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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

Product Category

q. skin care liquid

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

VITATEKA

First Printing Date

16.02.2025

Last Checking

20.02.2025

Table of contents

PART 1 - Description of Cosmetic Product

Formula Code

-

Commercial Name

CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

CPNP reference product:

First Printing Date 16.02.2025 **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 ()

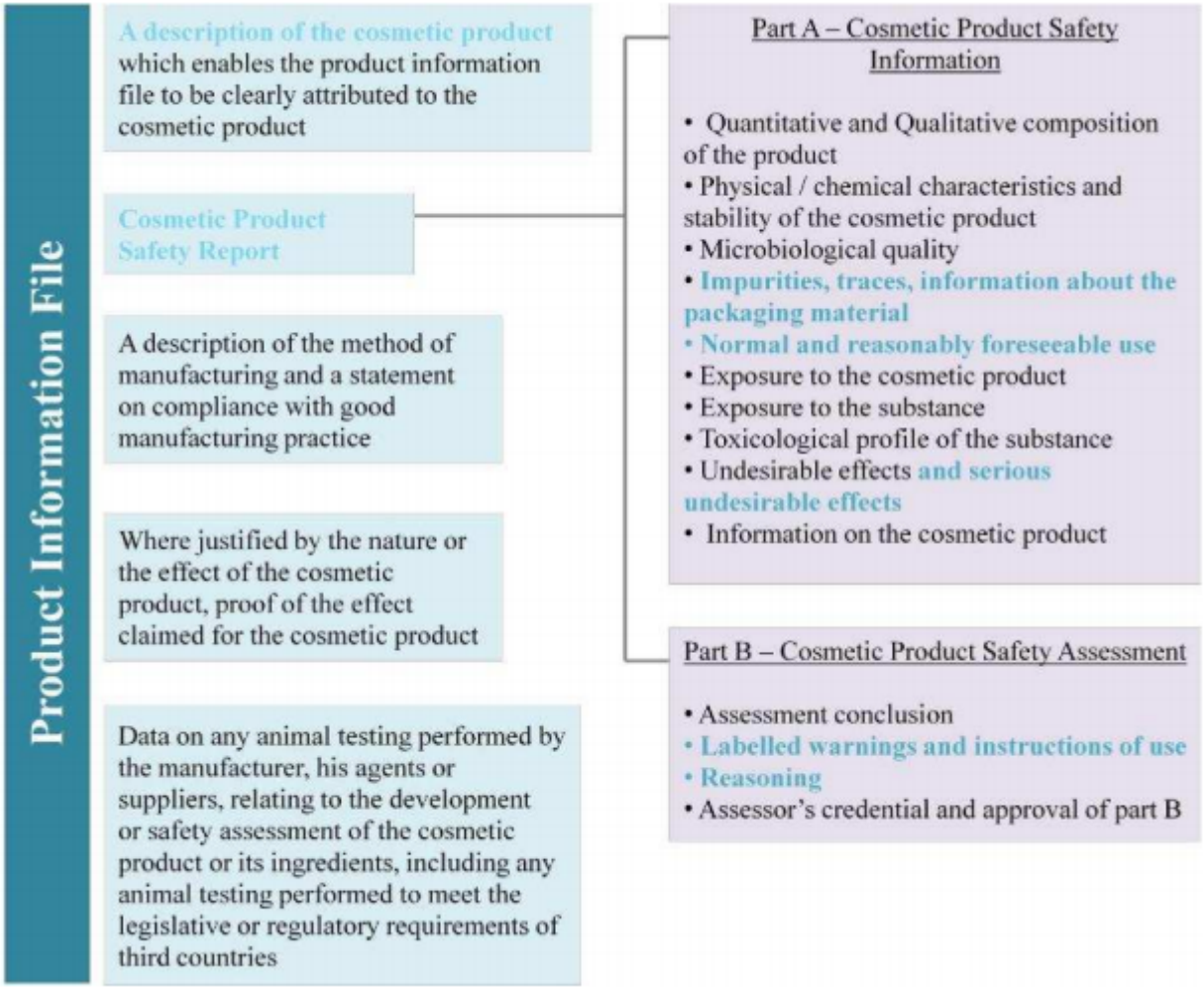
Phone N.

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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	49.300000	AQUA		100.0000	7732-18-5	231-791-2	SOLVENT
2	GLYCERINE	10.000000	GLYCERIN		100.0000	56-81-5	200-289-5	DENATURANT, HAIR CONDITIONING, HUMECTANT, ORAL CARE, PERFUMING, SKIN CONDITIONING, SKIN PROTECTING, SOLVENT, VISCOSITY CONTROLLING
3	CAPRYLIC CAPRIC TRIGLYCERIDE	5.000000	CAPRYLIC/CAPRIC TRIGLYCERIDE		100.0000	73398-61-5/ 65381-09-1	277-452-2/ 265-724-3	FRAGRANCE, PERFUMING, SKIN CONDITIONING - OCCLUSIVE, SOLVENT
4	AAKOEMU PCP	5.000000	POTASSIUM CETYL PHOSPHATE		100.0000	84861-79-0; 19035-79-1	284-374-2	SURFACTANT - CLEANSING, SURFACTANT - EMULSIFYING
5	CETEARYL ALCOHOL	5.000000	CETEARYL ALCOHOL		100.0000	67762-27-0 / 8005-44-5	267-008-6	EMULSION STABILISING, OPACIFYING, SKIN CONDITIONING - EMOLLIENT, SURFACTANT - CLEANSING, SURFACTANT - EMULSIFYING, SURFACTANT - FOAM BOOSTING, VISCOSITY CONTROLLING
6	dimethycone	5.000000	DIMETHICONE		100.0000	63148-62-9 / 9006-65-9 / 9016-00-6		ANTIFOAMING, SKIN CONDITIONING, SKIN CONDITIONING - EMOLLIENT, SKIN PROTECTING
7	GLYCERYL STEARATE	5.000000	GLYCERYL STEARATE		100.0000	31566-31-1	250-705-4	SKIN CONDITIONING - EMOLLIENT, SURFACTANT - EMULSIFYING

* 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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

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

8	HELIANTHUS ANNUUS SEED OIL	5.000000	HELIANTHUS ANNUUS SEED OIL		100.0000	84776-03-4 / 8001-21-6/ 164250-88-8	-/ 232-273-9/ -	SKIN CONDITIONING - EMOLLIENT, SKIN CONDITIONING - MISCELLANEOUS, SKIN CONDITIONING - OCCLUSIVE, SOLVENT
9	STEARIC ACID	5.000000	STEARIC ACID		91.0000	57-11-4	200-313-4	CLEANSING, EMULSION STABILISING, FRAGRANCE, REFATTING, SURFACTANT - CLEANSING, SURFACTANT - EMULSIFYING
10			GLYCERIN		9.0000	56-81-5	200-289-5	DENATURANT, HAIR CONDITIONING, HUMECTANT, ORAL CARE, PERFUMING, SKIN CONDITIONING, SKIN PROTECTING, SOLVENT, VISCOSITY CONTROLLING
11	Euxyl PE 9010	1.000000	PHENOXYETHANOL	*	91.5000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
12			ETHYLHEXYLGLYCERIN		8.5000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
13	CAMPHOR	0.500000	CAMPHOR	*	100.0000	464-49-3 / 76-22-2	207-355-2	DENATURANT, FRAGRANCE, PLASTICISER
14	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
15	COSROMA TLJ011	0.500000	AQUA		64.0000	7732-18-5	231-791-2	SOLVENT
16			COLLAGEN		35.0000	9007-34-5	232-697-4	HAIR CONDITIONING, MOISTURISING, SKIN CONDITIONING
17			PHENOXYETHANOL	*	0.9000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE

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

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

Qualitative and Quantitative Composition of Cosmetic Product

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

18			ETHYLHEXYLGLYCERIN		0.1000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
19	D-GLUCOSAMINE SULFATE	0.500000	GLUCOSAMINE SULFATE		100.0000	29031-19-4	249-379-6	SKIN CONDITIONING
20	D-PANTHENOL 75 W	0.500000	PANTHENOL		75.0000	81-13-0 / 16485-10-2	201-327-3	ANTISTATIC, HAIR CONDITIONING, SKIN CONDITIONING
21			AQUA		24.9900	7732-18-5	231-791-2	SOLVENT
22			CITRIC ACID		0.0100	77-92-9 / 5949-29-1	201-069-1	BUFFERING, CHELATING, FRAGRANCE
23	EDETA® BD	0.500000	DISODIUM EDTA		100.0000	139-33-3 --- 6381-92-6	205-358-3	CHELATING, VISCOSITY CONTROLLING
24	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
25	MUMIO ASPHALTUM PUNJABIANUM EXTRACT	0.500000	AQUA		79.0000	7732-18-5	231-791-2	SOLVENT
26			ASPHALTUM EXTRACT		20.0000			Anti-inflammatory, antioxidant, anti-acne
27			PHENOXYETHANOL	*	0.9000	122-99-6	204-589-7	ANTIMICROBIAL, PRESERVATIVE
28			ETHYLHEXYLGLYCERIN		0.1000	70445-33-9	408-080-2	DEODORANT, SKIN CONDITIONING
29	Triethanolamine pure	0.500000	TRIETHANOLAMINE	*	100.0000	102-71-6	203-049-8	BUFFERING, FRAGRANCE, SURFACTANT - CLEANSING, SURFACTANT - EMULSIFYING
30			AQUA		0.0000	7732-18-5	231-791-2	SOLVENT
31	BENZYL NICOTINATE	0.100000	BENZYL NICOTINATE		100.0000	94-44-0	202-332-3	ANTISTATIC, SKIN CONDITIONING
32	SODIUM CHONDROITIN SULFATE	0.100000	SODIUM CHONDROITIN SULFATE		100.0000	9007-28-7 / 9082-07-9	232-696-9	ANTISTATIC, HAIR CONDITIONING, 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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

PRODUCT DESCRIPTION

Product Family 3. Non rinse-off Products

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

Product Type q. skin care liquid

MASSAGE CREAM

INGREDIENTS

AQUA GLYCERIN POTASSIUM CETYL PHOSPHATE CAPRYLIC/CAPRIC TRIGLYCERIDE HELIANTHUS ANNUUS SEED OIL GLYCERYL STEARATE CETEARYL ALCOHOL DIMETHICONE STEARIC ACID PHENOXYETHANOL CARBOMER CAMPHOR DISODIUM EDTA TRIETHANOLAMINE MENTHOL GLUCOSAMINE SULFATE PANTHENOL COLLAGEN SODIUM CHONDROITIN SULFATE BENZYL NICOTINATE ASPHALTUM EXTRACT 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

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

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

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

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product
2	EDETA® BD	0.500000	Trisodium nitrilotriacetate (NTA)	5064-31-3	225-768-6	0.1	0.0005

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	TITRIMETRIC METHOD	Carc. 2: H351; Eye Irrit. 2: H319; Met. Corr. 1: H290	% w >=5 Carc. 2 H351

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product
3	GLYCERINE	10.000000	Sodium chloride	7647-14-5	231-598-3	0.001	0.0001

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	TITRIMETRIC METHOD	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			1,2,4-Butanetriol	42890-76-6	-	0.0035	0.00035

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	Ph Eur. 10 th Edit	-	

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product

Raw Materials Impurities List

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

5	GLYCERINE	10.000000	Aldehydes	50-00-0	200-001-8	0.009	0.0009

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	GC	Acute Tox. 2: H330, Acute Tox. 3: H311 , H301, Carc. 1B: H350, Skin Corr. 1B: H314, Skin Sens. 1A: H317	% w >=25 Skin Corr. 1B H314, 5<= % w <25 Skin Irrit. 2 H315, % w >=25 Eye Dam. 1 H318, 5<= % w <25 Eye Irrit. 2 H319, % w >=0,2 Skin Sens. 1 H317, % w >=5 STOT SE 3 H335

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product
6			Diethylene glycol	111-46-6	203-872-2	0.1	0.01

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
Regulation (EC) No 1272/2008	USP	Acute Tox. 4: H302; STOT RE 2: H373	

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product
7			AQUA	7732-18-5	231-791-2	0.5	0.05

REGULATORY (C&L, annex Regolationn)	ANALYSIS METHOD	TOXICOLOGY	NOTES
-	AOCS Ca 2e-84	Non toxic	

N	RAW MATERIAL TRADE NAME	% R.M. in Prod.	IMPURITY CHEMICAL NAME	CAS N.	EINECS N.	% in Raw Mat.	% In Product
8	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			

Raw Materials Impurities List

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

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
AQUA	7732-18-5	0.050000	0.007392	4000.000	541126	541126	541126	541126	541126	541126
PARAFFIN	8002-74-2	0.025000	0.003696	5.000	1353	1353	1353	1353	1353	1353
Diethylene glycol	111-46-6	0.010000	0.001478	200.000	135318	135318	135318	135318	135318	135318
Diethanolamine	111-42-2	0.001500	0.000222	80.000	360360	360360	360360	360360	360360	360360
Aldehydes	50-00-0	0.000900	0.000133	82.000	616541	616541	616541	616541	616541	616541
Trisodium nitrilotriacetate (NTA)	5064-31-3	0.000500	0.000074	19.000	256757	256757	256757	256757	256757	256757
1,2,4-Butanetriol	42890-76-6	0.000350	0.000052	0.230	4423	4423	4423	4423	4423	4423
Sodium chloride	7647-14-5	0.000100	0.000015	1207.000	80466667	80466667	80466667	80466667	80466667	80466667

Part 2A
Normal and Reasonably Predictable Use

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

Formula Code	-
Commercial Name	CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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		50.139950	7.412690	45000.00	**6071**	**6071**	**6071**	**6071**	**6071**	**6071**
GLYCERIN	56-81-5		10.450000	1.544928	10000.00	**6473**	**6473**	**6473**	**6473**	**6473**	**6473**
CAPRYLIC/CAPRIC TRIGLYCERIDE	73398-61-5/ 65381-09-1		5.000000	0.739200	1000.00	**1353**	**1353**	**1353**	**1353**	**1353**	**1353**
CETEARYL ALCOHOL	67762-27-0 / 8005-44-5		5.000000	0.739200	750.00	**1015**	**1015**	**1015**	**1015**	**1015**	**1015**
DIMETHICONE	63148-62-9 / 9006-65-9 / 9016-00-6		5.000000	0.739200	1000.00	**1353**	**1353**	**1353**	**1353**	**1353**	**1353**
GLYCERYL STEARATE	31566-31-1		5.000000	0.739200	2000.00	**2706**	**2706**	**2706**	**2706**	**2706**	**2706**
HELIANTHUS ANNUUS SEED OIL	84776-03-4 / 8001-21-6/ 164250-88-8		5.000000	0.739200	9250.00	**12514**	**12514**	**12514**	**12514**	**12514**	**12514**
POTASSIUM CETYL PHOSPHATE	84861-79-0; 19035-79-1		5.000000	0.739200	800.00	**1082**	**1082**	**1082**	**1082**	**1082**	**1082**
STEARIC ACID	57-11-4		4.550000	0.672672	1000.00	**1487**	**1487**	**1487**	**1487**	**1487**	**1487**
PHENOXYETHANOL	122-99-6	*	0.924000	0.136604	500.00	**3660**	**3660**	**3660**	**3660**	**3660**	**3660**
CAMPHOR	464-49-3 / 76-22-2	*	0.500000	0.073920	250.00	**3382**	**3382**	**3382**	**3382**	**3382**	**3382**

* 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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

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**
DISODIUM EDTA	139-33-3 --- 6381-92-6		0.500000	0.073920	500.00	**6764**	**6764**	**6764**	**6764**	**6764**	**6764**
GLUCOSAMINE SULFATE	29031-19-4		0.500000	0.073920	2149.00	**29072**	**29072**	**29072**	**29072**	**29072**	**29072**
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**
COLLAGEN	9007-34-5		0.175000	0.025872	8600.00	**332406**	**332406**	**332406**	**332406**	**332406**	**332406**
ASPHALTUM EXTRACT			0.100000	0.014784	33.30	**2252**	**2252**	**2252**	**2252**	**2252**	**2252**
BENZYL NICOTINATE	94-44-0		0.100000	0.014784	20.00	**1353**	**1353**	**1353**	**1353**	**1353**	**1353**
SODIUM CHONDROITIN SULFATE	9007-28-7 / 9082-07-9		0.100000	0.014784	1000.00	**67641**	**67641**	**67641**	**67641**	**67641**	**67641**
ETHYLHEXYLGLYCERIN	70445-33-9		0.086000	0.012714	100.00	**7865**	**7865**	**7865**	**7865**	**7865**	**7865**
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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

ASPHALTUM EXTRACT (CAS:)

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

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

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

no data

SKIN IRRITATION AND CORROSIVITY

no data

MUCOSAE IRRITATION AND CORROSION (eye irritation)

no data

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

no data

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

no data

PHOTOINDUCED TOXICITY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

no data

DATA ON MAN

no data

BIBLIOGRAPHY

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

BENZYL NICOTINATE (CAS: 94-44-0)

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

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

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

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

LD50 oral (mouse) 2188 mg/kg

SKIN IRRITATION AND CORROSIVITY

Causes skin irritation

MUCOSAE IRRITATION AND CORROSION (eye irritation)

Causes serious eye irritation

SKIN SENSITISATION

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

no data

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

no data

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

not bioaccumulative according: Log Pow 2.4

DATA ON MAN

no data

BIBLIOGRAPHY

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

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

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

250 -- - ECHA, European Chemical Agency

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

SKIN IRRITATION AND CORROSIVITY

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

MUCOSAE IRRITATION AND CORROSION (eye irritation)

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

SKIN SENSITISATION

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

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

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

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

CARCINOGENICITY

no data

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

REPRODUCTIVE TOXICITY

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

TOXICOKINETIC (ADME studies)

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

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

CAPRYLIC/CAPRIC TRIGLYCERIDE (CAS: 73398-61-5/ 65381-09-1)

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

1000 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/16019/7/6/1
Additional information:Studies on oral repeated dose toxicity were available for the following Category members (CAS No.):
73398-61-5, 8001-79-4, 91845 -19-1 and for medium- and long-chain triglyceride mixtures.
All available studies resulted in oral NOAELs of 1000 mg/kg bw/d or greater than 1000 mg/kg bw/d.
Studies on dermal repeated dose toxicity were available for the following Category member (CAS No.): 73398-61-5.
A subacute (28 days) dermal NOAEL of 2000 mg/kg bw/d for rabbits was reported.

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

LD50 oral (mice) >5000 mg/kg bw
LD50 dermal (rat)> 2 000 mg/kg bw
Additional information:
All available acute toxicity studies within this Category showed that Fatty Acid Glycerides are non-toxic via the oral, dermal or inhalation exposure route.
Studies on acute oral toxicity were available for the following members of this category (CAS No.):
31566-31-1, 67701-26-2, 67701-33-1, 73398-61-5, 8001-78-3, 85251-77-0, 91744-13-7 and medium and long chain triglycerols (Matulka, 2006).
The acute oral LD50 for rats and mice in all studies was found to be greater than 2000 or 5000 mg/kg bw.
Studies on acute dermal toxicity were available for the following members of this category (CAS No.): 91845-19-1, 620-67-7, 555-43-1.
The acute dermal LD50 in rats in all studies was found to be greater than 2000 mg/kg bw
One study on acute inhalation toxicity was available for the following member of this category (CAS No.): 73398-61-5.
No signs of systemic toxicity occured in male rats upon acute inhalation exposure to the maximum attainable concentration of Triglycerides, mixed decanoyl and octanoyl (CAS No.: 73398-61-5).

SKIN IRRITATION AND CORROSIVITY

not irritating
Additional information:
Studies on skin irritation/corrosion were available for the following category members (CAS No.): 31566-31-1, 67701-26-2, 67701-33-1, 73398-61-5, 85251-77-0, 91052-54-9, 91744-13-7. No skin irritation potential was observed in any of these studies.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritating
Additional information:
Studies on eye irritation were available for the following category members (CAS No.): 67701-26-2, 67701-33-1, 73398-61-5, 8001-78-3, 85251-77-0, 91744-13-7. No eye irritation potential was observed in any of these studies.

SKIN SENSITISATION

not sensitising
Additional information:
Studies on skin sensitisation of were available for the following Fatty Acid Glycerides category members (CAS No.): 91845-19-1, 620-67-7, 142-18-7, 555-43-1, 73398-61-5 (animal and human skin sensitisation test).
All available skin sensitisation studies showed that Fatty Acid Glycerides are not skin sensitising.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
All available in vitro and in vivo genotoxicity studies were found negative, indicating that Fatty Acid Glycerides have no genotoxic potential.
Available in vitro genotoxicity studies on Fatty Acid Glycerides (CAS No.):
- Ames Test: 67701-26-2, 8001-78-3, 91744-13-7, 73398-61-5 and medium and long-chain triglycerides
- Chromosome Aberration: 8001-79-4 and medium and long-chain triglycerides
- Mammalian gene mutation test in vitro (HPRT): medium and long-chain triglycerides
- Sister Chromatide Exchange: 8001-79-4
Available in vivo genotoxicity studies on Fatty Acid Glycerides (CAS No.):
- Micronucleus assay: 8001-79-4, 91845-19-1 and medium and long-chain triglycerides

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
For Glycerides, C8-18 and C18-unsatd. mono- and di-, acetates (CAS No. 91052 -13 -0) a NOAEL for parental fertility of 1000 mg/kg bw/d in rats could be identified.
For Castor oil (CAS No. 8001-79-4) a NOAEL for parental fertility of 5000 mg/kg bw/d in rats and 15000 mg/kg bw/d in mice could be identified.
For Glycerides, C8-18 and C18-unsatd. mono- and di-, acetates (CAS No. 91052 -13 -0) a developmental NOAEL of 1000 mg/kg bw/d was found in rats.
Intravenously administered 20% lipid emulsion containing a 3:1 ratio of MCT (Medium Chain Triglycerides):LCT (Long Chain Triglycerides) revealed a NOAEL of 4280 mg/kg bw/day.

TOXICOKINETIC (ADME studies)

Not bioaccumulative
Additional information:
Absorption:
The mechanism of the intestinal fat absorption has been studied with C14 labeled fat (combinations of corn oil and palmitic acid) in rats with the intestinal lymph duct cannulated (Borgström, 1951). The recoveries in the lymph of the fat fed varied widely. Diarrhoea occurred in some animals especially after feeding hydrolysed corn oil. In all three groups of experiments maximum recoveries were found after 24 hours, i.e. 80.9, 85.0 and 87.5 % of the activity given. These results indicate that most of the absorbed fat is transported via the lymphatic channels to the systemic circulation whether fed as glycerides or free fatty acids. The proportions of neutral fat and phospholipids in the lymph were in all three cases about the same. 90% of the fatty acids were present in the neutral fat and the remaining 10 % in phospholipids. The neutral fat consisted chiefly of triglycerides; cholesterol and cholesterol esters representing only a minor part of this fraction. No free fatty acids or soaps appeared in the lymph. The results indicated that glycerides might be completely hydrolysed in the intestinal lumen of the rat and then resynthesized in the intestinal wall.
In another study with soybean oil the oral absorption in rats when fed at 17% of the diet was found to be 95 -98% (Nolen, 1972).
The distribution of the fatty acids in the triglycerides of the lymph was determined upon oral administration of triglycerides of known structure to rat (Mattson and Volpenhein, 1961).The extent of absorption of palmitic acid depended on the form in which it was fed (rates between 52 an 96 %). Absorption was greatest when palmitic acid was fed as β-palmitoyl diolein, and least when it was fed as the free acid.
Metabolism:
Fatty Acid Glycerides (mono-, di-, and tri-esters of carboxylic acids with glycerol) have a common metabolic fate that involves stepwise hydrolysis to the carboxylic (e.g. fatty) acids and glycerol. Carboxylic acids and glycerol feed into physiological pathways like the citric acid cycle, sugar synthesis, and lipid synthesis. Fatty Acid Glycerides constitute a large part of the human diet. Triglyceride fats are a major source of calories in the human diet.
Matulka (2009) summarized that the metabolism of Medium chain triglycerides in the canine is a process whereby lipases from the buccal cavity and pancreas release the fatty acids in the gastrointestinal tract where they are absorbed. Unlike long chain triglycerides (LCT), where long chain fatty acids (LCFA) form micelles and are absorbed via the thoracic lymph duct, MCFA are most often transported directly to the liver through the portal vein and do not necessarily form micelles. Also, MCFA do not re-esterify into MCT across the intestinal mucosa. MCFA are transported into the hepatocytes through a carnitine-independent mechanism, and are metabolized into carbon dioxide, acetate, and ketones through b-oxidation, and the citric acid cycle.
Adolph (1999) summarized that lipids are not only structural building blocks of cells and tissues but at the same time suppliers of C- atoms for a number of biosynthetic pathways as well as carriers of essential fatty acids and fat-soluble vitamins. In addition, fatty acids are precursors of prostaglandins and other eicosanoids and therefore have important metabolic functions. Fatty acids can be divided into three groups, saturated, monounsaturated, and polyunsaturated fatty acids.
Each class of fatty acids has a preferential specific role. Saturated fatty acids (medium or long-chain) are more devoted to energy supply, but one should not forget their specific structural role. The polyunsaturated fatty acids of the n–3 and n–6 families have very important structural and functional roles and ideally should not be utilized for energy purposes.
Excretion (Lipolysis):
Typical dietary lipids from vegetable oils, termed long-chain triacylglycerols (LCT), are degraded by salivary, intestinal and pancreatic lipases into two fatty acids and a monoacyl glycerol; whereas, MCT are degraded by the same enzymes into three fatty acids and the simple glycerol backbone. Medium-chain fatty acids (MCFA) are readily absorbed from the small intestine directly into the bloodstream and transported to the liver for hepatic metabolism, while long-chain fatty acids (LCFA) are incorporated into chylomicrons and enter the lymphatic system. MCFA are readily broken down to carbon dioxide and two-carbon fragments, while LCFA are re-esterified to triacylglycerols and either metabolized for energy or stored in adipose tissue.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Metabolism upon parenteral application in humans:
In a human volunteer study on the use of Medium and Long Chain Triglycerides for parenteral nutrition different types of lipid emulsions were infused to male volunteers (see 7.10.5, Schulz, 2002). Biomonitoring of blood triglycerid levels upon single bolus, short time infusion, 12 -hour low concentration infusion and 8 -hour higher concentration infusion revealed that intravenous application of triglycerides in human subjects at concentrations of 100 mg/kg bw/h were well tolerated resulting in a dynamic equilibrium.
Sensitisation data:
- Frequency, level, duration of symptoms observed:
24 and 48 hours after challenge application a original induced site and a virgin (not induced) site (the volar forearm) was observed for skin irritation.
NO. OF PERSONS WITH/OUT REACTIONS COMPARED TO STUDY POPULATION
- Number of subjects with positive reactions on induction application: 0 (24 h exposure, reading 48 h after exposure)
- Number of subjects with positive reactions on challenge application: 0 (readings 24 and 48 h after exposure)
- Number of subjects with negative reactions: 54
The test substance was not skin sensitising in a repeated insult patch test in 54 volunteers.

BIBLIOGRAPHY

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

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.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

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

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

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

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

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

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

Additional information:
Acute oral toxicity

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

ClinicalSigns. Few, if any signs of toxicity were reported following oral administration of the linear alcohols ranging from C6 to C22 alcohols. At doses approaching acute lethality

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

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

Acute inhalation toxicity

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

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

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

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

Acute Dermal Toxicity

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

For the linear alcohols in the range, C6 - C10 most of the reported LD50values in rabbits are in the range 2000 - 4000 mg/kg. For the alcohols C12and higher the acute dermal LD50values were 8000 mg/kg or higher. Although some incidental LD50values below 2000 mg/kg were reported, these values generally represented the maximum dose tested. Substances with a chain length beyond C18 have not been tested but on the basis of the consistent low acute dermal toxicity for alcohols with a chain-length of C16 and below and the consistently low oral acute toxicity for the category as a whole it is expected that aliphatic alcohols in the range C18 – C22 are of a low order of acute dermal toxicity.

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

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

SKIN IRRITATION AND CORROSIVITY

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

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

MUCOSAE IRRITATION AND CORROSION (eye irritation)

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

SKIN SENSITISATION

not sensitising

Additional information:
Respiratory sensitisation.

There are no Respiratory sensitisation studies available.

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

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

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

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

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

DERMAL/PERCUTANEOUS ABSORPTION

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

MUTAGENESIS / GENOTOXICITY

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

In vitro Studies

Bacterial tests

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

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

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

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

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

Non-bacterial test

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

In vivo Studies

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

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

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

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

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

CARCINOGENICITY

not carcinogenic

Studies in animals.

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

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

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

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

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

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

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

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

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

REPRODUCTIVE TOXICITY

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

Additional information:
Oral exposure

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

NOAELrat = 2000mg/kg bw/day

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

NOAELrabbit = 2000mg/kg bw/day

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

NOAELrat = 1000mg/kg bw/day

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

NOAELrat = 1000mg/kg bw/day

Dermal exposure:

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

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

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

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

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

NOAELMaternal: (840 mg/kg bw d)

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

Inhalation exposure:

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

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

NOAECrat = 3500mg/m3

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

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

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

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

No NOAEC identified : 100 mg/kg bw d)

TOXICOKINETIC (ADME studies)

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

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

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

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

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

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

PHOTOINDUCED TOXICITY

not phototoxic

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

DATA ON MAN

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

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

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

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

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

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

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

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

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

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- ECHA https://echa.europa.eu/

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

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

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

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

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

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

SKIN IRRITATION AND CORROSIVITY

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

MUCOSAE IRRITATION AND CORROSION (eye irritation)

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

SKIN SENSITISATION

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

DERMAL/PERCUTANEOUS ABSORPTION

No data

MUTAGENESIS / GENOTOXICITY

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

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

CARCINOGENICITY

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

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

• The substance is not classified for mutagenicity; and

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

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.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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.

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- ECHA https://echa.europa.eu/
- FOOD AND DRUG ADMINISTRATION FDA

COLLAGEN (CAS: 9007-34-5)

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

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

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

LD50 oral (mice) 50 ml/kg

SKIN IRRITATION AND CORROSIVITY

no data

MUCOSAE IRRITATION AND CORROSION (eye irritation)

no data

SKIN SENSITISATION

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

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

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

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

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

PHOTOINDUCED TOXICITY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

no data

DATA ON MAN

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

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

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

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

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

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

SKIN IRRITATION AND CORROSIVITY

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

MUCOSAE IRRITATION AND CORROSION (eye irritation)

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

SKIN SENSITISATION

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

DERMAL/PERCUTANEOUS ABSORPTION

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

MUTAGENESIS / GENOTOXICITY

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

CARCINOGENICITY

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

REPRODUCTIVE TOXICITY

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

TOXICOKINETIC (ADME studies)

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

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

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

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

BIBLIOGRAPHY

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

DISODIUM EDTA (CAS: 139-33-3 --- 6381-92-6)

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

500 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/14817/7/6/2
Additional information:
Once the survivors were placed on a control diet the diarrhea, when present, subsided the within 24 hours. The animal that had previously received 5000 mg/kg bw/day Na2H2EDTA still had low food consumption and died within l week. All other animals survived this 4-week period . The animals that had received 2500 mg/kg bw/ day Na2H2EDTA gained weight more slowly than did the other animals and weighed significantly less than controls at the end of the 4-week withdrawal period. The chelating agent was not detectable in the urine after 2-3 days, nor in the feces after 7 days. The autopsies revealed no significant findings.
- EGTA was better tolerated in the diet than EDTA

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

LD50 oral (rat) 2 800 mg/kg bw
LOAEC inhalation (rat) ca. 30 mg/m³ air

SKIN IRRITATION AND CORROSIVITY

Not classified as skin irritant / corrosive
Additional information:
Irritant / corrosive response data:
- 20 h application: a very slight erythema was observable in one animal which was fully reversible within 24 h; a well defined erythema was observable in animal 2, which was fully reversible within 72 h.
- 1-15 min exposure did also cause no edema or erythema
- A well defined erythema was observed on the ear of both animals which was fully reversible within 48 h.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

Not classified as eye irritant / corrosive
Additional information:
Irritant / corrosive response data:
Both animals showed some redness of the conjunctivae (score 1), 24 h after application of the test susbtance. The same effect was observed in the talcum powder treated eye. This effect was fully reversible 48 h in animal 1 and at least within 8 days in animal 2.

SKIN SENSITISATION

not sensitising
Additional information:
The Magnusson Klingman Test according to OECD Test Guideline 406 using Na2EDTA (purity 91 %) was chosen as key study. This test was performed under GLP by BASF (2000). 10 test animal and 5 control animals were used. A 0.5 % substance concentration in corn oil was used for intradermal induction and a 30 % test concentration for topical induction. Control animals were treated with corn oil as vehicle control. The challenge was conducted with 30 % Na2EDTA in corn oil. 3/10 test animals showed a discrete patchy erythema 24 h after patch removal, after 48 h 0/10 showed a patchy erythema. 7 days later a re-challenge was conducted using 30 % substance in corn oil. 1/10 test animals exhibited a discrete patchy erythema after 24 h, which was reversible within 48 h. Control animals did not exhibit skin reaction after challenge or re-challenge. The positive control group using 20 % mercaptobenzodiazol induced positive skin sensitisation reactions in 7/10 animals at the 24 and 48 h reading.
With Na3EDTA a Repeated Insult Patch Test gave a negative result (0/10 animals) (Henck et al., 1980). Within 10 days the animals received 4 topical treatments (0.1 mL) of 10 % Na3EDTA in dipropyleneglycolmethylether; at the third treatment Freud"s adjuvants was injected additionally. 2 weeks after the last treatment the challenge was conducted using 10 % Na3EDTA in dipropyleneglykolmethylether. Within the same test Henck et al. also tested for cross-sensitisation between the known skin sensitizer ethylenediamine (EDA) and Na3EDTA. Animals were sensitized with EDA and challenged topically with Na3EDTA on the one flanc and EDA on the other. None of the animals reacted positive after the challenge with Na3EDTA, but all of the animals which were challenge with EDA showed a slight to marked erythema and slight edema. Therefore, it was concluded that Na3EDTA does not cross-sensitize with EDA.
Two studies on dogs with airway hyperresponsiveness using Na2EDTA have been performed. In those dogs bronchoconstriction can be induced.
However, considering the fact that no adverse acute or chronic respiratory health effect was reported in workes exposed to Na4EDTA or edetic acid, these results do not warrant a labeling according to EU or GHS critieria.

DERMAL/PERCUTANEOUS ABSORPTION

SKIN ABSORPTION
- The maximum activity detected in urine was 0.001%

MUTAGENESIS / GENOTOXICITY

not considered to be classified for genetic toxicity under Regulation (EC) No 1272/2008
Additional information:
Several in vitro and in vivo tests using Na2EDTA are available. Additional information of EDTA free acid and other Na salts of EDTA have been used for the overall risk assessment. Na salts of EDTA were tested negative in several ames tests. Na salts of EDTA were tested negative in several mouse lymphoma assays. Only one mouse lymphoma assay using edetic acid was positive. However, it was not clear whether this effect was due to the test substance or the pH change. Several other in vitro tests have been performed, and in general EDTA was not genotoxic in vitro.
In vivo, somatic cells in mice (bone marrow cells) showed negative results with respect to the endpoints micronuclei, aneuploidy and sister chromatid exchanges. In germ line cells negative results were obtained for induction of structural chromosomal aberrations in spermatogonia, for induction of aneuploidy in primary and secondary spermatocytes, and also for induction of dominant lethals. A positive result was obtained in a micronucleus test with spermatids after ip application, indicating that aneugenic effects may be induced in specific phases of spermatogenesis (late spermacytogenesis). The effect was linked to the use of an extremely high dose in the LD50 range. Since the induction of aneuploidy is based on a threshold mode of action, the potential for induction of aneuploidy will not be expressed at low doses. Furthermore, the effects may be indirect, resulting from the lower intracellular bioavailability of essential elements. On balance, EDTA and its sodium salts may show a low aneuploidogenic potential at extremely high doses. On the basis of the various negative findings and the assumption of a threshold mode of action for aneugens, it can be concluded that EDTA and its sodium salts are not mutagenic for humans.
This result was also confirmed by the independent evaluation of the MAK Commission for the Investigation of Health Hazards of Chemical Compounds in the work area (MAK, 46. Lieferung, 2009).

CARCINOGENICITY

substance is not considered to be classified for carcinogenicity under Regulation (EC) No 1272/2008, as amended for the tenth time in Regulation (EU) No 2017/776.
Additional information:
A standard carcinogenicity study on mice and rats using Na3 EDTA did not demonstrate that the test substance is carcinogenic in experimental animals. 50 male and 50 female Fischer 344 rats were administered with 3750 and 7500 ppm (equivalent to about 248 and 495 mg/kg bw/day) daily in the diet for 103 weeks. Matched control groups were composed of 20 male and 20 female animals. The average body weights of treated males and females were comparable to those of the matched controls throughout the study. No treatment-related clinical signs were observed and no statistically significant differences in survival noted. Inflammatory and degenerative changes were observed in about the same frequency in all groups. The lesions appeared to be related to age and not to the administration of the test substance. A high incidence of tumors has been observed in the reproductive and endocrine systems and low incidences occurred in the hematopoietic, respiratory, integumentary, and digestive systems. No neoplasms were observed in the nervous, musculoskeletal, or urinary systems. No tumor appeared in a statistically significant positive trend in either dose groups or sexes. A variety of endocrine tumors were found, some types occurring only in treated animals. However, these tumors occurred in low numbers and have frequently been seen in untreated animals in other studies. Therefore, they are probably unrelated to treatment. In a similar study in mice, 50 male and 50 female B6C3Fl mice were administered with the same dose concentrations (3750 and 7500 ppm, equivalent to about 469 and 938 mg/kg bw/day) daily in the feed for 103 weeks. Matched control groups were composed of 20 male and 20 female animals. In male mice only the high-dose group showed a decrease in average body weight compared to the controls throughout most of the study period. In female mice average body weights of the treatment groups were depressed in a dose-related manner during the study period, although the effect was small. No treatment-related clinical signs were observed and no statistically significant differences in survival noted. Inflammatory and degenerative changes were observed in about the same frequency in all groups. The lesions appeared to be related to age and not to the administration of the test substance. A variety of neoplasms were found in both treated and control animals that were well known from historical controls of the same strain. There was a high incidence of tumors in the hematopoictic, endocrine, digestive, and respiratory systems. The incidence of neoplasms in other systems was variable. For all tumor types observed no statistical significance were seen between incidences in dose groups and control groups. With the exception of a splenic hemangioma in a control female and a 3750 ppm-male, all of the tumors of the hematopoietic system were malignant lymphomas or leukemias. The distribution of endocrine tumors varied little between treated and control mice. For all groups, the incidences of hepatic neoplasms were considerably higher in males than in females. Liver tumors occurred in the 3750 ppm-dose (10/44, 22 %) and 7500 ppm-dose (10/47, 21 %) male groups. Percentage was approximately the same as in the male controls (3/19, 16 %). Primary neoplasms of the respiratory system were observed in both treated and control groups. The highest incidence of pulmonary neoplasms was found in the 7500 ppm-dose male mice (control: 2/18, 11 %; 3750 ppm: 8/44, 18 %; 7500 ppm: 12/45, 26 %). This may suggest a treatment related effect. Lung tumors were frequently seen in mice of this strain and age, and therefore, the increase of incidence in this mouse study is probably not related to treatment. In conclusion, the non-significantly increased incidence of some tumor types observed in the study provides no clear evidence of carcinogenic effects in the mice.

REPRODUCTIVE TOXICITY

adverse effect observed
NOAEL: 250 mg/kg bw/day
Additional information:
2 fertility studies using Na2EDTA are available. However, those studies are of limited reliability. Therefore, a multigeneration study with CaNa2EDTA has been used for the risk assessment. This did not give evidence for adverse effects on reproductive performance and outcome for doses of up to 250 mg/kg bw/day. For estimating a NOAEL, other studies were not taken into consideration because of methodological flaws. Hence, the NOAEL is 250 mg/kg bw/day for CaNa2EDTA.
The toxic and teratogenic effects of Na2EDTA were studied in female CD rats following different routes of administration (dietary, gavage, s.c) during g.d. 7-14 (Kimmel, 1977). Dietary exposure to 3 % Na2EDTA amounting to an average dose of 954 mg Na2EDTA/kg bw/day resulted in reduced food intake, severe diarrhea and severe weight loss in the dams during treatment and produced a significant proportion of fetal deaths (about 33% resorptions/litter), significantly lower average fetal weight and gross external, internal and

skeletal malformations in about 71% of the survivors. Treatment with 1500 or 1250 mg Na2EDTA/ kg bw/day administered by gavage (respectively 625 mg/kg and 750 mg/kg twice daily) resulted in severe toxicity to the dams (7 out of 8 animals died in the 1500 mg dose group), in particular 36 % maternal deaths, significantly reduced weight gain, and diarrhea in the 1250 mg dose group and a significantly higher proportion of (about 21 %) malformed survivors. Treatment with 375 mg/kg bw administered subcutaneously produced signs of severe pain (vocalisations and shock) to the dams and resulted in 24 % maternal deaths, significantly reduced food intake and maternal weight loss during the period of treatment. Fetal toxicity (about 32 % resorptions/litter, significantly reduced fetal weight) and a rate of about 4 % malformed survivors/litter were reported for this route of application.
In a further developmental study, pregnant Sprague-Dawley rats were exposed during various periods of gestation to purified diets adjusted to either 100 or 1000 ppm zinc (provided as zinc carbonate) and containing 2 or 3 % Na2EDTA corresponding to 1000 or 1500 mg/kg bw daily intake (Swenerton & Hurley, 1971). The groups of 8 to 16 females had been set on the control diet at least 5 days before breeding and mated to normal stock-fed males. The evaluation of treatment related effects to the dams was not indicated in this study, except for the report on moderate to severe diarrhea in all females that were fed diets containing Na2EDTA. While obviously complete reproductive failure occurred with the 3 % Na2EDTA/100 ppm zinc diet fed during g.d. 0-21, with the 2 % Na2EDTA/100 ppm zinc diet reproductive outcome was essentially comparable to that of controls, however, with lower mean body weight of the pups and with 7 % malformed of the fullterm fetuses. Exposure to the 3 % Na2EDTA/100 ppm zinc diet during the period of g.d. 6-14 and 6-21 resulted in respectively 40 % and 54 % dead or absorbed fetuses, reduced number of dams with live pubs, clearly reduced mean fetal body weight and ratios of respectively 87 % and 100 % malformed living offspring. Gross malformations comprised cleft palate, severe brain deformities, eye defects, micro- or agnathia, syndactyly, clubbed legs and tail anomalies. The reported fetotoxic and teratogenic effects were similar to those from earlier experiments with zinc deficient diets administered to pregnant rats for various periods of during gestation (Hurley, 1966). In contrast, the live offspring of dams fed 3 % Na2EDTA supplemented with 1000 ppm zinc from g.d. 6-21 did not exhibit any malformations, and the mean number of live pups/litter and the mean fetal body weight were comparable to those of controls. The authors concluded from this study that Na2EDTA ingested during pregnancy was teratogenic, whereas supplementation with zinc prevented the detrimental effects of EDTA. It was suggested that the congenital anomalies caused by EDTA were due specifically to zinc deficiency. This was also supported by zinc analyses of fetuses (Hurley & Swenerton, 1966), where clearly lower zinc contents were found in fetuses from deficient mothers in comparison to those from zinc supplemented dams, indicating that the reported effects rather occur because of a direct lack of zinc in fetal tissues than from indirect effects of maternal metabolism on fetal development.
EDTA and four of its salts were evaluated for their teratogenic potential in CD albino rats (Schardein et al., 1981). Groups of 20 females were treated by gavage during g.d. 7-14 with 1000 mg EDTA/kg bw/day as well as with equimolar doses of disodium, trisodium, calcium disodium and tetrasodium edetate (dissolved and suspended in phosphate buffer with final pH values ranging from 3.9 to 9.2). The dose level had been selected from preliminary studies with edetic acid in which there had been some evidence of both maternal and fetotoxicity under the same experimental conditions. For the dams significant drug-related reactions including diarrhea and depression of activity were reported. The former occurred in all drug groups with highest incidences for tetrasodium edetate (90 %) and edetic acid (80 %) and lowest incidence for calcium disodium edetate (10 %). Three dams died during treatment with disodium edetate. Besides slightly decreased food intake in all test groups, treatment with all of the test compounds caused reduced weight gain in the dams during the treatment period. The mortality index of offspring in all treated groups as measured by postimplantation loss was comparable to that of the vehicle and untreated control group. None of the test compounds significantly affected litter size at term or mean fetal body weight when compared to either control. Fetuses were examined for external, visceral and skeletal anomalies. Incidental findings of skeletal anomalies did not reveal a definitive pattern regarding treatment with a particular compound. The authors stated that under these experimental conditions no teratogenic effects were evidenced even at maternally toxic doses.
Toxicity to reproduction: other studies
Additional information
Several in vitro tests for teratogenicity have been performed. In a study of Schmid (1985) 9.5 days old rat embryos were cultured in heat inactivated male rat serum containing Aroclor induced liver S9-mix and 10 - 300 µg/ml EDTA (unclear whether the free acid or a salt was tested). After 48 h incubation no effects on crown-rump and head length or degrees of differentiation were observed. There were also no malformations observed. In another study there was also no interference with normal cell differentiation of murine neuroblast cells (clone N1E-115) (no information regarding the concentrations available) (Mummery, 1984). However, severe cytotoxicity was observed with an EC 100 of 292

µg/mL and an NEC of 2.9 µg/mL.
(1984) conducted a teratogenic test in vitro with cell cultures of forelimb buds and midbrains of 13 day old rat embryos. He reported that up to 500 µg/mL EDTA had no effect on forelimb bud differentiation, but inhibited CNS differentiation at with an IC50 of 2.8 µg/mL and an NEC of 1 µg/mL. 292 µg/mL EDTA also inhibited the cell differentiation to myotubes and ganglia in Oregon R Drosophila embryonic cultures (Bournias-Vardiabasis,1983).
In an additional study by (1984) 40 mg/kg bw of EDTA sodium salt were administered to rabbits on the 12th day of gestation. 16 h later embryos were removed and midbrain and forelimb buds cultured for 5 days. EDTA inhibited cell culture development by less than 20%. It was stated that EDTA interferes with the cell culture development.
In a not very reliable study by Gassett (1977) 0.1 or 3% EDTA solution were dropped into the eye of 4 rabbits 6 times a day. The treatment was performed from sixth to the eighteenth day of gestation. Fetuses were obtained by cesarian section at day 29 of gestation. No teratogenic effect was reported for both EDTA concentrations, however at the 3% dose group the number of fetuses alive dropped from 23 in the 0.1% dose group to 8. In parallel the number of aborted or resorbed fetuses increased from 3 to 19.
Two additional reports on the treatment of pregnant woman with CaNa2EDTA are available. In one case an 8 months pregnant woman was treated for 7 days with 75 mg/kg bw/day CaNa2EDTA for lead poisoning (Angle, 1964). 4 weeks later the mother delivered of normal infant (3.2 kg); developmental assessment of this boy at age 4 3/4 revealed nothing abnormal.
In the other case a 7th month pregnant woman was treated with 0.5 g CaNa2EDTA/day intravenously 3 times a week for 4 weeks (Abendroth, 1971). The delivered infant was healthy and a follow up check at age of 4 also revealed nothing abnormal.

TOXICOKINETIC (ADME studies)

Some poorly reported toxicokinetics studies using the disodium salt of EDTA have been performed. Additionally studies using Ca and Na salts of EDTA are available. According to the dissociation equilibrium of edetic acid, administration of different sodium salts will result in the formation of various anionic species of EDTA in dependence on the intestinal pH value. In whatever salt EDTA is administered, it is likely to chelate metal ions in vivo. Therefore, the studies using CaNa2EDTA have been used as read-across (see chapter 13 for read-across justification). It can be assumed that the systemic absorption from the intestinal tract is low. The obtained data can be used to predict that dermal absorption should be even lower. Additionally absorbed EDTA does not undergo any biotransformation and is excreted unchanged.
In toxicokinetics studies on humans as well as rats the CaNa2 and Na salts of EDTA are poorly absorbed from the gastrointestinal tract (2 to 18 % in rats; less than 5 % in humans) CaNa2EDTA does not penetrate the skin, only 0.001 % were absorbed within 24 h of administration. Intravenously applied EDTA is rapidly excreted in urine (humans 50. % within the first hour 98 % within 24 h; rats: 95 % to 98 % within 6 h). These data were also confirmed by the independent evaluation of the MAK Commission for the Investigation of Health Hazards of Chemical Compounds in the work area (MAK, 46. Lieferung, 2009).
Discussion on bioaccumulation potential result:
In a study conducted by Foreman et al. (1953), 50 mg/kg bw of 14C-labelled calcium salt of EDTA were administered to rats orally (gavage), intraperitoneally, intravenously or intramuscularly. After oral application calcium EDTA was poorly absorbed from gastrointestinal tract (2 - 18 % within 24 h). Most of the administered dose was excreted by feces 80 - 95 % and much less in urine (2 - 18 %). After parenteral application 95 - 98 % (i.v.: 96.09 %; i.p.: 98.67 %; i.m.: 95.35 %) of the radioactivity was excreted in urine within 6 h after application, while less than 0.1 % was exhaled as CO2. None of these tissues contained at this time point more than 0.5 % of the radioactivity administered.
Two additional studies on the toxicokinetics of CaNa2EDTA after i.p. application are available. In one study rats got 10 injections of 300 - 436 mg/kg bw/day 14 C-labelled CaNa2EDTA. 66 to 92 % of the administered dose were recovered in urine while generally less than 5 % were excreted by feces. 24 h after the last injection kidneys showed less than 0.1 % of the radioactivity (Doolan, 1967). In the other study, 18 rats got a single i.p. application of 400 mg/kg bw 14[C]CaNa2EDTA. Within 22 h, 80 % of the radioactivity were excreted in urine, while the concentration in kidney homogenate was approximately 0.1 - 0.2 % during this time period (Miller, 1986).
The effects of s.c. application of CaNa2EDTA on Zn, Cu and Mn metabolism were investigated in female dogs. CaNa2EDTA was applied with a dose of 280 mg/kg bw/ every 6 hours for 54 h. Urine was collected every 6 h and the Zn, Cu and Mn content analysed. CaNa2EDTA application increased the urinary excretion of Zn, Cu and Mn significantly

(Ibim, 1992).
In addition, in poorly documented studies by Yang (1964) the toxicokinetics of Na2EDTA were analysed in rats. After gavage application of 47.5, 95 and 142.5 mg/kg bw the amount of EDTA ingested was proportional to the amount of urinary excretion with a peak excretion 4 h after application. After gavage administration of 400 mg/kg bw to weanling and adult rats roughly 90 % of the dose were recovered in feces, while only 5.3 % (adults) - 8.6 % (weanlings) were recovered in urine within 48 h. It was therefore assumed that most of the orally applied EDTA is not absorbed. After a single gavage application of ca. 475 mg/kg bw to rats, the gastrointestinal tract was removed in intervals up to 32 h and the EDTA content analysed. All EDTA passed through the stomach within 12 h and 93 % of the dose was recovered in the colon after 32 h, which demonstrated a poor absorption from GI tract. The EDTA contents of the small intestine and urine reached a maximum about 4 h after dosage. Urinary excretion over the period of 32 h cumulated to 6 % of the dose. In an additional study, Yang stated that of a dietary dose of 300, 600 and 3000 mg/kg bw 82 %, 44 % and 45 % could be recovered in urine and feces. However, it is unclear were the residual percentage of Na2EDTA remained.
Foreman & Trujillo (1954) studied the toxicokinetics of 14C-CaNa2EDTA in young, healthy male volunteers. 4.2 mg/person were applied i.v. or i.m. 50 % of the dose was excreted in urine within 1 h (i.v.) or 2.5 h (i.m.). Within 24 h, > 98 % of the dose was excreted in urine after both applications. The half-live blood clearance was 1 h 5 min (i.v.) or 1.5 h (i.m.) respectively. Additionally, Foreman administered 14C-CaNa2EDTA orally at a dose of 1.5 mg/person. CaNa2EDTA was poorly absorbed from gastrointestinal tract. Within 72 h, 91 % of the dose was excreted in feces and 4.2 % in urine. No test substance could be detected in blood.
Discussion on absorption rate:
In a study on young, healthy, male volunteers Foreman & Trujillo (1954) investigated the dermal absorption of CaNa2EDTA. 3 mg of a mixture of 14C-labelled and unlabelled substance was prepared in water soluble base. The past was applied over an area of 100 cm² for 24 h under occlusive conditions. In one study Na salt was used instead of Ca salt. The maximum activity in the urine was 0.001 % of the administered dose.

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Exposure related observations in humans:
- The study indicates that CaNa2EDTA passes through the body unchanged and is excreted via the kidney by both glomerular filtration and tubular excretion.
- The turnover time from the blood is approximately 1 h after iv administration.
- It is poorly absorbed from the GI-tract.
- It does not penetrate the skin.

BIBLIOGRAPHY

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

no data

BIBLIOGRAPHY

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

GLUCOSAMINE SULFATE (CAS: 29031-19-4)

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

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

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

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

LD50 oral (rat) > 8000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

not classified as skin irritant

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not classified as eye irritant

SKIN SENSITISATION

no data

DERMAL/PERCUTANEOUS ABSORPTION

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

MUTAGENESIS / GENOTOXICITY

no data

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

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

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

BIBLIOGRAPHY

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

GLYCERIN (CAS: 56-81-5)

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

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

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

SKIN IRRITATION AND CORROSIVITY

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

MUCOSAE IRRITATION AND CORROSION (eye irritation)

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

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

SKIN SENSITISATION

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

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

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

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

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

CARCINOGENICITY

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

REPRODUCTIVE TOXICITY

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

TOXICOKINETIC (ADME studies)

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

PHOTOINDUCED TOXICITY

not phototoxic

DATA ON MAN

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

BIBLIOGRAPHY

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

GLYCERYL STEARATE (CAS: 31566-31-1)

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

2000 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/2133/7/6/1

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

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

SKIN IRRITATION AND CORROSIVITY

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

MUCOSAE IRRITATION AND CORROSION (eye irritation)

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

SKIN SENSITISATION

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

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

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

CARCINOGENICITY

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

REPRODUCTIVE TOXICITY

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

TOXICOKINETIC (ADME studies)

Bioaccumulation of fatty acids takes place, if their intake exceeds the caloric requirements of the organism.

In the study by St-Pierre (2004) with 12-[1-14C]acetoxy-octadecanoic acid-2,3-diacetoxy-propyl ester (surrogate of Glycerides, castor-oil-mono, hydrogenated, acetates (CAS 736150-63-3), systemic distribution of the radiolabelled material was confirmed in rats. Radioactivity was detected in all tissues and organs sampled (adipose tissue, gastrointestinal tract and content, kidneys and adrenals, liver, thymus and the remaining carcass) with highest levels recovered in the gastrointestinal tract, liver and the remaining carcass. Due to excretion and absorption of the radiolabelled material, the radioactivity content in the gastrointestinal tract decreased rapidly over the course of the study (168 h). This was similar for the radioactivity recovered in liver, whereas the radioactivity found in the carcasses was nearly constant at the selected time points, indicating that the radiolabelled material may have been distributed to other tissues than the ones selected for analyses. Based on the results of this study, no bioaccumulation potential was observed for 12-acetoxy-octadecanoic acid-2,3-diacetoxy-propyl ester.

Metabolism

Glycerol can be metabolised to dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, which can then be incorporated in the standard metabolic pathways of glycolysis and gluconeogenesis. Fatty acids are degraded by mitochondrial β-oxidation which takes place in the most animal tissues and uses an enzyme complex for a series of oxidation and hydration reactions resulting in the cleavage of acetate groups in form of acetyl CoA. The alkyl chain length is thus reduced by 2 carbon atoms in each β-oxidation cycle. The complete oxidation of unsaturated fatty acids such as oleic acid requires an additional isomerisation step. Alternative pathways for oxidation can be found in the liver (ω-oxidation) and the brain (α-oxidation). Thus iso-fatty acids such as isooctadecanoic acid have been found to be activated by acyl coenzyme A synthetase of rat liver homogenates and to be metabolised to a large extent by ω-oxidation. Each two-carbon unit resulting from β-oxidation enters the citric acid cycle as acetyl CoA, through which they are completely oxidized to CO2. Acetate, resulting from hydrolysis of acetylated Glycerides, is readily absorbed and feeds naturally into physiological pathways of the body and can be utilized in oxidative metabolism or in anabolic syntheses (CIR, 1983, 1987; IOM, 2005; Lehninger, 1998; Lippel, 1973; Stryer, 1996; WHO, 1967, 1974, 1975, 2001; Adolph, 1999).

Excretion

As far as Glycerides are not hydrolysed in the gastrointestinal tract, they are excreted in the faeces.

In general, the hydrolysis products glycerol and fatty acids are catabolised entirely by oxidative physiologic pathways ultimately leading to the production of carbon dioxide and water. Glycerol, being a polar molecule can readily be excreted in the urine. Small amounts of ketone bodies resulting from the oxidation of fatty acids are excreted via the urine (Lehninger, 1998; IOM, 2005; Stryer, 1996).

In rats given a single dose of 12-[1-14C]acetoxy-octadecanoic acid-2,3-diacetoxy-propyl ester at 5000 mg/kg bw, the mean total recovery of radioactivity in the excreta of the 72 h period post-dose was 108.5% of the dose (urine, 6.5%; faeces, 24.5%; CO2, 77%; and cage wash, 0.5%). Most of the recovered radioactivity (97.5%) was excreted by 24 h post dose (St-Pierre, 2004). The results thus confirm that Glycerides are mainly excreted as CO2 in the expired air as a result of metabolism.

A detailed reference list is provided in the technical dossier (see IUCLID, section 13) and within the CSR.

PHOTOINDUCED TOXICITY

non phototoxic

DATA ON MAN

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

BIBLIOGRAPHY

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

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

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

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

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

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

SKIN IRRITATION AND CORROSIVITY

Not expected to be classified as corrosive/irritant to skin

MUCOSAE IRRITATION AND CORROSION (eye irritation)

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

SKIN SENSITISATION

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

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

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

CARCINOGENICITY

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

REPRODUCTIVE TOXICITY

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

TOXICOKINETIC (ADME studies)

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

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

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

BIBLIOGRAPHY

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

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

- 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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

REPRODUCTIVE TOXICITY

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

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

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

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

TOXICOKINETIC (ADME studies)

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

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

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

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

The authors observed that 2-phenoxyethanol was nearly completely metabolised. In urine and bile, less than 0.7% of the dose had been assigned to the parent compound. The parent compound was mainly metabolised to phenoxyacetic acid (PAA) by oxidation of the terminal hydroxyl group to carboxylic acid(up to 64% of the dose). Seven further metabolites were identified with up to < 10% of the applied dose. The other metabolic changes of14C-phenoxyethanol were either ring sulfation after hydroxylation or conjugation

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

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

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

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

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

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

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

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

References:

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

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

POTASSIUM CETYL PHOSPHATE (CAS: 84861-79-0; 19035-79-1)

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

800 -- - https://safety365.sevron.co.uk/substances/accessSDS/SDS-55012-58ca23ed9e3986.91027818

Additional information:
NOAEL (Oral, rat) : 800 mg/kg bw/d
Sub-chronic toxicity study (90-day)

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

LD50 (rat): > 5 000 mg/kg
LD50 (rat): > 2 000 mg/kg (OECD Test Guideline 402)

SKIN IRRITATION AND CORROSIVITY

not skin irritant
Additional information:
Skin corrosion/irritation : No skin irritation (rabbit, OECD Test Guideline 404)

MUCOSAE IRRITATION AND CORROSION (eye irritation)

Accoroding CLP: Causes serious eye damage.
Additional information:
Mild eye irritation (rabbit, OECD Test Guideline 405, 10% solution) temporary redness: Risk of serious damage to eyes.

SKIN SENSITISATION

not sensitizer
Additional information:

Did not cause sensitization on laboratory animals. (guinea pig, OECD Test Guideline 406)

DERMAL/PERCUTANEOUS ABSORPTION

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

Additional information : The product passes into and partly through the skin of rats and pigs.
https://safety365.sevron.co.uk/substances/accessSDS/SDS-55012-58ca23ed9e3986.91027818

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
not mutagenic (Ames test)

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not toxic to reproductive

TOXICOKINETIC (ADME studies)

The substance or mixture is not classified as specific target organ toxicant, single exposure.

PHOTOINDUCED TOXICITY

not induce phototoxicity
Additional information:
not phototoxic (guinea pig)
no photoallergenic skin reaction (guinea pig, CTFA Test Guideline)

DATA ON MAN

Did not cause sensitization. (human)
No skin irritation (human, Patch Test 24 Hrs.)

BIBLIOGRAPHY

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

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

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

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

LD50 oral (rat) >10000 mg/kg bw

SKIN IRRITATION AND CORROSIVITY

irritant

MUCOSAE IRRITATION AND CORROSION (eye irritation)

irritant

SKIN SENSITISATION

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

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

no data

TOXICOKINETIC (ADME studies)

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

BIBLIOGRAPHY

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

STEARIC ACID (CAS: 57-11-4)

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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

1000 -- - ECHA, https://echa.europa.eu/registration-dossier/-/registered-dossier/15163/7/6/1
Additional information:
Reliable studies on oral repeated dose toxicity are available for the following category members:
Subchronic: NOAEL oral = ca. 5000 mg/kg bw/d; CAS# 143-07-7, C12 (Fitzhugh 1960)
Subchronic: NOAEL oral = 1000 mg/kg bw/d; CAS# 112-85-6, C22 (Nagao 2002)
No data are available for repeated dose toxicity after dermal exposure and inhalation, respectively.

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

LD50 oral (rat) > 5 000 mg/kg bw
LD50 dermal (rabbit) > 2 000 mg/kg bw
LC50 inhalation (rat) > 0.162 mg/L air (nominal)
Additional information:
Oral
Acute oral toxicity by C18 fatty acid (stearic acid) was evaluated in a study performed in accordance to OECD guideline 401, where in a limit test five male and five female Wistar rats received 10 mL/kg bw stearic acid in DMSO at concentration of 5000 mg/kg bw by gavage (Kästner, 1981). Clinical signs including ruffled fur, strong salivation and much diminished activity appeared approximately 20 minutes after dosing, but subsided within 24 hours after dosing. Since only one male died on day 13 after dosing, the LD50 for stearic acid was found to be >5000 mg/kg bw.
In another guideline study in accordance with GLP and OECD guideline 401 and EU method B.1, a LD50 of >2000 mg/kg bw was found when five male and five female Wistar rats were given oral doses of 10 mL/kg bw containing 2000 mg/kg bw stearic acid dissolved in propylene glycol (Daamen, 1989). One female showed dyspnoea, lethargy and bloody nose encrustation on the day of dosing and died. The pathologiocal examination revealed petichiae in the thymus. Apart from one male showing bloody eye encrustation on the day of dosing, no other clinical signs of toxicity were noted during the 14 day observation period.
Another study was available which was performed according to GLP and OECD guideline 401. Five male and five female Sprague-Dawley rats received an oral application of 6000 mg/kg bw by gavage and were observed for mortality and clinicl signs for 14 days. Only two females showed subnormal weight gains, but no their clinical signs were noted. The pathological examination did not reveal any substance related effects. Since no mortality occurred, the LD50 was found to be >6000 mg/kg bw (Jones, J.R., 1979).
Inhalation
Inhalation of fatty acids as vapour is not expected due to the low vapour pressure of < 1 mmHg. Therefore, only very limited data on acute inhalative toxicity of fatty acids is available.
However, the identified uses include spraying tasks where exposure to an aerosol of fatty acids can occur like use in cleaning agents.
The only available data on acute inhalation toxicity of fatty acids are data of a published inhalation risk test with C8 fatty acid (octanoic acid; Smyth, 1962). No mortality of rats was reported after a 4-hour exposure to a saturated atmosphere which corresponds to a value of >0.1521 mg/L air based on QSAR calculation (Danish EPA Database, 2004).
Although not reported in this study, respiratory irritation/corrosion as primary effect is expected for fatty acids with a chain length ≤C12 due to the corrosive/irritation properties of the short- and mid-chain fatty acids C6 – C12, respectively.
In more detail, C8 fatty acids show corrosive properties to the skin at concentrations >70%. C9 fatty acid (at a concentration of >50%) and C10 fatty acid is irritating to skin and eyes, respectively. C12 fatty acid is not irritating to skin but is found to be irritating to eyes when applied with a concentration >70%.
Members of the category with a chain length >C12 are only causing negligible effects when applied to the skin or eyes. Their respiratory uptake would therefore not lead to irritation, but they would be included in the pulmonary surfactant of the respiratory tract which is mainly composed of large portions of phospholipids based on long chain fatty acids.

Since in industrial and professional applications inhalation exposure is controlled by ventilation systems, personal protective equipment, and measuring devices, the inhalation exposure can be considered to be sufficiently controlled.
Thus, it can be concluded that acute inhalation of fatty acids can cause irritation of the respiratory tract leading to classification and therefore no further testing shall be performed due to animal welfare reasons.
Dermal
Limited data is available on acute dermal toxicity of fatty acids since C8 fatty acid show corrosive properties at concentrations >70%, C9 (at a concentration of >50%) and C10 fatty acids are irritating to skin, respectively. The consequence after dermal application of these substances would therefore be irritation/corrosion as the primary effect. All other members of the category with longer chain length are only causing negligible effects when applied to the skin.
A general prerequisite for systemic toxicity after dermal application is the permeability of the skin for the applied substance. Although the dermal penetration of fatty acids is very variable, in general they do not have significant systemic bioavailability (for details see IUCLID chapter 7.1).

Thus, no acute dermal toxicity by fatty acids is expected as it could be demonstrated by a LD50 value of >2000 mg/kg bw for C18 fatty acid (stearic acid) found in a in limit test performed according to internal company standards (Jones, 1979). Three male and three female New Zealand White rabbits received a dermal application of 2000 mg/kg bw stearic acid to 25% of the total body surface under occlusion for 24 hours. As result, slight diarrhoea was noted in one female animal on day 3 after treatment. All other animals appeared normal throughout the observation period. Laboured breathing on day 6 was noted in one male, which died the next day. Although the pathological examination revealed severe consolidation of the lungs, this finding was not considered to be substance related. Irritating effects were noted on the skin of all animals which were described as ranging from slight to severe. Four animals showed slight and moderate desquamation. Slight oedema and eschar formation were also noted in some animals during the first week of observation. However, these observed effects can be attributed to the severe conditions used for application which are not in line with current guidelines. However, a LD50 of >2000 mg/kg bw was found for stearic acid.
Although the dermal absorption of C18 fatty acid6 (stearic acid) with 0.00026 mg/cm2is lower compared to fatty acids with shorter chain lengths (e.g. C12 fatty acid: 0.005 mg/cm2), even single or repeated oral uptake of C12 fatty acid does not lead to systemic effects due to the physiological function within the body.
Moreover, dermal exposure can be considered to be sufficiently controlled in industrial and professional applications since the employees are wearing gloves and protective clothing. Thus, no acute dermal toxicity by fatty acids is expected and no further testing shall be performed due to animal welfare reasons.

SKIN IRRITATION AND CORROSIVITY

not irritating
Additional information:
Skin irritation by stearic acid was evaluated in a study performed in accordance with federal guidelines (International Bio-Research, 1974). 0.5 mL of stearic acid was applied to the abraded skin of 6 New Zealand White rabbits under occlusion for 24 hours.at 24 and 72 hours after application revealed no signs of irritation. Although a longer application under occlusion than suggested according to actual guidelines, the resulting scores are 0, both for erythema and edema, respectively. Based on this, stearic acid can be regarded as not irritating to skin.

MUCOSAE IRRITATION AND CORROSION (eye irritation)

not irritating
Additional information:
In a published study performed according to national guidelines, stearic acid was instilled into the eyes of six rabbits (Briggs et al., 1976). Mild conjunctival erythema was found in 2 animals at 24 and 48 hours while all signs of irritation hat subsided completely in 72 hours. Thus, a mean score of 0.2 for conjunctival erythema could be

The substance may contain few of lauric acid (C12), which is classified as R41/eye damage Cat 1. The specific concentration limit for the lauric acid is established as 70% based on a reliable experimental data. According to DPD (1999/45/EC) or CLP (1272/2008/EC) classification criteria for irritation/corrosion, stearic acid dose not fulfill the criteria for classification and thus a non-classification is warranted for this endpoint, as the concentration of C12 is lower than 70%.

SKIN SENSITISATION

not sensitising
Additional information:
Studies on skin sensitisation (animal and human skin sensitisation tests) are available for the following fatty acid category members:
CAS# 124-07-2, C8 (Opdyke, 1981)
CAS# 123-99-9, C9 (Lea, 1995)
CAS# 334-48-5, C10 (Sauter and Ritz, 1975)
CAS# 143-07-7, C12 (Gloxhuber and Potokar, 1979)
All available skin sensitisation studies showed that fatty acids are not skin sensitising.

DERMAL/PERCUTANEOUS ABSORPTION

no data

MUTAGENESIS / GENOTOXICITY

not mutagenic / genotoxic
Additional information:
Studies on genotoxicity are available for the following fatty acid category members:
in-vitro:
- Gene mutation in bacteria:
CAS# 142-62-1, C6: Ames: negative (Banduhn 1991)
CAS# 124-07-2, C8: Ames RL4: negative (Gloxhuber and Wallat 1981)
CAS# 90990-08-2, C8-18: Ames RL4: negative (Wallat 1982)
CAS# 67701-06-8, C12-18: Ames RL4: negative (Sterzel and Broschard 1999)
CAS# 143-07-7, C12: Ames RL4: negative (Gloxhuber and Wallat 1981)
CAS# 112-85-6, C22: Ames RL4: negative (Gloxhuber and Wallat 1981)
CAS# 112-85-6, C22: Ames: negative (Nakajima 2002)
- Gene mutation in mammalian cells:
CAS# 334-48-5, C10: Mouse Lymphoma Assay in-vitro: negative (Trenz 2010)
- Cytogenicity in mammalian cells:
CAS# 112-85-6, C22: Chromosomal Aberration test in-vitro: negative (Nakajima 2002)
in-vivo:
No data available.
All available data on genotoxicity showed that fatty acids are not genotoxic.
Endpoint Conclusion: No adverse effect observed (negative)

CARCINOGENICITY

no data

REPRODUCTIVE TOXICITY

not toxic to reproductive
Additional information:
Studies on reproductive toxicity by the oral route are available for the following category members:
CAS# 112-85-6, C22: NOAEL oral (fertility) = 1000 mg/kg bw/d; highest dose tested (Nagao 2002), OECD 422
No data are available for reproductive toxicity after dermal exposure and inhalation, respectively.

TOXICOKINETIC (ADME studies)

Absorption
Due to the role as nutritional energy source, fatty acids are absorbed from the lumen of the intestine by different uptake mechanisms depending on the chain length. Short- and medium chain fatty acids (C1 - C12) are rapidly absorbedviaintestine capillaries into the blood stream. For butyrate (C4) for example, an absorption rate of 1.9 µmol/cm2/h (= 167

µg/cm2/h) was found in the human intestine (McNeil et al., 1978). In contrast, long chain fatty acids (>C12) are absorbed into the walls of the intestinevilliand assembled intotriglycerides, which then are transported in the blood streamvialipoprotein particles (chylomicrons). This difference in the uptake mechanism of fatty acids is reflected by the percentage of absorption found when human infants were fed a diet containing different fat sources (Jensen et al., 1986). While an absorption of 99.9 % was found for C8 fatty acid, the long chain C18 fatty acid showed only 64.4 % absorption.
The dermal penetration of fatty acid is very variable based on the heterogeneous physico-chemical properties such as melting temperature, solubility and polarity. The polarity, for example, decreases with increasing chain lengths and/or the abolition of ionisable charged groups, so that they are less-water soluble but more permeable through lipophilic membranes like the skin. As an example, unsaturated long chain fatty acids like oleic acid (C18) have been shown to increase the transepithelial water loss significantly compared to shorter unsaturated fatty acids (Tanojo et al., 1998). Unsaturated long chain fatty acids are therefore used in pharmaceutical transdermal drugs as a flux enhancer for drugs that do not readily cross the skin-barrier on their own. However, the fatty acid itself remains within the lipophilic dermal layer due its polarity.
In contrast to the rapid uptake of fatty acidsviathe oral exposure route, fatty acids are in general poorly absorbed through skin, with a measured rate of less than 1 % after 24-hours exposure (Schaefer and Redelmeier, 1996). The dermal absorption of fatty acids ranged from moderate to very low according to QSAR calculations which are based on molecular weight, logPowand water solubility. The resulting calculated absorption rates are 0.021 mg/cm2for C8 octanoic acid, 0.005 mg/cm2for lauric acid (C12), and 0.26 µg/cm2for stearic acid (C18), respectively (Danish EPA Database, 2004). Thus, the dermal absorption is definitely lower than the absorption after oral uptake.
This was demonstrated in a study where excretion of azelaic acid was analyzed in urine after dermal application of six healthy male volunteers with a single treatment with 5 g of an anti-acne cream containing 20% azelaic acid and after oral application (Taeuber et al., 1992). While 61% of orally administered azelaic acid was detected in the urine, only 2.2% azelaic acid was found in the urine after dermal application.
The dermal uptake of fatty acid is further influenced by the fact that significant skin irritation/corrosion is observed for fatty acids with a chain length less than C10. In these cases local irritation/corrosion is considered as the primary effect.
Taken together the experimental and calculated data show that fatty acids are almost completely absorbed after oral intake, whereas only limited dermal uptake has to be expected.

Distribution and Metabolism
Fatty acids are absorbed through the intestine and transported throughout the body. Short chain fatty acids are taken up and transported complexed to albuminviathe portal vain into the blood vessels supplying the liver. Medium and long chain fatty acids are esterified with glycerol to triacylglycerides (TAGs) and packaged in chylomicrons (Spector, 1984). These are transportedviathe lymphatic system and the blood stream tohepatocytesin the liver as well as toadipocytesandmuscle fibers, where they are either stored (i.e. adipose tissue storage depots) or oxidized to yield energy. In addition, some cell types are known to synthesize medium and long chain fatty acidsviaelongation of shorter fatty acids (Hellerstein, 1999).
The quantitatively most significant oxidation pathway (β-oxidation pathway) is predominantly located in the cardiac and skeletal muscle. In a first step, the fatty acids are converted toacyl-CoAderivatives (aliphaticacyl-CoA) and transported into cells and mitochondria by specific transport systems. Then, theacyl-CoAderivatives are completely metabolized to acetyl-CoAor other key metabolites by the efficient enzymatic removal of the 2-carbon units from the aliphaticacyl-CoAmolecule (Coppack et al., 1994). The complete oxidation of fatty acidsviathe citric acid cycle leads to H2O and CO2(Coppack, 1994; MacFarlane, 2008). Other pathways for fatty acid catabolism also exist and include α- and ω-oxidation. The resulting main metabolites are acyl-carnitine, acetyl CoA, fatty acyl-CoA, propionyl-CoA and succinyl-CoA (Wanders et al., 2010).
Excretion
Fatty acids are metabolised by various routes in the body to provide energy. Besides this, fatty acids are stored as lipids in adipose tissue, used as part of cellular membranes, as well as precursors for signalling molecules and even long chain fatty acids. Thus, fatty acids are not expected to be excreted to any significant amount in the urine or faeces.

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

PHOTOINDUCED TOXICITY

no data

DATA ON MAN

Sensitisation data
Human Maximization test with 25 volunteers according to Kligman and Epstein, 1975 (Contact Dermatitis 1975:1:231-239)
NO. OF PERSONS WITH/OUT REACTIONS COMPARED TO STUDY POPULATION
- Number of subjects with positive reactions: 0/25
- Number of subjects with negative reactions: 25/25
- Number of subjects with equivocal reactions: 0/25
- Number of subjects with irritating reactions: 0/25
Exposure related observations in humans: other data
Six healthy male volunteers received a single topical treatment with 5 g of an anti-acne cream containing 20% azelaic acid (AzA) onto the face, the chest and the upper back. One week later 1 g of AzA was given orally to the same subjects as aqueous microcrystalline suspension. Following the two treatments the renal excretion of the unchanged compound was measured
TYPE OF EXPOSURE:
- Dermal: 1 g azelaic acid in 5 g cream (Skinoren, Schering AG) was applied to ca. 5 cm2 skin. 2 g to chest, 2 g onto the back and 1 g to the face.
One hour after application, the skin areas treated on the back and chest were covered with cotton tissue fixed with adhesive tape. After 24 h of exposure, the covering material was removed and the treated areas were washed with 25 ml of ethanol 70% (v /v)
- Oral: 1 week after dermal application subjects received 100 ml of an aqueous micro-crystalline suspension containing 1 g azelaic acid in the morning before the breakfast was served
TYPE OF EXPOSURE MEASUREMENT: Biomonitoring (urine) by HPLC
EXPOSURE PERIOD:
- Dermal: 24 hours
- Oral: single application
POSTEXPOSURE PERIOD:
- Dermal: up to 3 days
- Oral: up to 4 days
After dermal application of 5 g of cream containing 20% of Azelaic acid at a skin area dose of 5 mg /cm2 maximum concentrations 7.8 ± 3.2 µg/ ml (11.29 ± 0.5% of the dose applied) have been measured in the urine within the first 24 h. During the 2nd and 3rd d 0.76 +0.49% and 0.12 + 0.15% of the dose, respectively, was excreted unchanged with the urine. The total amount of Azelaic acid excreted unchanged with the urine within 3 d was determined to 2.2 ± 0.7% of the dose.
After oral administration a mean concentration of Azelaic acid of 424 + 104 µg/ml was found in the 0-24 h urine samples, corresponding to 61.2+ 8.8% of the dose administered. Excretion was complete within 24 h.

BIBLIOGRAPHY

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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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

RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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.

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RELEVANT ENDPOINTS FOR THE INGREDIENTS TOXICOLOGICAL PROFILE

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

- Safety data sheets
-
-TOXNET database on toxicology

- ECHA database on REACH registered substances
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Part 2A
Adverse Effects and Serious Adverse Effects

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

Formula Code -

Commercial Name CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

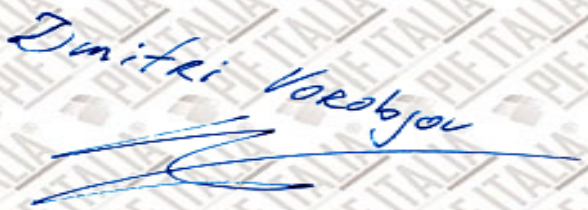
Inclusion on the: 15.04.2021 **N** .

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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 CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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

List of documents attached to the PIF

Formula Code	-
Commercial Name	CONCENTRATED CHONDROITIN WITH GLUCOSAMINE MASSAGE CREAM IN THE JOINT AREA

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