.0015

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008			

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
Hesperidine	520-26-3	0.002200	0.000325	1000.000	3076923	3076923	3076923	3076923	3076923	3076923
Diethanolamine	111-42-2	0.001500	0.000222	80.000	360360	360360	360360	360360	360360	360360
Diosmetin	520-34-3	0.001040	0.000154	50.000	324675	324675	324675	324675	324675	324675
Linarin	480-36-4	0.000840	0.000124	200.000	1612903	1612903	1612903	1612903	1612903	1612903
6-Iododiosmin	1431536-92-3	0.000200	0.000030	500.000	16666667	16666667	16666667	16666667	16666667	16666667
Acetoisovanillone	6100-74-9	0.000060	0.000009	900.000	100000000	100000000	100000000	100000000	100000000	100000000
Isorhoifin	520-27-4	0.000020	0.000003	1.000	333333	333333	333333	333333	333333	333333

Part 2A
Normal and Reasonably Predictable Use

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

Formula Code	-
Commercial Name	CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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		86.822450	12.835831	45000.00	**3506**	**3506**	**3506**	**3506**	**3506**	**3506**
PROPYLENE GLYCOL	57-55-6		10.000000	1.478400	5300.00	**3585**	**3585**	**3585**	**3585**	**3585**	**3585**
PHENOXYETHANOL	122-99-6	*	0.917250	0.135606	500.00	**3687**	**3687**	**3687**	**3687**	**3687**	**3687**
CARBOMER	9007-20-9 / 9003-01-4 / 76050-42-5 / 9062-04-8 / 9007-16-3 / 9007-17-4		0.500000	0.073920	1000.00	**13528**	**13528**	**13528**	**13528**	**13528**	**13528**
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**
TRIETHANOLAMINE	102-71-6	*	0.500000	0.073920	1000.00	**13528**	**13528**	**13528**	**13528**	**13528**	**13528**
PANTHENOL	81-13-0 / 16485-10-2		0.375000	0.055440	1000.00	**18038**	**18038**	**18038**	**18038**	**18038**	**18038**
AESCULUS HIPPOCASTANUM FLOWER EXTRACT	8053-39-2		0.100000	0.014784	400.00	**27056**	**27056**	**27056**	**27056**	**27056**	**27056**
DIOSMINE	520-27-4		0.100000	0.014784	200.00	**13528**	**13528**	**13528**	**13528**	**13528**	**13528**
TROXERUTIN	7085-55-4 / 31511-30-5		0.100000	0.014784	67.00	**4532**	**4532**	**4532**	**4532**	**4532**	**4532**
ETHYLHEXYLGLYCERIN	70445-33-9		0.085250	0.012603	100.00	**7935**	**7935**	**7935**	**7935**	**7935**	**7935**

* 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 GEL BALM HORSE CHESTNUT TROXERUTIN

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		0.000050	0.000007	250.00	**35714286**	**35714286**	**35714286**	**35714286**	**35714286**	**35714286**

* 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 GEL BALM HORSE CHESTNUT TROXERUTIN

AESCULUS HIPPOCASTANUM FLOWER EXTRACT (CAS: 8053-39-2)

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

400 -- - EMA, https://www.ema.europa.eu/en/documents/herbal-report/assessment-report-aesculus-hippocastanum-l-semen-final-revision-1_en.pdf

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

LD50 oral (rat) >2000 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

not mutagenic / genotoxic
Additional information:
In the Ames mutagenicity test, using Salmonella typhimurium strain TA 98, a commercial dry extract of seeds (no further information on the extract available in the reference) gave a negative response without activation, but a weekly positive response (factor 2-3) with S9 activation. Fluid extracts of horse-chestnut seed gave a weakly positive response (factor 2-3) without activation and a negative response with activation. The authors suggested that quercetin is possibly the main mutagenic principle in these extracts (Schimmer et al., 1994; ESCOP, 2003).

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
Following daily oral administration of a horse chestnut seed extract (dry extract, DER 5:1, extraction solvent ethanol 50% V/V, standardised for a content of 50 mg aescin in 240-290 mg extract) to rats and rabbits at 100 and 300 mg/kg bw, no significant effects compared to control animals were observed in teratogenicity studies. At 300 mg/kg bw to rabbits, a significant reduction ($p<0.001$) in the mean weight of the foetuses was observed. 300 mg/kg bw is approximately 30 times the recommended therapeutic dose for humans (Liehn et al., 1972).
Juvenile rats were treated with 2 times 5 mg/kg aescin at age 32 days. After they had reached fertility, kidneys, testes and sperm were examined. The high dose of aescin used did not affect fertility and a nephrotoxic activity could not be detected (von Kreybig and Prechtel, 1977).

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Clinical Data
The effect of an extract (DER 5:1, extraction solvent ethanol 50% V/V), contained in capsules with 240 to 290 mg of the extract, standardised to 50 mg aescin/capsule on trans-capillary filtration has been assessed by measuring capillary filtration coefficients in two clinical studies. In the first study (Pauschinger et al., 1953), oral administration of a single dose of the extract (300 mg, n=12) or placebo (n=14) to healthy volunteers, produced a significantly lower capillary filtration coefficient in the extract group. The second study (Bisler et al., 1986) had a double-blind, crossover design and involved 22 female patients with proven chronic venous insufficiency. The capillary filtration coefficient and the intravascular volume of the lower leg were determined by venous-occlusion plethysmography. 3 hours after oral administration of a single dose of 2 capsules (=100 mg of aescin) the capillary filtration coefficient had decreased significantly by 22% ($p=0.006$), compared to a slight increase with placebo. The intravascular volume was reduced 5% or more in comparison with administration of placebo, but this decrease was not significant. It was concluded that the extract had an inhibitory effect on oedema formation via a decrease in trans-capillary filtration and thus improved oedema-related symptoms in venous diseases of the legs. In a study of venous tone, a single dose of 150 mg of extract was administered orally to 23 healthy young subjects. A further 14 subjects received either 80 mg of extract or identical placebo capsules in a crossover design. Plethysmographic measurements taken before and 2 hours after administration showed that the extract dose-dependently increased venous tone (Nehring, 1966). Comparable results were obtained from a further study in which 12 healthy volunteers firstly received placebo and then a single oral dose of extract (360 mg, standardised to 90 mg of aescin). In contrast, intravenous administration of 20 mg of aescin had no effect on venous tone (Ehringer, 1968). Three hydrolases, β-N-acetylglucosaminidase, β -glucuronidase and arylsulphatase, catalyze the breakdown of proteoglycans, which constitute part of capillary walls. In the serum of varicose in patients the activity of these enzymes has been found to be markedly increased (by 60-120%) compared to healthy subjects; this may render the capillaries more permeable and fragile. In two studies, one with 10 patients and the other with 15 patients, oral administration of an extract of horsechestnut seeds (dry extract, 5:1, extraction solvent ethanol 50% V/V, 900 mg, standardised to 150 mg of aescin) daily for 12 consecutive days led to significant reductions in the activity of these enzymes ($p<0.01$ and $p<0.05$ respectively), of the same order of magnitude (about 30%) for each enzyme. It was hypothesized that horse chestnut seed extract does not inhibit the individual enzymes but has a protective action towards the site of enzyme release, the fragile lysosomal membrane (Enghofer et al., 1984).

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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

CARBOMER (CAS: 9007-20-9 / 9003-01-4 / 76050-42-5 / 9062-04-8 / 9007-16-3 / 9007-17-4)

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

1000 -- - ECHA, https://echa.europa.eu/et/registration-dossier/-/registered-dossier/22071/7/6/1

- Carbopol® Polymers Toxicology Studies: https://www.ulprospector.com/documents/1174279.pdf?bs=77&b=3734&st=20&r=eu&ind=personalcare
Additional information:
When dogs were chronically fed up to 1.0 g/kg/day carbomer (32 months), and when rats chronically received less than 4.0% carbomer in their diet (six and one-half months), there was no significant effect on body weight, food consumption, mortality, behavior or blood chemistries. Hematology, gross pathology, histology, and urinalyses of treated animals were comparable to those of controls. Rats fed carbomer at dietary levels of 0.1%, 0.5% or 5.0% for six and one-half months exhibited various organ weight changes. Dogs fed 0.5 or 1.0 g/kg/day carbomer for six and one-half months manifested gastrointestinal irritation and marked pigment deposition within Kupffer cells of the liver.

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

LD50 oral (rat) 1 500 mg/kg bw
LD50 dermal (rabbit) > 2000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

not irritating
Additional information:
SIPOMER B-CEA was tested for primary dermal irritation/corrosion in 3 New Zealand White rabbits. Each of the 3 rabbits received three 0.5 ml doses of the test article (a liquid) on a dry compress in a single dermal dose to 2.5 cm2clipped area of the skin. The doses were held in contact with the skin under a semi-occlusive patch for an exposure period of 3 minutes, 1 hour, and 4-hours, respectively. Cutaneous examinations were performed at removal of the dressing, after wiping of the remaining test article, then daily for up to 14 days.
Exposure for 3 minutes produced very slight erythema (score 1) in 2/3 animals at removal of the dressing. The effects resolved completely by the 24-hour observation time. No oedema was observed.
Exposure for 1 hour produced very slight erythema (score 1) in all 3 animals at removal of the dressing. On one site, erythema increased to well-defined (grade 2) at 72 hours. The effects resolved completely by day 7 (2/3 animals) or day 10 (1 animal). No oedema was observed.
Exposure for 4 hours produced very slight erythema (score 1), and very slight (2/3 animals) to well-defined oedema (1 animal). Oedema resolved completely by the 72-hour observation time. On 3 test sites, the erythema increased to well-defined by the 72-hour scoring and persisted at day 7 on one site. Additional findings included superficial lightening and desquamation on 3 sites and 1 site, respectively. These effects resolved completely by day 14. The individual mean scores for each animal were 1.33 – 1.33 – 1.33 for erythema, and 0.33 – 0.67 – 0.33 for oedema. (or PII: 1.92)
Based on these results, SIPOMER B-CEA should not be classified as a skin irritant according to GHS criteria.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

no data of eye irritation about exact compound. Analogue is acrylic acid. Due to the presence of up to 20% acrylic acid in the UVCB, using a direct analogy, Carbomer is considered as causing serious eye damage.

SKIN SENSITISATION

not sensitising
Additional information:
Some positive test results were obtained with acrylic acid in Guinea pigs. The effects were attributed to the presence of the impurity alpha,beta-Diacryloxypropionic acid in the test substance. Based on the in vivo data on the analogue acrylic acid, the registered substance is considered not to bear a skin sensitization potential.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
Based on 4 different Ames tests on its analogue acrylic acid up to concentrations ranging between 1000 and 5000 µg/plate with or without exogenous metabolic activation, the registered substance is considered to be devoid of mutagenic potential in bacterial systems.

Acrylic acid did not induce gene mutations in CHO cells (HGPRT locus) in one study but was positive in four distinct mouse lymphoma assays and in two in vitro chromosomal aberration tests. In the mouse lymphoma assays small colonies were induced preferentially, thus the mutagenic potential of acrylic acid seems to be limited to clastogenicity.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
At this tonnage band, the reproductive toxicity screening assay that is regulatorily required has not been provided, based on the existing higher-tier studies with the analogue acrylic acid: one two-generation (OECD 416) and one prenatal development (OECD 414) toxicity studies. Both studies showed no relevant reproductive or developmental effects.

TOXICOKINETIC (ADME studies)

low bioaccumulation potencial
Additional information:
In Vivo Studies:
C3H mice and Fischer 344 rats, respectively, were treated by gavage (40 or 150 mg/kg bw) with [1-14C]-acrylic acid. Mice rapidly absorbed and metabolised orally administered acrylic acid, with about 80% of the dose exhaled as 14CO2 within 24 h. Excretion in urine and faeces accounted for approximately 3% and 1% of the dose, respectively. Elimination of the 14C radiolabel from plasma, liver and kidney was rapid but it was slower from fat. The disposition of orally administered acrylic acid in rats was similar to the results obtained from mice. High-performance liquid chromatography (HPLC) analysis of rat urine and rat and mouse tissues indicated that absorbed AA was rapidly metabolized by the ß-oxidation pathway of propionate catabolism. No unchanged AA was detected 1 h after oral administration; however, several metabolites that were more polar than AA were measured, including 3-hydroxypropionate. Neither AA nor its metabolites were detected at later times after oral administration (Black et al., 1995).
Sprague-Dawley rats received single oral doses of [2,3-14C]-acrylic acid (4, 40 or 400 mg/kg bw in a 0.5 % aqueous methylcellulose solution). Within 8 hours, 35-60% of the dose was eliminated from the animal, mostly as expired CO2. After 72 hours, 44-65% of the radioactivity had been eliminated via expired air, while 2.9-4.3% remained in urine, 2.4-3.6% in faeces and 18.9-24.6% in tissues examined (adipose tissue 9-15%, liver 1.7-2.2%, muscle 6.5-7.5% and blood 0.8-1.1%) (De Bethizy et al., 1987).
The HPLC profile of metabolites observed in the urine of rats indicated two major metabolites. One of the major metabolites co-eluted with 3-hydroxypropionic acid. Radioactivity could not be detected at the retention times corresponding to that of 2,3-epoxypropionic acid or N-acetyl-S-(2-carboxy-2-hydroxyethyl)cysteine leading to the conclusion that AA is not epoxidized to 2,3-epoxypropionic acid in vivo. This result was supported by an in vitro study. Hepatic microsomes were prepared using conventional methods from rats and incubations were started by the addition of 10 µL of [2,3-14C]-acrylic acid. No epoxidized metabolites could be detected and the parent compound was recovered from the incubation mixture unchanged (DeBethizy et al., 1987).
In addition, Glutathione Depletion Studies were conducted in rats that were administered doses of 4, 40, 400 or 1000 mg/kg bw AA by gavage. One hour following oral administration of acrylic acid in rats a significant depletion of NPSH in the glandular stomach was reported at doses above 4 mg/kg bw. In the forestomach NPSH depletion

occurred at a dose of 1000 mg/kg bw. No significant effect of acrylic acid on NPSH in the blood or liver was observed (DeBethizy et al., 1987).
In Vitro Studies:
Dow Chemical (1979) have studied the metabolism of acrylic acid in rat tissue homogenates. Acrylic acid did not react with reduced glutathione either in the presence or absence of the soluble enzyme fraction. Non-protein sulfhydryl concentrations were not appreciably lower in blood after addition of acrylic acid in vitro (Dow Chemical, 1979; Miller et al., 1981).
The rate of 14CO2 formation from [14C]-acrylic acid was measured in vitro with preparations from rat liver hepatocytes. Rapid oxidation of acrylic acid to CO2 was observed. Mitochondria isolated from the liver homogenates were incubated with acrylic acid under the same conditions and yielded higher rates of acrylic acid-oxidation than homogenates. HPLC analysis of the mitochondrial incubation mixtures indicated 3-hydroxypropionic acid as a major metabolite of AA (Finch & Frederick, 1992).
Black et al. (1993) determined the rate of the in vitro oxidation of acrylic acid in 13 tissues of mice. The maximal rate of acrylic acid oxidation in kidney, liver and skin was 2890, 616 and 48 nmol/h/g, respectively. In remaining organs acrylic acid was oxidized at rates less than 40% of the rate in liver. 3-Hydroxypropionic acid was the only metabolite detected by HPLC analysis.
Acrylic acid oxidation rates and blood tissue partition coefficients were studied in slices of rat tissue using [1-14C]-acrylic acid. Acrylic acid oxidation in rat kidney and liver slices was described by saturable kinetics with maximal rates of about 4 and 2 µmol/h/g, respectively. Acrylic acid oxidation rates in 11 additional tissues were 40% or less than that in liver (Black & Finch, 1995).
Computational Modeling Data:
A hybrid computational fluid dynamics (CFD) and physiologically-based pharmacokinetic (PBPK) dosimetry inhalation model was constructed to estimate the regional tissue dose of acrylic acid in the rat and human nasal cavity, respectively (Frederick et al., 1998). This study provides a scientific basis for interspecies extrapolation of nasal olfactory irritants from rodents to humans. By using a series of short-term in vivo studies, in vitro studies with nasal explants, and computer modeling, regional nasal tissue dose estimates were made and comparisons of tissue doses between species were conducted. To make these comparisons, this study assumes that human and rodent olfactory epithelium have similar susceptibility to the cytotoxic effects of organic acids based on similar histological structure and common mode of action considerations. Interspecies differences in susceptibility to the toxic effects of acidic vapours are therefore assumed to be driven primarily by differences in nasal tissue concentrations that result from regional differences in nasal air flow patterns relative to the species-specific distribution of olfactory epithelium in the nasal cavity.
The rodent model uses two olfactory compartments to incorporate both the olfactory epithelium in the projection extending along the dorsal meatus and the ethmoid olfactory region. This model was based on a compartmental rat nasal model of Bush et al. (1998). The human model uses one olfactory compartment since the human nasal cavity lacks a counterpart for the rodent ethmoid olfactory region (Subramaniam et al., 1998). The liquid phase of the model of Bush et al. was modified to include the effect of buffering capacity on the ionization of the acid in the mucus, diffusion of both the ionized form of the acid and the non-ionized species, liquid:air partition coefficients, tissue:blood partition coefficients (Black and Finch, 1995), and metabolism of acrylic acid (Black and Finch, 1995).
A hybrid CFD-PBPK inhalation model was constructed with the aim to evaluate the relationship between inhaled acrylic acid vapour concentration and the tissue concentration in various regions of the nasal cavity of rats and humans, respectively. An explicit effort was made to derive the parameters for rat and human used in the model either from experimental data or from physicochemical principles without "fitting" model parameters (gas phase diffusivity: 0.1 cm2/sec; air minute volumes: 250 mL/min (rat), 7500 mL/min (human); blood flow to nasal cavity (human) estimated). Deposition of vapours in the rat nasal cavity is relatively insensitive to significant variation in the gas phase mass transport coefficients, but the human CFD-PBPK model was sensitive to variation in air phase and liquid phase parameters (liquid diffusivity, mucus:air partition coefficient).
Unidirectional simulations were conducted with the model at a flow rate of 500 mL/min (rat) to estimate the steady-state tissue concentration in the anterior olfactory epithelium lining the dorsal meatus of the rat nasal cavity over a wide range of acrylic acid vapour concentrations (0 to 25 ppm for one hour). A dose-response of acrylic acid exposures was simulated for an adult resting male rat and an adult resting male human using the appropriate inspiratory flow rate (based on the minute volumes of each species), nasal anatomy, and nasal air flow patterns from CFD simulations. The cyclic flow simulation was conducted for a reference resting rat and human exposed to 2 ppm acrylic acid for 3 min (minute volume 250 mL/min (rat), 7500 mL/min (human)).

The acute inhalation, and in vitro studies have demonstrated that the nasal olfactory epithelium is the most sensitive tissue to the effects of inhalation exposure to organic acids and that the sustentacular cells are the most sensitive cell type of this epithelium. The CFD-PBPK model simulations indicated that the olfactory epithelium of the human nasal cavity is exposed to two- to threefold lower tissue concentrations of a representative inhaled organic acid vapour, acrylic acid, than the olfactory epithelium of the rodent nasal cavity when the exposure conditions are the same. The magnitude of this difference varies somewhat with the specific exposure scenario that is simulated. The increased olfactory tissue dose in rats relative to humans may be attributed to the large rodent olfactory surface area (greater than 50% of the nasal cavity) and its highly susceptible location (particularly, a projection of olfactory epithelium extending anteriorly in the dorsal meatus region). In contrast, human olfactory epithelium occupies a much smaller surface area (less than 5% of the nasal cavity), and it is in a much less accessible dorsal posterior location. In addition, CFD simulations indicated that human olfactory epithelium is poorly ventilated relative to rodent olfactory epithelium. These studies suggest that the human olfactory epithelium is protected from irritating acidic vapours significantly better than rat olfactory epithelium due to substantive differences in nasal anatomy and nasal air flow.
Discussion on absorption rate:
The absorption of [14C]-acrylic acid from acetone, water, and phosphate buffer was measured through human and mouse skin in vitro. Membranes were mounted in glass diffusion cells and acrylic acid was applied in each solvent at 0.01 %, 0.1 %, 1 %, and 4 %, respectively (100 µL/cm2) under occlusive conditions. Samples were taken from the receptor solutions at recorded times, between 0 and 32 hr, and assayed for 14C content which was regarded as equivalent to acrylic acid. Steady state absorption rates were calculated to be between 0.007 µg/cm2/hr (human, 0.01 % AA in phosphate buffer) and 201 µg/cm2/hr (mouse, 4 % AA in acetone). Thus, absorption rates were influenced by the vehicle (acetone > water > phosphate buffer) and were proportional to the applied concentration in each vehicle. Mouse skin was 3 times more permeable than human skin under the conditions of this in vitro study (BAMM 1988).
C3H mice and Fischer 344 rats, respectively, were treated dermally (10 or 40 mg/kg bw in acetone) with [1-14C]-acrylic acid. After cutaneous application to mice, about 12% of the dose was absorbed, while the remainder was apparently evaporated. Approximately 80% of the absorbed fraction of the dose was metabolised to 14CO2within 24 h. Excretion in urine and faeces each accounted for less than 0.5% of the dose. Elimination of radioactivity from plasma, liver, and kidney was rapid; however, levels in fat were higher at 72 h (0.5% of the higher dose) than at 8 h (0.1% of the higher dose). After cutaneous administration to rats, 19-26% of the dose was absorbed. Disposition of the absorbed fraction of the dose was similar to results found in mice. Results from an in vitro experiment with rat skin (Frantz cell) showed that at least 60 % of the applied dose evaporated and about 25% was absorbed, confirming the in vivo results. High-performance liquid chromatography (HPLC) analysis of rat urine and rat and mouse tissues indicated that absorbed AA was rapidly metabolized by the ß-oxidation pathway of propionate catabolism (Black et al., 1995).

PHOTOINDUCED TOXICITY

not induce phototoxicity
Additional information:
Clinical studies with carbomer and its various salts showed that these polymers have low potential for skin irritation and sensitization at concentrations of 0.5%, 5.0%, 10.0% and 100%. When tested on humans at 1.0% concentration, carbomer and the various salts also demonstrated low potential for skin irritation and sensitization. Further, formulations containing up to 0.25% carbomer demonstrated low potential for human skin irritation, sensitization, phototoxicity, and photo-contact allergenicity.

DATA ON MAN

Human Repeated Insult Patch Tests Carbopol homopolymer was impregnated into a 1" X 1" square piece of surgical gauze and moistened with 0.2 mL distilled water just prior to application to the skin of 54 human volunteers. In order to evaluate the skin irritation and sensitization potential of this product, a series of 12 applications was conducted with each panelist during the primary/induction phase. On four consecutive days of weeks 1, 2 and 3, the patch containing the test material was applied to its designated site. The patches were removed and the contact sites were examined 24 hours after each application. Following a one week rest period (week 4) a challenge phase was conducted on week 5 with 4 applications of the test material on a virgin site of each volunteer. Carbopol homopolymer produced no visible effect in 41 subjects out of 54 during the primary irritation/activation period. Faint or moderate reddening of the skin occurred on one occasion in 10 subjects, 2 times on one subject and 4 times on another subject. These effects would put Carbopol homopolymer in the category of a weak skin irritant. Two subjects out of 53 displayed solitary episodes of faint or moderate reddening in the challenge phase; however, the investigators concluded they did not display a sensitizing reaction. It was concluded that the results furnish no basis for contraindicating skin contact with Carbopol homopolymers under similar or less stringent conditions than the testing conditions used.

BIBLIOGRAPHY

- MSDS
- TOXNET database on toxicology
- CIR Cosmetic Ingredients Review
- ECHA https://echa.europa.eu/
- Carbopol® Polymers Toxicology Studies

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.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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.

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.

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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

DIOSMINE (CAS: 520-27-4)

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

200 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/21071/7/6/2

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

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

SKIN IRRITATION AND CORROSIVITY

not irritant to the skin
Additional information:
An in vitro skin irritation test of the test item was performed in a reconstructed human SkinEthic™ RHE epidermis model, according to OECD TG 439 (GLP study). Three epidermis units were treated with 16 mg test item for 42 minutes at room temperature. Exposure of the test item was terminated by rinsing with 25 x 1 mL of DPBS. The epidermis units were then incubated at 37°C for 41 hours 12 minutes in an incubator with 5% CO2. The viability of each disk was assessed by incubating the tissues with MTT, extracting the precipitated formazan crystals using isopropanol during 2 hours under gentle agitation in the dark, and measuring the concentration of formazan by determining the OD at 570 nm, just after dilution of the extracts 1:2 in isopropanol. Under test conditions, the mean corrected percent viability of the treated tissues was 70.8%, versus 1.0% in the positive control (5% Sodium Dodecyl Sulfate). Therefore, the test item is not irritant to the skin.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

study cannot be used for classification
Additional information:
An in vitro (ex vivo) study was conducted in order to determine the potential severe eye damaging effects of the test item according to the OECD guideline 438 under GLP conditions. Eyeballs were isolated from chickens killed for human consumption and after the appropriate preparation were exposed to either 30 mg of the test item, 30 mg of sodium hydroxide (positive control) or 30 µL of physiological saline (negative control). Three eyeballs were used in each group. Fluorescein retention, corneal opacity and corneal swelling were evaluated, then the results of each endpoint were assigned to ICE classes according to OECD guideline 438. According to the overall in vitro classification (UN GHS), no prediction can be made since the combinations of the 3 endpoints for the test item were 1 x IV, 2 x I.

SKIN SENSITISATION

not sensitizer
Additional information:
Skin sensitisation: Key study. Method according to OECD 422B, GLP study. The Stimulation Index (SI) was 0.78, 0.93 and 0.93 for the treated groups at 50%, 25% and 10%, respectively. Therefore, the test item has no sensitisation potential.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not genotoxic / mutagenic
Additional information:
Genetic toxicity in vitro. Weight of evidence: Four Ames tests for the analogue substance neohesperidin dihydrochalcone, all of them similar to OECD 471 (no GLP), were all negative. Based on the available information for the read-across approach, the target substance is deemed to be non-mutagenic.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
Weight of evidence: Read-across from analogue substance. Heusser and Oswald (1977) performed teratogenic toxicity studies for the analogue substance diosmin, sodium salt, which was administered by gavage to SIV rats and ICR mice, at doses of 100 and 50 mg/kg bw, respectively.
- In a study conducted to assess the teratogenicity potential of the sodium salt of diosmin, by a method similar to OECD 414 (no GLP), two groups of female SIV rats each were orally administered 100 mg/kg bw/d of test item from the 4th to the 14th post-coital days. Two further control groups were run in parallel. In one of the groups, the foetuses were delivered by laparotomy on the 21st day after conception and the sites of implantation and absorption in both horns of the uterus were determined. The foetuses were examined with respect to palatal clefts and malformations of the extremities and tail; the sex weight and length were determined; then, they were killed and their skeletons stained and examined. In the other treated group, delivery was by spontaneous birth and the development of the animals was followed. There was no reduction in number of foetuses, no increase in absorption sites, no significant alteration of rate of malformations, postnatal morbility, weight gain and development or histology of several organs. Thus, it was concluded that the test item does not have any teratogenic effects. The NOAEL for developmental toxicity in rat is greater than 100 mg/kg bw/d.
- In a study conducted to assess the teratogenicity potential of the sodium salt of diosmin, by a method similar to OECD 414 (no GLP), two groups of 11 female ICR mice each were orally administered 50 mg/kg bw/d of test item from the 4th to the 12th post-coital days. Two further control groups were run in parallel. In one of the groups, the foetuses were delivered by laparotomy on the 19th day after conception and the sites of implantation and absorption in both horns of the uterus were determined. The foetuses were examined with respect to palatal clefts and malformations of the extremities and tail; the sex weight and length were determined; then, they were killed and their skeletons stained and examined. In the other treated group, delivery was by spontaneous birth and the development of the animals was followed. There was no reduction in number of foetuses, no increase in absorption sites, no significant alteration of rate of malformations, postnatal morbility, weight gain and development or histology of several organs. Thus, it was concluded that the test item does not have any teratogenic effects. The NOAEL for developmental toxicity of the test item in mice is greater than 50 mg/kg bw/d.
Based on the available information for the read-across approach, the target substance is deemed to be non teratogenic.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

TOXICOKINETIC (ADME studies)

no bioaccumulation potential
Additional information:
Weight of evidence: An in vivo metabolism study in rats by Booth (1958) reports the absorption of the test item in the gastrointestinal tract after oral administration, and excretion as m-hydroxyphenylpropionic acid, and traces of m-coumaric acid and diosmetin. An in vitro tat liver perfusion model study by Perego (1993) reports rapid metabolization of the test item in the liver and excretion through bile as a glucuronide. An in vivo pharmacokinetics study in rats by Ma (2007) reports slow absorption of the test item in the gastrointestinal tract, probably due to the low solubility of the test item. Based on the information available, no concerns for the bioaccumulation of the substance were found.
Weight of evidence
- On a study by Booth et al. (1956), the metabolic fate of diosmin and other flavonoids was studied after oral ingestion by rats, at a dose of 400 mg/kg bw. The study meets generally accepted scientific principles. Based on the results, it can be concluded that the test substance can be absorbed in the gastrointestinal tract, and excreted through urine as m-hydroxyphenylpropionic acid, along with traces of m-coumaric acid and its aglycone diosmetin.
- On a study by Perego et al (1993), the metabolism of diosmin was studied in a model of rat liver perfusion, following basic scientific principles. Under test conditions, diosmin was actively metabolized by the liver in a short time, with a broad peak appearing in bile, and a small part of the initial amount of the substance was excreted in its original form and as the glucuronide.
- On a study by Ma (2007), the pharmacokinetic parameters of diosmin were determined after oral administration of three doses at levels of 225, 325, 425 mg/kg bw, by HPLC-UV method. The mean plasma concentration curves were found to fit a one compartment mode. The absorption was found to be slow, probably due to the low water solubility of the compound.
Based on the information available, no concerns for the bioaccumulation of the substance were found.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Exposure related observations in humans: other data
An open study on hospital outpatients was performed to assess the safety, efficacy and acceptability of a micronized flavonoid formulation (90% diosmin) in the treatment of internal hemorrhoids of pregnancy. 50 pregnant women with acute hemorrhoids were given the test item orally for a median of 12 weeks (8 weeks before delivery and 4 weeks after delivery) and observed for adverse effects and acceptability of treatment. The treatment was divided into 3 phases: a 7 day loading phase, in which the patients were given 6 tablets for 4 days (ca. 675 mg diosmin per day) and 4 tablets per day for 3 days (ca. 1800 mg diosmin per day), in a divided dose after lunch and dinner; an antenatal phase, and a post-natal phase, in both of which the patients were given 2 tablets per day (ca. 900 mg diosmin per day) in a divided dose after lunch and dinner. Under the conditions of the study, no adverse effects were observed on pregnancy, fetal development, birth weight, infant growth or feeding.

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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

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/

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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

PANTHENOL (CAS: 81-13-0 / 16485-10-2)

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

1000 -- - ECHA, European Chemical Agency. Additional information:A read across approach was performed with the supporting substance DL-Ethyl Panthenol. In a 90 day subchronic GLP and guideline study in rats, the test item showed a NOAEL of 1000 mg/kg bw/day. In addition oral exposure of rats for 28 days resulted in a NOAEL of 1000 mg/kg bw/day. In a supporting subchronic oral toxicity study with DL- Panthenol the voluntary consumption of the test item by male and female rats in drinking water in the concentrations of 200, 50 and 20 mg/kg bw/day for a 90 day period showed essentially negative results. The no observed adverse effect level (NOAEL) under the conditions of this study was considered to be 200 mg/kg bw/day. In conclusion no adverse effects releated on DL- Panthenol could be observed after oral exposure for 90 days.

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

LD50 (oral) rat > 2 000 mg/kg bw
LD50 (dermal) rat > 2 000 mg/kg bw
Additional information:
Oral
DL-Panthenol has not been tested for acute oral toxicity. Instead a read across approach from the supporting substance DL-Ethyl Panthenol was performed. For justification of read across please refer to the attachment in IUCLID5 section 13. In an acute oral toxicity study, groups of fasted, approx. 10 weeks old Wistar rats (5/sex) were given a single oral dose of DL-Ethyl Panthenol in water at a dose of 2000 mg/kg bw and observed for 14 days. No animals died during the study. No clinical signs were observed during the study period. The body weight gain shown by the animals over the study period was considered to be similar to that expected of normal untreated animals of the same age and strain. Macroscopic post mortem examination of the animals at termination did not reveal any abnormalities. The Oral LD50 was determined to be > 2000 mg/kg bw.
The close structural similarity between DL-Ethyl Panthenol and Panthenol strongly suggest that the LD50 for DL-Panthenol is also > 2,000 mg/kg bw.
Dermal
In an acute dermal toxicity study, groups of young adult (8 weeks old) Wistar rats (5/sex) were dermally exposed to DL-Ethyl Panthenol for 24 hours to (25 cm2 surface) at a limit doses 2000 mg/kg bw. Animals then were observed for 14 days.
No mortality occurred during the study period. No clinical signs of ill health or behavioural changes were observed during the study period. Abnormalites in the treated skin area included scabs in one male between days 5 and 9. The body weight gain shown by the animals over the study period was considered to be similar to that expected of normal untreated animals of the same age and strain. However, three females showed low body weight gain over the second week of the study. Macroscopic post mortem examination of the animals at termination revealed a yellowish hard nodule in the papillary process of the liver in one female and pelvic dilation of the kidney in one male. These findings are incidentally noted among the animals of this age and strain and are considered not related to treatment with the test substance. The dermal LD50 value of DL-Ethyl Panthenol in rats was established as exceeding 2000 mg/kg body weight.
Inhalaltion
Testing of inhalation toxicity of DL-Ethyl Panthenol was waived, as exposure via inhalation was not considered relevant.
Justification for selection of acute toxicity – oral endpoint
The close structural similarity between DL-Ethyl Panthenol and Panthenol strongly suggest that the LD50 for DL-Panthenol is also > 2000 mg/kg bw. For justification of read across please refer to the attachment in IUCLID5 section 13.
Justification for selection of acute toxicity – inhalation endpoint
Exposure via inhalation is not considered relevant, due to unlikely exposure via inhalation.
Justification for selection of acute toxicity – dermal endpoint
The close structural similarity between DL-Ethyl Panthenol and Panthenol strongly suggest that the LD50 for DL-Panthenol is also > 2000 mg/kg bw. For justification of read across please refer to the attachment in IUCLID5 section 13.

SKIN IRRITATION AND CORROSIVITY

not irritating
Additional information:
The test item DL-Ethylpanthenol was tested for skin irritation/corrosion to the intact rabbit skin in a test with three New Zealand White albino rabbits according to OECD guideline 404/EU method B.4 and under GLP. 0.5 mL of the test substance was applied to the intact skin of the shaved area on one flank on the shaved skin of the animals. The test area was wrapped with surgical tape. After 4 hours the wrapping was removed, the remaining test substance washed off and the application site observed for any signs of irritation/corrosion for 72 hours. No skin irritation was caused by DL-Ethylpanthenol after 4 hours of exposure in any of the three rabbits. There was no evidence of a corrosive effect on the skin. No staining of the treated skin by the test substance was observed. No symptoms of systemic toxicity were observed in the animals during the test period and no mortality occurred.
According to the results obtained in this study, DL-Ethylpanthenol was considered not irritating to the rabbit skin.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritating
Additional information:
DL-Ethylpanthenol was tested for eye irritation in a GLP study compliant to OECD 405/EU Method B.5. Instillation of 0.1 ml of DL-Ethylpanthenol into one eye of each of the animals resulted in effects on the iris in two animals and on the conjunctivae in all three animals. Iridic irritation, grade 1, was observed on day 1 in the two animals and had resolved within 24 hours. The irritation of the conjunctivae consisted of redness and chemosis of the conjunctival tissues and discharge. The irritation had resolved completely within 7 days in two animals and within 14 days after instillation in the third animal. Treatment of the eyes with 2% fluorescein, 24 hours after test substance instillation revealed no corneal epithelial damage in any of the animals. There was no evidence of ocular corrosion. No staining of peri-ocular tissues by the test substance was observed.
DL-Ethylpanthenol was considered as not irritating to the rabbit eye.

SKIN SENSITISATION

not sensitising
Additional information:
In the key GLP and guideline study, DL-Panthenol was tested for skin sensitization in the Buehler test according to OECD guideline 406/EU method B.6. In the test group of 20 Pirbright White Dunkin Hartley guinea pigs, the test substance was applied undiluted in the induction and challenge application. A control group of 10 animals was used. Based on the results of this study and applying the evaluation criteria it was concluded that DL-Panthenol does not have a sensitizing effect on the skin of the guinea pig in the BUEHLER Test under the test conditions chosen.Based on the results of this study and applying the evaluation criteria it was concluded that DL-Panthenol does not have a sensitizing effect on the skin of the guinea pig in the BUEHLER Test under the test conditions chosen.
A read across approach was performed with the supporting substance DL-Ethylpanthenol. For justification of read across please refer to the attachment in IUCLID5 section 13.
In a supporting GLP and guideline study, the skin sensitizating properties of DL-Ethylpanthenol were evaluated in a Maximization test with guinea pigs according to OECD guideline 406/EU method B.6. A test group of 10 albino guinea pigs and a control group of 5 animals were investigated for signs of skin hypersensitivity after intradermal and epidermal exposure. Under the conditions used in this study, exposure of DL-Ethylpanthenol induced no sensitisation.
Migrated from Short description of key information:
DL-Panthenol was tested for its sensitizing effect on the skin of the guinea pig in the BUEHLER Test. It was concluded that DL-Panthenol does not have a sensitizing effect on the skin of the guinea pig in the BUEHLER Test under the test conditions chosen. A read across approach was performed in addition with the supporting substance DL-Ethylpanthenol. DL-Ethylpanthenol showed no sensitization in a maximization test with guinea pigs.
Justification for selection of skin sensitisation endpoint:
GLP and guideline study.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information from genetic toxicity in vitro:
Bacterial reverse mutation assay:
The substance DL-Panthenol was tested for its mutagenic potential based on the ability to induce point mutations in selected loci of several bacterial strains, i.e. Salmonella typhimurium and Escherichia coli, in a reverse mutation assay. Standard plate test (SPT) and Preincubation Test (PIT) both with and without metabolic activation with liver homogenate of Aroclor 1254 -pretreated male Sprague-Dawley rats were applied. Two independent experiments were carried out: 1st Experiment Strains: TA 1535, TA 100, TA 1537, TA 98, E. coli WP2 uvrA Doses: 0; 20; 100; 500; 2500 and 5000 µg/plate Vehicle: Water Type of test: Standard plate test with and without S-9 mix Number of plates: 3 test plates per dose or per control 2nd Experiment Strains: TA 1535, TA 100, TA 1537, TA 98, E. coli WP2 uvrA Doses: 0; 20; 100; 500; 2500 and 5000 µg/plate Vehicle: Water Type of test: Preincubation test with and without S-9 mix Number of plates: 3 test plates per dose or per control Negative controls treated with the vehicle (water) and positive controls treated with 2-aminoanthracene, N-methyl-N''-nitro-N-nitrosoguanidine, 4-nitro-o-phenylendiamine, 9-aminoacridine, or 4-nitroquinoline-N-oxide were included in each replicate.
According to the results of the present study, DL-Panthenol was considered to be not mutagenic.
Mammalian cell gene assay:
Read across to the supporting substance DL-Ethylpanthenol was done. For justification of read across please refer to the attachment in IUCLID5 section 13. In a mammalian cell gene mutation assay, in chinese hamster V79 cells cultured in vitro were exposed for 4 hours to DL-Ethyl Panthenol, at concentrations of 150, 300, 600, 1200, 2400 µg/mL in the presence and absence of mammalian metabolic activation S9 mix (rat liver). In a second test the chinese hamster V79 cell cultures were exposed to the same concentrations for 24 hours in the absence of metabolic activation. DL-Ethyl Panthenol was tested up to concentrations of 2400 µg/mL (approx 10 mM). No relevant cytotoxic effect was observed in the first experiment as relative cloning efficiency 1 did not go below 50 %. In the second experiment cytotoxicity was noted at 300 µg/mL and above. No substantial dose dependent increase of the mutation frequency exceeding the threshold of three times the mutation frequency of the corresponding solvent control occured with and without metabolic activation. Furthermore there was no dose dependent trend even below the threshold mentioned above as indicated by the missing statistical significance. Therefore, the data of this study are judged as non-mutagenic. The positive controls induced a distinct increase in mutant colonies and thus, showed the sensitivity of the test and the activity of the metabolic activation system. This study is classified as acceptable. This study fulfills the requirements of the Guideline OECD 476 for in vitro mutagenicity (mammalian forward gene mutation) data.
Chromosome aberration assay:
Read across to the supporting substance DL-Ethylpanthenol was done. For justification of read across please refer to the attachment in IUCLID5 section 13. DL-Ethyl Panthenol was assessed as to its ability to induce chromosomal aberrations in human peripheral blood lymphocytes in vitro.Without metabolic activation doses between 333 and 5000 µg/mL were tested after 24 hours continous treatment. With metabolic activation (S9- mix, rat) doses between 1000 and 5000 µg/mL were tested after a 3 hours pulse treatment. Two independent experiments were performed at a fixation period of 24 hours. Additionally the highest dose of 5000 µg/mL was tested in one experiment at a fixation period of 48 hours (i.e. after a 48 h continuous treament in absence and a 3 hours pulse treatment in presence of S9- mix).
The sensitivity of the test system and the activity of the metabolic activation were demonstrated by using the direct acting mutagen mitomycin-C (MMC-C) and the promutagen cyclophosphamide (CP) as positive controls. Both substances increased significantly the rate of chromosome aberrations.
The highest dose assayed was the maximal recommended one. Cytotoxicity as measured by reductions in the mitotic indices (MI) was observed after continuous (24 and 48 hours) exposures to DL-Ethyl Panthenol in both experiments. Exposure to DL-Ethyl Panthenol did not raise the rate of cells with chromosome aberrations.
Based on the close structural similarity of D-and DL-Panthenol and due to the metabolism of DL Ethyl Panthenol to Panthenol it can be assumed that also DL-Panthenol is neither genotoxic nor mutagenic.

CARCINOGENICITY

no data

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REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information: Based on the results of the developmental toxicity/ teratogenicity study and the 90-days- oral repeated dose toxicity study (NOAEL = 1000 mg/kg bw/ d) with DL- Ethyl Panthenol, DL -Pantenol is not classified according to EU Directive 67/548/EEC or EU Regulation (EC) No 1272/2008. For justification of read across please refer to the attachment in IUCLID5 section 13.
Short description of key information:
The assessment of toxicity to fertility was done by a read across approach from DL- Ethyl Panthenol. No adverse effects on spermatogenic endpoints (testicular and epididymal sperm numbers, sperm production rate, motility, and the percentage of morphological normal sperm), estrous cycle and reproductive organs could be observed in a subchronic 90- day oral toxicity study with DL- Ethyl Panthenol (see section 7.5.1). The close structural similarity between DL-Ethyl Panthenol and Panthenol strongly suggest that there are also no adverse effects on spermatogenic effects with DL- Panthenol.
Developmental toxicity (read across):
The objective of the study was to determine the potential of DL-Ethyl Panthenol to induce developmental toxicity after maternal exposure from implantation to 1 day prior to expected parturition, to characterize maternal toxicity at the exposure levels tested and to determine a no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity. The study was conducted in compliance with GLP regulations and in accordance with regulatory guidelines, including OECD 414.
The test item, DL- Ethyl Panthenol, in the vehicle (deionized water), was administered orally by gavage to 3 groups of 25 bred female Crl:CD(SD) rats once daily from gestation days 6 through 19. Dosage levels were 250, 500, and 1000 mg/kg/day administered at a dosage volume of 10 mL/kg. Dosages were selected following a range-finding study in which systemic exposure was demonstrated in the pregnant rat. A concurrent control group composed of 25 bred females received the vehicle on a comparable regimen. The females were approximately 14 weeks of age at the initiation of dose administration. All animals were observed twice daily for mortality and moribundity. Clinical observations, body weights, and food consumption were recorded at appropriate intervals. On gestation day 20, a laparohysterectomy was performed on each female. The uteri, placentae, and ovaries were examined, and the numbers of fetuses, early and late resorptions, total implantations, and corpora lutea were recorded. Gravid uterine weights were recorded, and net body weights and net body weight changes were calculated. The fetuses were weighed, sexed, and examined for external, visceral, and skeletal malformations and developmental variations.
The analyzed dosing formulations were within the requested limits (85% to 115%), homogeneous, and stable after 10 days of refrigerated storage. All females survived to the scheduled necropsy on gestation day 20. There were no test article-related clinical observations noted at any dosage level. Additionally, there were no test article-related maternal macroscopic findings noted at the scheduled necropsy. There were no test article-related effects on body weights, body weight gains, net body weights, net body weight gains, or food consumption at any dosage level tested. Based on the parameters evaluated, including postimplantation loss, litter size, mean fetal body weights, and fetal sex ratios, intrauterine growth and survival were unaffected by test article administration at all dosage levels tested. There were no test article-related external, visceral, or skeletal malformations or developmental variations observed at any dosage level tested.
There were no test article-related clinical findings or effects on maternal body weight, body weight gains, or food consumption observed at any dosage level. In addition, there were no test article-related effects on embryo/fetal development at any dosage level. Based on the results of this study, a dosage level of 1000 mg/kg/day, the highest dosage level evaluated, was considered to be the no-observed-adverse-effect level (NOAEL) for maternal toxicity and embryo/fetal development when DL- Ethyl Panthenol was administered orally by gavage to bred Crl:CD(SD) rats. Based on these data it can be concluded that animals fed with DL-Ethyl Panthenol are concurrently exposed to Panthenol. Due to structure similarity and the absence of any effect in the developmental toxicity study with DL-Ethyl Panthenol in rats up to the highest tested dose of 1,000 mg/kg bw/d, it is highly likely that DL- Panthenol shows any developmental toxicity.

TOXICOKINETIC (ADME studies)

Absorption:
With a molecular weight of 205.25 g/mol, a logKow value of -1.02 and a water solubility of 562.3 g/L DL□ Panthenol is likely to be absorbed in the GI tract. Due to the high water solubility the substance may not diffuse across plasma membranes. More likely gastro-intestinal absorption of DL- Panthenol is triggered by passage through aqueous pores or carriage with the bulk passage of water which is favoured for small (molecular weight around 200 g/mol), water soluble substances. Since there is an active transport mechanism for Pantothenic acid, active transport may also be likely for DL- Panthenol. It remains unclear if the active transport is enantiomer- specific as only the D- form of Pantothenic acid is transported. Nevertheless, extensive gastrointestinal absorption is expected for DL□ Panthenol based on physical chemical properties.
Based on the low vapour pressure of 0.0036 Pa DL□ Panthenol does not vaporise in a sufficient manner to become available for inhalation exposure. Exposure to aerosols may occur. However, due to the high water solubility the substance is likely to solve in the mucus lining of the respiratory tract but subsequent systemic absorption is not likely.
The substance characteristics and physical-chemical properties indicate that dermal absorption is likely. The physical state favours quick dermal absorption with liquids taken up more readily than dry particulates. Data available for D- Panthenol show that dermal absorption occurred following topical administration to rats, which was proven by the higher urinary excretion of Pantothenic acid, the oxidation product of D- Panthenol, in comparison to controls (Erlemann et al, 1962).In vitro dermal penetration studies with D- Panthenol using rat and pig skin also showed that dermal penetration occurred (unpublished DSM Nutritional Products Reports, Klecak, 1985). In conclusion, the available data suggest that DL- Panthenol will be systemically absorbed after skin exposure.
Distribution:
Following oral and dermal absorption DL- Panthenol is likely to systemically distribute through extracellular compartments. Data obtained from oral subchronic repeated dose toxicity testing give not rise to any target organ specificity. As D- Panthenol was shown to be rapidly metabolised to Pantothenic acid it may be concluded that DL- Panthenol undergoes a first pass effect in liver after oral application, indicating that distribution of the parent compound is limited through oral routes. Furthermore, oral absorption may be limited by microbiological degradation in the intestine. However, systemic distribution following dermal exposure is expected for DL- Panthenol, based on the toxicokinetic behaviour of the pure D□ enantiomer of Panthenol (Erlemann et al, 1962). The low half life, based on the presumed rapid metabolic degradation and subsequent quick urinary excretion, indicate a low potential for bioaccumulation. In addition, the low logKow of -1.02 also indicates a very low bioaccumulation potential.
Metabolism:
Based on the chemical structure, the substance may be metabolised by phase I and II enzymes, mainly in the liver. Initial alcohol oxidation by cytochrome P450 monooxygenases (CYP) or alcohol and aldehyde dehydrogenases (ADH/ AlDH) will result in the generation of Pantothenic acid (vitamin B5). Results obtained from D- Panthenol indicate quick oxidation to Pantothenic acid and it is expected that DL- Panthenol is metabolised through the same enzymatic pathways. Further, a hydrolysis of the amide- bond is proposed resulting in 2,4□ Dihydroxy-3,3-dimethyl-butyric acid and 3- Hydroxypropylamine. The parent compound as well as Pantothenic acid and the hydrolysis products may be readily conjugated by phase II metabolising enzymes like Glucuronosyltransferases and Sulfotransferases. No conversion into a toxic metabolite is expected as indicated by in vitro genetic toxicity tests performed with DL□ Panthenol and DL- Ethyl Panthenol.
Excretion
Data obtained from testing with D- Panthenol in rats indicate, that topical administered substance is quickly metabolised to Pantothenic acid, which is rapidly excreted via the urine. Similar is expected for DL- Panthenol, as metabolism of the parent compound will result into Pantothenic acid as well, triggered by the same enzymatic pathways. If administered orally, excretion may also occur via faeces as metabolic degradation via the intestinal microflora is expected.
In conclusion, DL- Panthenol is expected to be systemically absorbed after oral and dermal exposure. Based on its physical chemical properties, the substance is not expected to diffuse into intracellular compartments. Moreover distribution through extracellular body fluids is likely. It is expected, that DL- Panthenol undergoes a first- pass effect in the liver after oral application. Metabolism will most likely include phase I enzymes and will result in the quick formation of Pantothenic acid. Excretion of the breakdown products will most likely occur via the urine. No bioaccumulation is expected.

PHOTOINDUCED TOXICITY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

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no data

DATA ON MAN

no data

BIBLIOGRAPHY

- Safety data sheets
-
-TOXNET database on toxicology

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

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

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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

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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 GEL BALM HORSE CHESTNUT TROXERUTIN

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

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

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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.

TRIETHANOLAMINE (CAS: 102-71-6)

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

1000 -- - ECHA, European Chemical Agency. Additional information: oral: In a sub-chronic oral toxicity study, a NOAEL of 1000 mg/kg bw/day was established, the highest dose tested.
dermal: In a sub-chronic dermal toxicity study, NOAELs of 125 and 250 mg/kg bw/day were established for local effects for males and females. Systemic NOAELs of 125 and 250 mg/kg bw/day were determined for males and females, respectively, based on kidney effects. Similar effects were observed in a sub-chronic dermal study in mice, performed according to the same protocol.
inhalation: In a sub-acute inhalation toxicity study with rats, a NOAEC for systemic effects of 0.5 mg/L was established, the highest dose tested. 0.02 mg/L (the lowest dose tested) was considered to be the NOAEC for local effects in females. Since slight local effects were observed in males, this concentration was determined to be the LOAEC for local effects in males.

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

LD50 (oral) rat 6 400 mg/kg bw
LC0 (inhhalation) rat 1.8 mg/m3, 8h: 1 chronic bronchitis, all other animals without findings
LD50 (dermal) rabbit > 2 000 mg/kg bw.
Additional information: Clinical signs: other: TEA derived from NH3: mild erythema at 24 hrs (intact and abraded skin) returning to normal on day 6 TEA derived from DEA: moderate erythema at 24 hrs (intact and abraded skin) returning to normal on day 10.
Oral toxicity
In an acute oral toxicity study (BASF AG, 1966), 5 Sprague-Dawley rats/sex/dose were exposed to 200 - 6400 mg/kg bw TEA by gavage and observed for 7 days. The LD50 was determined to be 6400 mg/kg bw for males and females. No deaths occurred at doses of 5000 mg/kg bw or below. At 200 mg/kg bw, slight agitation was observed up to 4 hours after exposure; at higher doses unsteady, elevated respiration, anancasm to chew, apathy, and reduced grooming was noticed. Two days after exposure, no clinical signs were observed. Gross pathology did not reveal any abnormalities.
Dermal toxicity
In a dermal limit test, rabbits were treated with 2000 mg/kg bw TEA on the intact or abraded skin and subsequently observed for a 14 -day period (EPA, 1989a). The test substance was either derived from NH3 (92% TEA) or DEA (88% TEA), both containing approximately 6.5% DEA. Mild erythema was observed following exposure to TEA derived from NH3 on the intact or abraded skin, returning to normal on day 6. Moderate erythema was observed following exposure to TEA derived from DEA on the intact or abraded skin, returning to normal on day 10. No mortality was observed, hence the LD50 was > 2000 mg/kg bw.
Inhalation toxicity
Due to its extremely low volatility, there is a lack of data documenting the acute inhalation toxicity. As good quality data for the oral and dermal route are available, in accordance with column 2 of REACH Annex VIII, a study regarding the inhalation route is not required. One limited report stated that whole-body exposure of rats to a saturated TEA atmosphere (approximately 1.8 mg/m3) at 20°C for 8 hours failed to cause any deaths. Therefore no LC50 value has been determined for this compound (BASF AG, 1966).

SKIN IRRITATION AND CORROSIVITY

not irritant for skin
Additional information: In a skin irritation test performed according to OECD guideline 404 (not GLP-compliant), three rabbits were exposed to TEA using an occlusive application for 4 hours. Erythema and edema were scored at 4, 24, 48, and 72 hours and the mean score was 0 in all animals. The test substance was not a skin irritant under the conditions of this study (BASF, 1983).Several other studies, in which rabbits were exposed for up to 20 hours, yielded similar results (BASF 1956, 1966, 1967, 1971).

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritant for eyes
Additional information: In an eye irritation test equivalent to OECD guideline 405 (non GLP-compliant), 6 rabbits/dose were exposed to undiluted TEA at dose volumes of 0.01, 0.03, and 0.1 mL. The eyes were not irrigated. Eyes were examined and scored according to Draize et al. (1944) 1, 3, 7, 14, and 21 days after dosing. TEA was not an eye irritant under the conditions of this study (Griffith, 1980). The same conclusion was reached in an eye irritation test (non GLP-compliant, according to internal BASF standards), in which 50 µL of the test substance was instilled into the eyes of 2 rabbits, and irritation was scored 10 min, 1 and 24 hours and 8 days after administration (BASF AG, 1971). In addition, no eye irritation was observed in response to the application of 0.5 mL 20% TEA in water at pH 10 and pH 8 (BASF AG, 1956). Two other studies (performed according to internal BASF standards) demonstrated some mild irritation due to the application of 50 µL undiluted TEA to the rabbit eye, which was not fully reversible within 8 days in one animal (BASF AG, 1966, 1967). Overall, TEA is judged not to be irritating to the eyes.

SKIN SENSITISATION

No sensitisation potential was reported in guinea pigs upon dermal sensitisation and challenge. Although allergic reactions to TEA have been reported, the substance is judged to have a very low sensitisation potential.
Additional information: The sensitising potential of TEA was investigated in a Guinea Pig Maximisation Test according to OECD TG 406 under GLP conditions (Hoechst, 1988). Based on the results of a pre-test, animals were dermally injected twice with 0.1 mL 2% TEA on day 1, followed by an epicutaneous induction (occlusive) with 0.5 mL undiluted TEA for 48 hours starting on day 9, and a dermal challenge (occlusive) with 0.5 mL 10% TEA for 24 hours on day 22. Dermal reactions were evaluated according to Draize 48 and 72 hours after the start of the dermal challenge. No clinical signs were noticed and all readings were negative.
Regarding the available human data, the positive reactions interpreted as allergic seem to be caused by exposure to TEA in cosmetics and/or topical therapeutic preparations possibly on damaged skin. The diagnosis of TEA contact sensitisation should therefore not be based on a positive patch test reaction alone but on a combination of history and -preferably -validation tests.
The negative experimental findings in animals and the level of exposure to TEA in the population, together with the low frequency of positive reactions to low TEA concentrations in patch-tested patients indicate a very low sensitisation potential in humans, and the risk of sensitisation to TEA on uncompromised skin seems to be very low (Lessmann, 2009).

DERMAL/PERCUTANEOUS ABSORPTION

Dermal absorption 15 mg/cm2.
Additional information:
On the basis of mass of triethanolamine per area of skin, the lowest dermal dose levels for rats and mice were equal at 1.09 mg/cm2. The skin of mice is thinner than that of rats, and this difference may explain the higher percentage of dose absorbed by mice. The highest dermal doses were 4 and 15 mg/cm2 for rats and mice, respectively.
Triethanolamine enhances its own absorption, and the pronounced difference between the species was not unexpected. The percent of dose absorbed in each species increased with increasing dose, but in rats, the increase was not statistically significant. Both species rapidly excreted the absorbed dose, primarily in urine. In rats, less than 1% of the dose was present in the tissue samples (except the dose site) 72 hours after treatment; the heart, kidney, liver, lung, and spleen contained elevated concentrations of radiolabel relative to blood.
60% to 80% of dermally applied 79 and 1120 mg/kg triethanolamine was absorbed by female mice within 72 hours.
Absorption in different matrices:
79 mg/kg bw group
Blood: 0.00590%
Dose site: 1.35%
Faeces: 7.80%
Urine: 48.2%
Total: 57.3%
14.6% remained unabsorbed (dosing appliance, skin gauze, skin wash)

1120 mg/kg bw group
Blood: 0.00627%
Dose site: 0.576%
Faeces: 13.0%
Urine: 67.7%
Total: 81.3%
6.75% remained unabsorbed (dosing appliance, skin gauze, skin wash)

MUTAGENESIS / GENOTOXICITY

Not mutagenic / genotoxic
Additional information
TEA was tested in the Ames reverse mutation assay using S. typhimurium strains TA 1535, TA 1537, TA 97, TA 98 and TA 100 at a concentration up to 10000 µg/plate with and without metabolic activation. Treatment with TEA was not associated with reverse mutations in any of the strains tested (Mortelmans, 1986). In another bacterial mutation assay using S. typhimurium strains TA 1535, TA 1537, TA 1538, TA 98, TA 100 and E. coli strains WP2 and WP2 uvrA, TEA was tested at concentrations up to 4000 µg/plate with and without metabolic activation. In this assay, TEA was not genotoxic in all the strains tested (Dean, 1985). TEA was also tested negative in a bacterial mutation study using S. typhimurium strains TA 1535, TA 1537, TA 1538, TA 98, TA 100 and E. coli strains WP2 and WP2 uvrA with and without metabolic activation at concentrations up to 2000 µg/plate (TSCATS, 1989). In a fourth mutation assay, using S. typhimurium strains TA 98 and TA 100 and E. coli strain WP2, TEA was tested at concentrations up to 20000 µg/plate with and without metabolic activation. In this assay, TEA was also tested negative (Innoue, 1982). Induction of chromosomal aberrations and sister chromatid exchanges was investigated in Chinese hamster ovary cells, exposed to concentrations up to 10100 µg/mL (which induced cytotoxicity). All tests were negative in the absence as well as the presence of metabolic activation (Galloway, 1987). TEA was also negative in the in vitro mouse lymphoma (L5178Y TK+/-) forward gene mutation assay (The Dow Chemical Company, 2010). Two independent assays at concentrations ranging from 50 to 1500 mg/mL in the absence and presence of an externally supplied metabolic activation (S9) system were performed. The highest concentration tested was the limit dose of 10 mM.
Based on the available information, IARC (2000) concluded that TEA was not mutagenic to Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 or TA 1538 in the presence or absence of exogenous metabolic activation in a number of studies. TEA did not induce mutations in Escherichia coli WP2 uvrA and WP2 try- in the presence or absence of exogenous metabolic activation in two studies. In a single study, TEA was not mutagenic to Bacillus subtilis strains carrying uvrA or uvrA and polA mutations in the presence or absence of exogenous metabolic activation. However, when TEA was mixed with sodium nitrite, mutations were induced in this system without exogenous metabolic activation; this activity was lost in the presence of exogenous metabolic activation.
TEA did not induce gene conversion in Saccharomyces cerevisiae in the presence or absence of exogenous metabolic activation in one study (TSCATS 1989A). In a single study, sex-linked recessive lethal mutations were not induced in Drosophila melanogaster by treatment with TEA either by diet or injection. Unscheduled DNA synthesis was not induced in rat primary hepatocytes exposed to TEA in two studies. TEA did not induce sister chromatid exchanges in Chinese hamster ovary cells in either the presence or absence of exogenous metabolic activation. Chromosomal aberrations were not induced in rat liver cells, Chinese hamster lung cells or Chinese hamster ovary cells by in-vitro exposure to TEA. It did not induce cell transformation in Syrian hamster embryo cells.

CARCINOGENICITY

not carcinogenic
Additional information
In a dermal carcinogenicity study in rats performed to a similar method as OECD guideline 451 and under GLP, Fischer rats (60/sex/dose) were dermally exposed to 0, 32, 63, or 125 mg/kg bw/day (males) and 0, 63, 125, or 250 mg/kg bw/day (females) TEA in acetone, 5 days/week for 103 weeks (NTP, 1999). Ten male and ten female rats from each group were evaluated at 15 months for organ weights and histopathology.The survival rate of females in the 250 mg/kg bw group was slightly less than that of the vehicle controls. The mean body weight of females administered 250 mg/kg bw ranged from 9% to 12% less than that of the vehicle controls between weeks 73 and 93. Male and female rats receiving triethanolamine had irritated skin at the site of application; in dosed females, the site of application also had a crusty appearance. The number of animals in which these findings were observed increased with increasing dose. At the 15-month interim evaluation, the absolute left and right kidney weights and relative right kidney weight of females administered 250 mg/kg bw were significantly greater than those of the vehicle controls.
The incidence of acanthosis at the site of application in males administered 125 mg/kg bw and the incidences of acanthosis, inflammation, and ulceration in dosed females were greater than in the vehicle controls at the 15-month interim evaluation and at the end of the 2-year study. Males in the 125 mg/kg bw group also had greater incidences of inflammation and ulceration than the vehicle controls, and females receiving 125 or 250 mg/kg bw had greater incidences of epidermal erosion than the vehicle controls at 2 years.

There were no skin neoplasms at or away from the site of application that were considered related to treatment with triethanolamine. At the end of the study, renal tubule adenomas were observed in seven dosed males and in one vehicle control female and one female in the 63 mg/kg group. One male in the 125 mg/kg bw group and one female in the 250 mg/kg bw group had renal tubule hyperplasia. Extended (step-section) evaluation of the kidneys of all male rats revealed additional renal tubule adenomas in one vehicle control male, one male in the 32 mg/kg bw group, two males in the 63 mg/kg bw group, and three males in the 125 mg/kg bw group (including one male from the 15-month interim evaluation). An oncocytoma was also identified in one male in the 32 mg/kg bw group. Hyperplasia was identified in eight additional vehicle control males and in 19 additional dosed males. The total incidences (combined standard and extended evaluations) of renal tubule adenoma in dosed male rats were slightly greater than the vehicle control incidence (vehicle control, 1/50; 32 mg/kg bw, 2/50; 63 mg/kg bw, 6/49; 125 mg/kg bw, 4/50). The total incidence of hyperplasia in dosed and vehicle control males was similar (9/50, 8/50, 7/49, 6/50). The severity of hyperplasia in males in the 32 and 125 mg/kg bw groups was greater than that in the vehicle controls.
Under the conditions of these dermal studies, there was equivocal evidence of carcinogenic activity of TEA in male rats based on a marginal increase in the incidences of renal tubule cell adenoma. There was no evidence of carcinogenic activity in female rats receiving 63, 125, or 250 mg/kg bw TEA. Based on these results, IARC (2000) concluded that there was no significant increase in the incidence of tumours at any site. Dosed rats had varying degrees of acanthosis and inflammation and ulceration, female rats had epidermal erosion at the site of skin application. 63 mg/kg bw/day was established to be the NOAEL for local effects in males, and the LOAEL in females, based on acanthosis and chronic active inflammation at the application site.

In a dermal carcinogenicity study in mice performed to a similar protocol as OECD guideline 451 and under GLP, B6C3F1 mice (50/sex/dose) were dermally exposed to 0, 200, 630, or 2000 mg/kg bw/day (males) and 0, 100, 300, or 1000 mg/kg bw/day (females) TEA in acetone, 5 days/week for 104 (males) or 105 (females) weeks (NTP, 2004). Survival of all dosed groups was similar to that of the vehicle control groups. Body weights of 2000 mg/kg bw males were less than those of the vehicle controls from weeks 17 to 37 and at the end of the study; body weights of dosed groups of females were similar to those of the vehicle controls throughout the study. Treatment-related clinical findings included skin irritation at the site of application, which increased with increasing dose and was more severe in males than in females. Gross lesions observed at necropsy included nodules and masses of the liver in dosed females. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in all dosed groups of females. The incidence of hemangiosarcoma of the liver in 630 mg/kg bw males was marginally increased. The incidences of eosinophilic focus in all dosed groups of mice were greater than those in the vehicle controls. Gross lesions observed at necropsy included visible crusts at the site of application in all dosed groups of mice. Treatment-related epidermal hyperplasia, suppurative inflammation, ulceration, and dermal chronic inflammation occurred at the site of application in most dosed groups of mice, and the incidences and severities of these lesions generally increased with increasing dose.
Under the conditions of this 2-year dermal study, there was equivocal evidence of carcinogenic activity of TEA in male B6C3F1 mice based on the occurrence of liver hemangiosarcoma. There was some evidence of carcinogenic activity in female B6C3F1 mice based on increased incidences of hepatocellular adenoma. Exposure to TEA by dermal application resulted in increased incidences of eosinophilic focus of the liver in males and females. Dosed mice developed treatment-related non-neoplastic lesions at the site of application.
In an oral carcinogenicity study in rats, Fischer rats (50/sex/dose) were daily exposed to 0, 1, or 2% TEA via the drinking water (corresponding to a dose of approximately 667 and 1333 mg/kg bw/day) for 2 years (Maekawa et al, 1986). In week 69, dose levels in females were reduced to 0.5 and 1% (corresponding to ca. 333 and 667 mg/kg bw/day), because of associated nephrotoxicity. A variety of tumours developed in all groups, but no statistically significant differences were observed to control levels. A positive trend towards increased occurrence of hepatic tumours in males and of uterine endometrial sarcomas and renal-cell adenomas in females was judged as not related to the treatment. It was concluded that TEA is not carcinogenic under these conditions in the Fischer rat, but is toxic to the kidneys.
In another oral carcinogenicity study, B6C3F1 mice (50/sex/dose) were administered 0, 1, or 2% TEA in the drinking water (corresponding to a dose of ca. 1600 and 3200 mg/kg bw/day) for 82 weeks (Konishi et al, 1992). Neoplasms developed in all groups including the control group, but no dose-related increase in tumour incidence was observed. No adverse effects were noted on survival and organ weights. Thus, no evidence for carcinogenic potential of TEA upon oral administration was found in mice.

TEA was evaluated in a genetically modified mouse skin papilloma model (Spalding, 1999, 2000). Doses up to 30 mg of TEA were administered topically to groups of 15 to 20 female Tg.AC mice five times per week for 20 weeks. The experimental design also included positive and negative controls. In contrast to the positive controls, which developed multiple papillomas, there were no increases in the incidences of skin tumours in mice receiving TEA.
Thus, TEA has been reported to cause an increased incidence of liver tumours in female B6C3F1 mice after dermal application, but not in males nor in Fischer 344 rats (NTP 1999, 2004). Effects on choline metabolism have been suggested to play a role in hepatic tumorigenesis in mice. Choline deficiency induces liver cancer in rodents, and TEA could compete with choline uptake into tissues. In a mechanistic study, the potential of TEA to cause choline deficiency in the liver of mice as a mode of tumorigenesis was investigated (Stott, 2004). Groups of female B6C3F1 mice were administered TEA at 0 or the maximum tolerated dose (MTD) of 1000 mg/kg bw/day (trail I), and 0, 10, 100, 300 or 1000 mg/kg bw/day (trial II) in acetone, 5 days/week for 3 weeks. Female CDF rats were also administered 0 or an MTD dose of 250 mg/kg bw/day TEA (trial II) in a similar manner. No clinical signs of toxicity were noted, and upon sacrifice, levels of hepatic choline, its primary storage form phosphocholine (PCho), and its primary oxidation product betaine, were determined. A statistically significant decrease in PCho and betaine was observed at the high dosage (26-42%) relative to controls and dose-related, albeit variable, decrease was noted in PCho levels. Choline levels were also decreased 13-35% at the high dose level in mice. No changes in levels of choline or metabolites were noted in treated rats. A subsequent evaluation of the potential of TEA to inhibit the uptake of 3H-choline by cultured Chinese hamster ovary cells revealed a dose-related effect upon uptake. It was concluded that TEA may cause liver tumours in mice via a choline-depletion mode of action and that this effects is likely caused by inhibition of choline uptake. A similar mechanism was identified for hepatic tumorigenesis in mice upon exposure to the structural analogue substance DEA. This non-genotoxic mechanism displays interspecies differences in sensitivity with humans being much more resistant. Therefore, based on the available data, TEA is not considered carcinogenic for humans.

REPRODUCTIVE TOXICITY

Effect on fertility: via oral route
NOAEL (rat) 1 000 mg/kg bw/day
Effect on developmental toxicity: via oral route
NOAEL (rat) 300 mg/kg bw/day
Additional information:
For the endpoint developmental toxicity/teratogenicity a WoE Approach is conducted using results from the registered substance TEA and studies performed with the structurally analogous substance MEA-HCl (CAS 2000-42-7).
In a reproduction/developmental toxicity screening study with TEA, performed according to OECD guideline 421, Wistar rats (10/sex/dose) were exposed by gavage to 0, 100, 300 or 1000 mg/kg bw/day during a premating period of 2 weeks and a mating period (max. 2 weeks) for both sexes, during approximately 1 week post-mating for males, and during the entire gestation period as well as 4 days of lactation for females. Food consumption, body weight, clinical signs, mating and reproductive performance (including determinations of the number of implantations and the calculation of the postimplantation loss in females) were examined in parental animals. At necropsy, animals were assessed for gross pathology and selected organs were weighed and examined histopathologically. In pups, bodyweight, viability and macroscopic changes were recorded. At necropsy on PND 4, all pups were examined macroscopically for external and visceral findings. At the high dose of 1000 mg/kg bw/day, a decreased number of implantation sites, increased postimplantation loss and a lower average litter size were observed. No adverse effects were observed regarding reproductive performance, fertility or systemic toxicity at any dose level. Thus, the NOAEL for systemic toxicity as well as for reproductive performance and fertility in parental animals was established at 1000 mg/kg bw/day, the NOAEL for postnatal toxicity in the offspring was 1000 mg/kg bw/day, and the NOAEL for prenatal developmental toxicity was determined to be 300 mg/kg bw/day (BASF SE, 2010).
In a Chernoff-Kavlok teratogenicity screening test, CD-1 mice were exposed to TEA by gavage in 3 phases: 1) 3 virgin females were exposed to 10, 100 of 1000 mg TEA/kg bw/day during 5 consecutive days; 2) 2 -4 mated females were exposed to 600, 1200, 2400, 4800 or 9600 mg TEA/kg bw/day on gestation days (GD) 6 -15; 3) 50 mated females were exposed to 1125 mg TEA/kg bw/day on GD 6 -15. In the main study (phase 3), exposure to TEA did not produce any evidence of developmental or maternal toxicity. Therefore, the NOAEL for maternal toxicity and developmental toxicity was established at 1125 mg/kg bw/day (NTP, 1987).

As no developmental toxicity study (OECD guideline 414) is available for TEA, read across with the structural analogue MEA, for which developmental toxicity studies are available, is applied.
In a GLP-compliant prenatal developmental toxicity study with rats, performed according to OECD guideline 414 (BASF SE, 1994) pregnant Wistar rats were exposed to the structure analogue MEA by gavage at dose levels 0, 40, 120, 450 mg/kg bw/day on days 6 - 15 of gestation. Signs of maternal toxicity were observed at the highest dose, manifested as reduced food consumption, lower mean body weights and impaired body weight gain. No reproductive and developmental toxicity parameters were affected. The NOAEL for developmental effects was thus established to correspond to 450 mg/kg bw/day; the NOAEL for maternal toxicity was 120 mg/kg bw/day.
In another comparable to guideline prenatal developmental toxicity study (Liberacki, 1996) rats and rabbits were exposed. Pregnant Sprague-Dawley rats were exposed dermally to 0, 10, 25, 75 and 225 mg/kg bw/day of MEA. Rats administered 225 mg MEA/kg bw/day exhibited a treatment-related increased incidence of skin irritation and the body weight gain was significantly decreased during the exposure period. Despite maternal effects observed among dams in the high dose group, reproductive and developmental toxicity parameters among exposed rats were unaffected at all dose levels. The NOAEL for maternal toxicity was set at 75 mg/kg bw/day and the NOAEL for developmental toxicity was set at the highest dose level of 225 mg/kg bw/day.
In the rabbit study exposure was via the dermal route to 0, 10, 25, and 75 mg/kg/day of MEA. The rabbits in the mid and high dose group exhibited signs of skin irritation, severe at the highest dose level. No treatment-related effects were observed on reproductive and developmental toxicity parameters. The NOAEL for maternal toxicity was set at 10 mg/kg bw/day and the NOAEL for developmental toxicity was set at the highest dose level of 75 mg/kg bw/day (Liberacki,1996).
In a preliminary study on the prenatal toxicity of MEA, female rats (10/dose) were exposed to 0, 50, 150, 300 or 500 mg/kg bw/day by gavage on gestation days 6 -15. Maternal toxicity was observed at the high dose only, and included reduced food consumption, impaired body weight gain, decreased total protein and albumin levels, and a thickened wall of the forestomach in 3 dams. No adverse effects on the fetuses occurred. Therefore, NOAELs for maternal toxicity and teratogenicity were established at 300 and 500 mg/kg bw/day (the highest dose tested), respectively (BASF SE, 1992).
For the structural analogue substance MEA a two generation reproduction toxicity study of the hydrochloric acid performed in Wistar rats with dietary administration demonstrated clear NOAELs for systemic and reproductive toxicity including fertility at 300 mg /kg bw/day. Only at the highest dose, 1000 mg/kg bw/day, were minor effects noted. Males at this high dose levels showed minor effects on fertility in the form of decreased absolute and relative weights of epididymides and cauda . However, there was no histomorphological correlate of these findings in the organs, no effect upon testes or testicular sperm count, and no effect upon mating performance. Females at this dose level revealed decreased numbers of implants and increased resorption rates resulting in smaller litters associated with indications of systemic toxicity. There was virtually no effect on the pre- and postnatal development of the progeny in both generations up to the limit dose level of 1000 mg/kg bw/day representing a clear NOAEL for developmental toxicity (ACC and Cefic, 1994).
Based on the results of the screening studies with TEA (oral route, rats and mice) and the available developmental toxicity studies with rats and rabbits (oral and dermal route of exposure) with MEA, TEA is not considered to be a developmental toxicant.
Reproductive toxicity was also not identified as an additional concern during substance evaluation (cf. Substance Evaluation Report, August 2015).
Mode of Action Analysis / Human Relevance Framework
Available data indicate the capability of Ethanolamines to impair choline homeostasis. This underlines the hypothesis of an involvement of choline and an impaired choline uptake and/or metabolism after Ethanolamine exposure as “mode-of-action”. Rodents appear to be more sensitive towards effects on choline homeostasis and effects observed have been assessed to lack human relevance. For more details please refer to "Justification for non-classification" and to the Read Across Justification in IUCLID Section 13.
Justification for classification or non-classification:
Classification, Labelling, and Packaging Regulation (EC) No 1272/2008
The available information is reliable and suitable for classification purposes under Regulation (EC) No 1272/2008. Based on available experimental information, the test substance is not classified for toxicity to reproduction or developmental toxicity according to Regulation (EC) No 1272/2008 (CLP), as amended for the tenth time in Regulation (EU) No 2017/776.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

The basis for this non-classification is as follows:
1. Effects on reproductive parameters were affected only in the presence of clear parental toxicity. In a standard screening study to OECD TG 421 (BASF, 2010), Triethanolamine (TEA) was administered by gavage (vehicle water) to groups of 10 male and 10 female Wistar rats at dose levels of 0, 100, 300, or 1000 mg TEA/kg bw/day. At the highest dose level there was a statistically significant decrease in litter size and increase in post-implantation loss. The number of implantation sites was decreased by 20%, but this was not statistically significant. A reduction in maternal bodyweight gain during gestation is attributed to the smaller litter sizes in the high dose group. There were no treatment-related effects on postnatal survival or pup bodyweights. Although bodyweights in the high dose group were ca. 8% higher than control, this was not statistically significant and probably reflects, if anything, the smaller litter sizes. For the structural analogue Monoethanolamine (MEA) a two generation reproduction toxicity study in Wistar rats with dietary MEA-HCl administration demonstrated clear NOAELs for systemic and reproductive toxicity including fertility at 300 mg MEA-HCl/kg bw/day. Only at the highest dose, 1000 mg/kg bw/day, were minor effects noted. Males at this high dose levels showed minor effects on fertility in the form of decreased absolute and relative weights of epididymides and cauda epididymidis and, in the F0 generation only, a significantly lower number of homogenization resistant caudal epididymal sperm compared to control. However, there was no histomorphological correlate of these findings in the organs, no effect upon testes or testicular sperm count, and no effect upon mating performance. Females at this dose level revealed decreased numbers of implants and increased resorption rates resulting in smaller litters associated with indications of systemic toxicity. There was virtually no effect on the pre- and postnatal development of the progeny in both generations up to the limit dose level of 1000 mg/kg bw/day representing a clear NOAEL for developmental toxicity.
2. Effects of Ethanolamines can be explained by perturbation of choline-homeostasis as these effects have also been reported to occur in choline-deficient states either by nutritional choline deficiency or by genetic knockout of key enzymes such as choline kinase mimicking a choline deficient state as well. Thus, Ethanolamines-induced effects are plausibly secondary and in consequence of perturbation of choline homeostasis. This underlines the hypothesis of an involvement of choline and an impaired choline uptake and/or metabolism after Ethanolamine exposure as “mode-of-action”.
3. Rodents appear to be more sensitive towards effects on choline homeostasis and effects observed have been assessed to lack human relevance. Choline is an essential nutrient; however, rodents appear to be more susceptible towards an impaired choline-homeostasis than humans. Leung et al. (2005) summarized the evidence why humans are less susceptible for choline-deficiency than rodents in the context of the carcinogenicity endpoint (further references given within the original article):“…choline is an essential nutrient in all mammals, the proposed mechanism of DEA-induced choline deficiency is qualitatively applicable to humans. However, there are marked species differences in susceptibility to choline deficiency, with rats and mice being far more susceptible than other species including humans.
These differences are attributed to quantitative differences in the enzyme kinetics controlling choline metabolism. Rats and mice rapidly metabolize choline to betaine in the liver and it is likely that choline oxidase activity determines choline requirements and controls species sensitivity to choline deficiency.
For example, choline oxidase activity is much lower in primates than rodents and primates are less sensitive to choline deficiency. Humans have the lowest choline oxidase activity of all species and are generally refractory to choline deficiency, with evidence of choline deficiency observed only after prolonged fasting, significantly depressed liver function or deficient parenteral feeding. It is noteworthy that there was no evidence of GJIC inhibition in human hepatocytes treated with DEA or cultured in choline-deficient media.”
For TEA it is reported that it decreases the hepatic levels of Phosphatidylcholine and Betaine, the primary oxidation product, up to 26-42% indicating a disturbance when TEA is given dermally to female B6C3F1 mice (Stott, 2004) at the high dose of 1000 mg/kg bw/day. In this study by Stott et al. (2004) no changes on hepatic Phosphatidylcholine and Betaine were reported in F344-derived rats. However, only a single dose of 250 mg TEA/kg bw/day was tested in female rats for 3 weeks (5days/week). Higher doses of TEA applied orally as it has been done in the available OECD 421 might cause the same effects as observed in mice. Furthermore, a strain difference in rats’ sensitivity to choline depletion cannot be excluded. TEA also inhibited the ^{3}H-choline uptake in vitro in Chinese hamster ovary cells.
Moore and co-workers investigated the potential role of choline antagonism in the aetiology of Monoethanolamine (MEA)-induced implantation loss. When administered to pregnant rats during gestation days (GD) 1–3, 4–5, or 6–7, MEA had no effect upon implantation success. In a second experiment, MEA was administered either in the diet or by oral gavage from two weeks prior to mating through to GD 8. Parallel groups also received a diet supplemented with choline. In the absence of supplementary choline, MEA induced early resorptions, statistically significant only when administered in the diet. A slight reduction in implantation success was ameliorated by supplementary choline. It was concluded that implantation is affected by MEA only when exposure starts before mating; that dietary administration is more effective than gavage dosing; and that interference

with choline homeostasis may play a role in the aetiology of this lesion. Two possible molecular targets were hypothesized for amine alcohols: the platelet activating factor (PAF) and the endocannabinoids. PAF is a choline-derived phospholipid autacoid, which is critical in pre-implantation development and implantation (Moore et al. 2018). Studies show that injection of a specific PAF antagonist into the uterine horn of pregnant rats once during GD 1-4 reduced the number of implanted embryos significantly (Acker et al., 1988). Competition between choline and ethanolamine for uptake into local tissues or within the pathways for PAF synthesis might explain the ameliorating effect of choline supplementation upon MEA-induced implantation loss (Moore et al., 2018).
In a OECD TG 443 study performed with the structural analogue DEA the platelet activating factor (PAF) concentration in serum of the F0 females was reduced dose-dependently when regarding medians with a decrease of 31% in test group 3 (1000 ppm) compared to controls. As supporting evidence, in the OECD TG 443 study which is available for DEA a clear decrease in the choline levels was seen. The analytical results demonstrated the clear presence of choline in all plasma samples from the animals dosed with the test substance DEA (100 ppm, 300 ppm and 1000 ppm dosed animals) and in those from control, non-dosed animals. In general, it can be stated that the presence of the test substance DEA led to a reduction in the content of choline in the plasma samples analysed. This effect appears to be dose-dependent, in that higher dose levels were associated with greater choline reduction. This effect is most clearly visible at lower dose levels (100 ppm and 300 ppm), at which dramatic plasma choline levels could be seen. At higher dosing levels, although further minor plasma choline content reduction was observed, this was by no means as drastic. Furthermore, also in the offspring the analytical results demonstrated the clear presence of choline in all liver samples from the animals dosed with the test substance DEA (100 ppm, 300 ppm and 1000 ppm dosed animals) and in those from control, non-dosed animals. This was true from all time points investigated (4-day old pups, 22-day old pups and ~90-day old adolescents). In general, it can be stated that the presence of the test substance DEA led to a reduction in the content of choline in the liver samples analyzed. This effect appears to be dose-dependent, in that higher dose levels were associated with greater choline reduction, but only up to moderate dosing levels (300 ppm and 100 ppm, depending on the sampling day). At higher dosing levels, no further dramatic liver choline content reduction was observed. This effect was however, not observed in 4-day old animals, in which no clearly definable dose dependent trend is evident. In 22-day old animals this effect could be clearly observed, although the choline levels of the 100 ppm dosed animals have not yet attained minimal concentrations. In ~90-day old animals the effect is dramatic in that the liver choline levels of all non-control animals have reached an approximate minimum. Only a relatively minor further dose-dependency can be observed at this time point.
For DEA various mechanistic in vitro and in vivo studies identified that choline depletion is the key event in hepatic carcinogenicity. DEA decreased gap junctional intracellular communication (GJIC) in primary cultured mouse and rat hepatocytes; induced DNA hypomethylation in mouse hepatocytes; decreased phosphatidylcholine synthesis; and increased S-phase DNA synthesis in mouse hepatocytes, but had no effect on apoptosis. All of these effects were mediated by the inhibition of choline sequestration, and were prevented with choline supplementation. No such effects were noted in human hepatocytes in vitro. Apparent differences in the susceptibility of two different mice strains (B6C3F1 > C57BL) were noted. B6C3F1 mice are extremely sensitive to non-genotoxic effects and are susceptible to spontaneous liver tumors. Moreover, chronic stimulation and compensatory adaptive changes of hepatocyte hypertrophy and proliferation are able to enhance the incidence of common spontaneous liver tumors in the mouse by mechanisms not relevant to humans (adapted from the DEA OECD SIAR, 2009).
However, there are marked species differences in susceptibility to choline deficiency, with rats and mice being far more susceptible than other species including humans. It is reported that primates are much more resistant towards adverse effects of choline□deficiency and associated changes (Hoffbauer and Zaki, 1964). Moreover, quantitative data underline this species difference: choline oxidase, the key enzyme in converting choline into betaine is highly active in rodents whereas it plays a minor role in Humans (Sidransky & Faber, 1960). The reaction / metabolism with betaine occur mainly in the liver and is of minor importance for the overall metabolism of homocysteine in humans; it is of major significance only in rodents. This is because betaine is derived from choline, a pathway of minimal importance and hence of little relevance in primates, who have a paucity of choline oxidase in the liver (Lieber and Packer, 2002). Choline metabolism is connected to Phosphatidylcholine and Betaine. The latter is reported to be central for the synthesis of SAM (S-Adenosyl-Methionine), a principle methylating agent for biosynthetic pathways and maintenance of critical gene methylation patterns (Stott et al. 2004; Zeisel and Blusztajn, 1994).
Taken together, similar effects on pre- and/or post-implantation losses were observed for Mono-, Di- and Triethanolamine. Additionally, Ethanolamines show similar effects on choline-metabolism. It is likely that the effects of TEA and its structurally analogues substances MEA and DEA on pre- and post-implantation in laboratory animals are mediated by

effects on choline homeostasis rather than through direct embryo toxicity. These effects are inhibition of choline-uptake in the liver, subsequent perturbation of choline-homeostasis, with subsequent impairment of C1-metabolism, DNA-methylation, lipid metabolism, and intercellular communication. These effects are judged to be relevant for systemic toxicity of this group of substances, but are not evaluated to be direct effects on reproductive toxicity. However, rodents appear to be more sensitive towards effects on choline homeostasis and effects observed have been assessed to lack human relevance. Furthermore, effects observed for TEA on reproduction were observed in the presence of systemic toxicity and are regarded as secondary effect.
Therefore, TEA is not subjected for classification on toxicity to reproduction or developmental toxicity according to Regulation (EC) No 1272/2008,as amended for the tenth time in Regulation (EU) No 2017/776. Reproductive toxicity was also not identified as an additional concern during substance evaluation (cf. Substance Evaluation Report, August 2015).

TOXICOKINETIC (ADME studies)

1. Physical-chemical properties
TEA (MW 149.2 g/mol) is a liquid with a measured melting point of 20.5°C, a measured boiling point of 336.1°C at 1013.25 hPa, a measured vapour pressure of 0.00029 hPa at 21°C, and a dissociation constant (pKa) of 7.86 at 25°C. The octanol-water partition coefficient (log Pow) is -2.3 at 25°C, and the substance is fully miscible with water.
2. Data from acute and repeated dose toxicity studies
Acute toxicity data indicate low toxicity: in rats the oral LD50 was 6400 mg/kg bw, no mortality was observed at or below 5000 mg/kg bw. Clinical signs (elevated respiration, anancasm to chew, apathy, reduced grooming) disappeared 2 days after dosing, and gross pathology at necropsy revealed no abnormalities (BASF AG, 1966). In an acute dermal toxicity study in rabbits, no mortality was observed up to the limit concentration and the LD50 was established to be > 2000 mg/kg bw (TSCATS, 1989). Due to its extremely low vapour pressure, exposure to TEA vapour is very unlikely. One report stated that whole-body exposure of rats to an atmosphere saturated with TEA vapour (concentration not given) at 20°C for 8 hours failed to cause any deaths, therefore no LC50 value was established (BASF AG, 1966).
In an oral repeated dose study, rats were administered 0 - 1000 mg/kg bw/day in the diet for 91 days. Since no adverse effects were observed, the NOAEL was established to be 1000 mg/kg bw/day (TSCATS, 1989). In a sub-chronic dermal toxicity study, rats were treated with 0 - 2000 mg/kg bw/day on the skin for 90 days (Battelle Columbus Laboratories, 1987a). At the highest doses, decreases in body weight, irritation and inflammation at the site of application were observed - ranging from minimal acanthosis at the lower doses to chronic active inflammation, erosion and ulceration in higher dose groups - accompanied by haematologic changes. NOAELs for local effects were determined to be 125 and 250 mg/kg bw/day for males and females, respectively. The NOAEL for systemic effects was established at 125 mg/kg bw/day, based on renal effects (i.e. increased kidney weight). Similar effects were observed in a sub-chronic dermal toxicity study in mice, receiving 0 - 4000 mg/kg bw/day TEA on the skin for 90 days (Battelle Columbus Laboratories, 1987b). The kidneys were identified as the target organ at lower doses, accompanied by increased liver weights at the top dose level. Dermal irritation and inflammation was noted at the site of application. In an 28 -day inhalation toxicity study in rats, exposed to 0 - 0.5 mg/L TEA for 6 hours/day and 5 hours/week, the NOAEC for systemic effects was established at 0.5 mg/L since no adverse systemic effects were observed. The NOAEC for local effects (laryngeal inflammation) was determined to be 0.02 mg/L for females; since slight inflammation was still observed in males, this concentration was designated the LOAEC for local effects in males (BASF AG, 1993).
3. Absorption, distribution, metabolism, excretion

Studies in experimental animals indicated that TEA is absorbed through the skin. No data on oral and inhalation exposure is available. Besides data regarding the dermal route, data on the i.v. route is also available. Differences in the rate of absorption between rats and mice have been described regarding dermal exposure. In mice, most of the topically applied14C-TEA is absorbed, and only 2% to 11% is detected at the site of application after 48 hours (Dow 1988,1989; Stott, 2000). The dermal absorption of TEA in rats was less extensive and much slower than in mice (Dow, 1988,1989). An absorption, distribution, metabolism, and excretion study by the NTP (2004) found that after 72 hours of exposure, only 20% to 30% of the applied dermal dose of TEA (68 or 276 mg/kg) was absorbed in rats and 60% to 80% was absorbed in mice (79 or 1120 mg/kg). These differences in absorption have been attributed either to the different doses used in comparative studies or to species-specific factors. No differences in tissue distribution were noted after i.v. or dermal exposure (NTP, 2004).

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

The elimination of14C-TEA-derived radioactivity from the blood of mice after a 1 mg/kg intravenous injection displays two-phase elimination kinetics with an initial rapid distribution phase (0.3-0.6 hour half-life) followed by a slower elimination phase (10-hour half-life) (Dow, 1988,1989; Stott, 2000). Radioactivity in blood after dermal application of 2000 mg/kg neat TEA declined in a bi-exponential manner through 3-hour post-dosing with a rapid initial phase (half-life of 1.9 hr) followed by a slower terminal phase (half-life of 31 hr)(Stott, 2000). Both rats and mice rapidly excreted the absorbed dose, primarily in urine (followed by faeces) after i.v. and dermal exposure. Regarding dermal exposure, in rats, less than 1% of the dose was present in the tissue samples (except the dose site) 72 hours after treatment; the heart, kidney, liver, lung, and spleen contained elevated concentrations of radiolabel relative to blood (NTP, 2004).
In addition to animal studies, human skin penetration of TEA was tested in vitro using diffusion cell techniques (Kraeling, 2003). Oil-in-water emulsions containing 1% or 5%14C-TEA were added to the stratum corneum side of 200-300 µm thick human skin sections and penetration of radioactivity into and through the skin (into a receptor fluid, sampled up to 24 hours after application) was determined. At pH 8.0, 1.1 and 1.2% of the dose was absorbed into the receptor fluid with a total penetration of 22.0 and 16.5% for 1 and 5% TEA, respectively. At pH 7.0, 0.43 and 0.28% was absorbed into the receptor fluid with a total penetration of 9.8 and 5.8% after 24 hours for 1 and 5% TEA, respectively. After 48 hours at pH 7.0, 0.68 and 0.60% was absorbed into the receptor fluid with a total penetration of 9.6 and 6.9%, for 1 and 5% TEA respectively. This pH-related difference reflects the higher percentage of unionised test material at pH 8.0.
Specific investigations: other studies
Clinical Observations and Body Weights
No effects of dosing upon the clinical appearance, body weights, or weight gains of mice or rats were noted. In addition, no evidence of dermal irritation of dosing solutions was noted during the dosing period.
In Vivo Choline and Choline-Related Metabolites
In the initial mouse trial (Trial I), a 1000 mg/kg bw/day TEA dosage caused statistically identified decreases in betaine (26%) and PCho (35%) levels relative to vehicle treated controls. A smaller decrease in hepatic choline concentration (13%) was also observed, which was not statistically identified. In a subsequent dose-response experiment (Trial II mice), all three measured parameters were statistically identified by Trend Test as changing over the dose range, despite a noticeable degree of variability in the data. PCho levels were decreased by 18-20% at 100-300 mg/kg bw/day and by 42% at 1000 mg/kg bw/day compared to controls. Hepatic betaine levels were also decreased across most dosages, with minimal levels observed at the high dosage (29% decrease), and choline levels of high-dose-group mice were depressed by 35% compared to controls. Pairwise statistically significant changes were limited to high-dose groups. Administration of 250 mg/kg bw/day TEA to male CDF rats failed to cause a significant change in any measured parameter.
In Vitro Choline Uptake
TEA caused a statistically identified decrease in the uptake of 3H-choline by growing CHO cells. A dose-related decrease in uptake occurred from 0.67 mM to 1.34 mM concentrations, reaching a maximal inhibition of approximately 60-70% of control at 1.34 to 3.4 mM over the 10-min dosing period. A more pronounced response to DEA was observed, with a dose-related decrease in 3H-choline uptake observed from 0.048 to 0.15 mM, reaching a maximal inhibition of approximately 75% of control at 0.19 to 1.9 mM.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

skin irritation path test: In a study with 6 human volunteers, 2 cm2-patches soaked with the test material were applied for 24 hours to the upper arm, and skin irritation was scored upon patch removal and 24 hours thereafter (BASF AG, 1930). Besides slight biting and reddening in 1 subject, no irritation was observed and thus, the test substance was judged non-irritating.

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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-TOXNET database on toxicology

- ECHA database on REACH registered substances
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TROXERUTIN (CAS: 7085-55-4 / 31511-30-5)

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

67 -- - https://www.sciencedirect.com/science/article/abs/pii/S1382668913002639

Additional information:
Troxerutin has undergone numerous clinical trials in human subjects; even with high doses (4 or 7 g per day) it had an excellent safety and tolerability

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

LD50 oral (rat) 27160 mg/kg

SKIN IRRITATION AND CORROSIVITY

no data

MUCOSAE IRRITATION AND CORROSION (eye irritation)

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

no data

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not genotoxic
Additional information:
Troxerutin, a flavonoid derivative, used in vascular diseases was studied in 4 mutagenicity tests: the Ames test, the point mutation test (V79/HPRT), the in vitro metaphase analysis in human lymphocytes and the micronucleus test in mice. The aglycone trihydroxyethylquercetin (THEQ) and quercetin were studied too. Troxerutin was not mutagenic, whereas quercetin was positive in the Ames test, V79 cells and in vitro metaphase analysis. THEQ was negative in the Ames test. The substitution of quercetin with hydroxyethyl groups in 7,3'' and 4'' positions abolished mutagenic activity of quercetin.

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Troxerutin has undergone numerous clinical trials in human subjects; even with high doses (4 or 7 g per day) it had an excellent safety and tolerability

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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- ECHA https://echa.europa.eu/
- Environmental Toxicology and Pharmacology. Volume 37, Issue 1, January 2014, Pages 174-184:
Oral supplementation with troxerutin (trihydroxyethylrutin), modulates lipid peroxidation and antioxidant status in 1,2-dimethylhydrazine-induced rat colon carcinogenesis

Part 2A
Adverse Effects and Serious Adverse Effects

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

Formula Code -

Commercial Name CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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

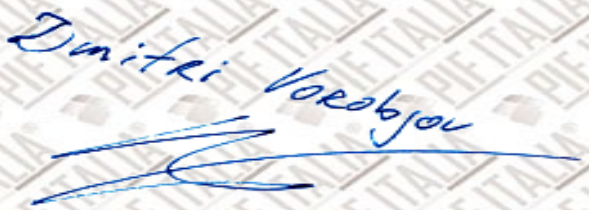
Inclusion on the: 15.04.2021 **N** .

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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 GEL BALM HORSE CHESTNUT TROXERUTIN

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- EMA, European Medical Agency

List of documents attached to the PIF

Formula Code	-
Commercial Name	CONCENTRATED GEL BALM HORSE CHESTNUT TROXERUTIN

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