Scientific Committee on Consumer Safety

SCCS

OPINION ON

Dihydroxyacetone - DHA
(1,3-Dihydroxy-2-propanone)
CAS No. 96-26-4

The SCCS adopted this document
at its plenary meeting on 03-04 March 2020

ACKNOWLEDGMENTS

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This Opinion has been subject to a commenting period of a minimum eight weeks after its initial publication (from 07 November 2019 until 20 January 2020). Comments received during this time period are considered by the SCCS. For this Opinion, only parts of the SCCS answers to questions 1 and 2 have been switched and completed.

1. ABSTRACT

The SCCS concludes the following:

1. In light of the data provided, does the SCCS consider Dihydroxyacetone safe when used as hair colouring ingredient in leave-on applications up to a maximum concentration of 6.25 %?

On the basis of data provided, the SCCS considers Dihydroxyacetone safe when used as hair colouring ingredient in leave-on applications (non-oxidative) up to a maximum concentration of 6.25%.

2. Does the SCCS have any further scientific concerns with regard to the use of Dihydroxyacetone in cosmetic products?

The use of Dihydroxyacetone as hair colouring ingredient in leave-on applications (non-oxidative) up to a maximum concentration of 6.25% together with the use of self-tanning lotion and face cream containing up to a maximum concentration of 10% Dihydroxyacetone is considered safe.

Keywords: SCCS, scientific opinion, preservative, Dihydroxyacetone (DHA), 1,3-Dihydroxy-2-propanone, CAS 96-26-4, EC 202-494-5, Regulation 1223/2009

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on Dihydroxyacetone (DHA) CAS N° 96-26-4, preliminary version of 30-31 October 2019, final version of 03-04 March 2020, SCCS/1612/19

About the Scientific Committees

Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

These Committees are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and they are made up of scientists appointed in their personal capacity.

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SCCS

The Committee shall provide Opinions on questions concerning health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Dihydroxyacetone (DHA) with the chemical name 1,3-Dihydroxy-2-propanone (CAS No. 96-26-4, EC. No 202-494-5) is a cosmetic ingredient with the reported functions of skin conditioning, reducing and tanning. Currently DHA is not regulated under the Cosmetic Regulation (EC) No. 1223/2009.

In 2008, Commission' services received a dossier from industry to support the safe use of DHA in cosmetic products. In its corresponding Opinion, SCCS/1347/10, the SCCS concluded that *"Based upon the available data, the SCCS is of the Opinion that the use of Dihydroxyacetone as a self-tanning ingredient in cosmetic formulations up to 10% will not pose a risk to the health of the consumer." In addition, the SCCS "considers that the use of Dihydroxyacetone as a self-tanning ingredient in spray cabins up to 14% will not pose a risk to the health of the consumer".*

With the current submission, received in May 2019, the applicant requests to assess the safety of DHA intended to be used as hair colouring ingredient in leave-on applications up to a maximum concentration of 6.25 %.

Terms of reference

1. *In light of the data provided, does the SCCS consider Dihydroxyacetone safe when used as hair colouring ingredient in leave-on applications up to a maximum concentration of 6.25 %?*

2. *Does the SCCS have any further scientific concerns with regard to the use of Dihydroxyacetone in cosmetic products?*

3. OPINION

3.1 Chemical and Physical Specifications

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Dihydroxyacetone (INCI name)

3.1.1.2 Chemical names

Chemical name:
1,3-Dihydroxy-2-propanone

CAS/IUPAC names:
1,3-Dihydroxyacetone
1,3-Dihydroxypropan-2-one
Dihydroxyacetone

Ref: 1

3.1.1.3 Trade names and abbreviations

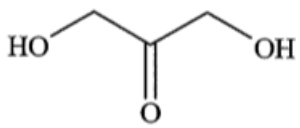
1,3-Dihydroxydimethyl ketone
Propane-1,3-diol-2-one
DHA

Ref: 1

3.1.1.4 CAS / EC number

CAS: 96-26-4
EC 202-494-5

3.1.1.5 Structural formula



3.1.1.6 Empirical formula

$C_3H_6O_3$

3.1.2 Physical form

White to almost white fine crystalline free-flowing powder, possibly with granular parts.

3.1.3 Molecular weight

Molecular weight: 90.08 g/mol

3.1.4 Purity, composition and substance codes

A certificate of analysis (CoA) is provided for the DHA batch VL720150 and can be considered as representative for DHA for use in cosmetic products. This batch has been used for toxicological evaluation in the following studies:

- Local Lymph Node Assay in Mice
- Embryo-foetal developmental toxicity study by the oral route in rats
- 14-day and 13-week oral toxicity (gavage) studies in rats

Ref: 2

The chemical characterization of DHA was performed using two different batches, VP840150 and VL720150, by means of [^{1}H]- and [^{13}C]-NMR spectra (spectra available).

Ref: 3

Further information in this respect can be obtained from the former SCCS Opinion on DHA (SCCS/1347/10 (4)):

Certificates of analysis are available for 4 different batches of 'Dihydroxyacetone extra pure for cosmetics'. The results are summarized below:

Purity according to specifications	Batch number	Measured	Ref.
98.0-102.0%	VL720150	100.3%	5
	VP182150	99.5%	6
	VP182250	99.8%	7
	VP173050	100.0%	8

3.1.5 Impurities / accompanying contaminants

A representative impurity profile of DHA is provided in the CoA for the DHA batch VL720150 and is shown in the table below.

Parameter *Test-Method*		Ergebnis *Result*	Einheit *Unit*
Appearance	White to almost white finecrystalline to freeflowing powder	conforms	-
Identification *(IR)*	conforms to structure	conforms	-
Assay *(periodatometric titration)*	98.0 – 102.0 %	100.3	%
Appearance of solution	< 20 Hazen	< 10	Hazen
pH-value	4.5 – 6.0	4.6	-
Heavy metals *(as Pb)*	< 0.001 %	< 0.001	%
As *(Arsenic)*	< 0.0003 %	< 0.0003	%
Fe *(Iron)*	< 0.002 %	< 0.002	%
Protein *(colorimetric)*	< 0.1 %	< 0.1	%
Glycerol *(TLC)*	< 0.5 %	< 0.5	%
TLC-Test	Passes test	Conforms	-
Formic acid *(IC)*	< 25 ppm	9.2	ppm
Formaldehyd *(HPLC)*	< 70 ppm	18.7	ppm
Sulfated ash *(600°C)*	< 0.10 %	< 0.01	%
Water *(according to Karl Fischer)*	< 0.15 %	0.07	%
Microbiological purity	< 100 CFU/g	< 100	CFU/g

Ref: 2

Again, further information in this respect can be obtained from the former SCCS Opinion on DHA (SCCS/1347/10):

Impurities: Heavy metals (as Pb) ≤ 0.001%
Arsenic ≤ 0.0003%
Iron ≤ 0.002%
Protein ≤ 0.1%
Glycerol ≤ 0.5%
Water ≤ 0.2%
Formic Acid ≤ 30 ppm
Formaldehyde ≤ 50 ppm

Microbiology: Total viable aerobic count ≤ 100 CFU/g
E. Coli absent in 1g
Pseudomonas aeruginosa absent in 1g
Staphylococcus aureus absent in 1g
Candida albicans absent in 1g
Salmonella species absent in 10g

Ref: 5-8

3.1.6 Solubility

Water (without correction for purity) = 930 g/L (RSD 2.7%) at 20°C (batch VP983050, purity: 100.2%), according to EC A.6 and OECD 105 (1995).

Ref: 9

Taken from SCCS/1347/10:
Ethanol: soluble

3.1.7 Partition coefficient (Log P_{ow})

Log P_{ow}= -1.95 at 20°C (batch VP983050), according to EC A.8 and OECD 107 (flask method).

Ref: 10

3.1.8 Additional physical and chemical specifications

- Organoleptic properties (colour, odour, taste if relevant): /
- Melting point: 96.5°C (EC A.1 and OECD 102)
- Boiling point: 188°C (EC A.2 and OECD 103)
- Flash point: /
- Vapour pressure: the vapour pressure values are extrapolated (EC A.4 and OECD 104)

T / °C	p / hPa	p / Pa
20	2.4×10^{-5}	2.4×10^{-3}
25	5.8×10^{-5}	5.8×10^{-3}
50	3.3×10^{-3}	3.3×10^{-1}

- Relative density: D_4^R = 1.52 g/cm^3, at ambient temperature compared to water at 4°C
- Viscosity: /
- Surface tension: σ= 68.9 mN/m at 20°C (OECD 115)
- pKa:
- pH: pH value (5% in water), according to analytical report:

pH according to specifications	Batch number	Measured	Ref.
4.0 - 6.0	VL720150	4.6	2
	VP182150	5.0	3
	VP182250	4.7	4
	VP173050	5.0	5

- Refractive index: /
- Flammability: not highly flammable

Ref: 11

- UV/visible light absorption spectrum
  0.02172 g of dihydroxyacetone was dissolved in 20 ml water. The UV-Vis spectroscopy shows an absorption band at 271 nm, which is in agreement with the C=O-chromophores of the proposed structure. UV /Vis absorption spectrum of DHA (Batch VP195350) in water is presented in Figure below.

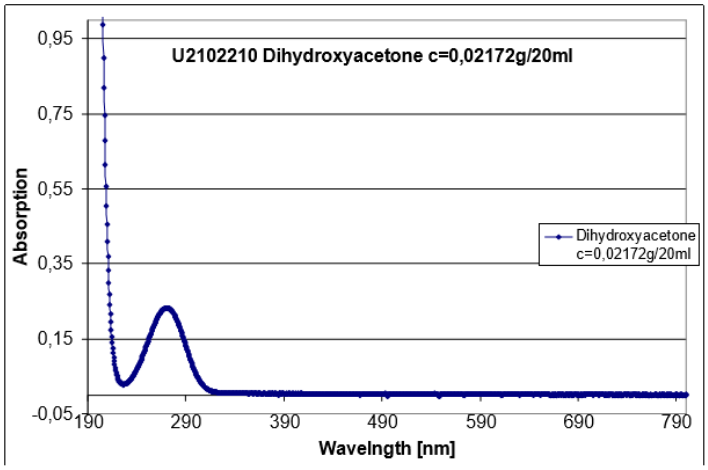


Fig. 1 Absorption spectra of Dihydroxyacetone

Ref: 12

SCCS comment: As shown in the DHA absorption spectrum in water there is a peak at 271 nm, but no absorption in the UVA/Vis wavelength range (320 – 800 nm).

Storage conditions: shipped in wet ice, stored at +2°C to +8°C.

Ref: 13

3.1.9 Homogeneity and Stability

The results of accelerated aging tests indicated that the DHA containing hair coloring foam tested in the *in vitro* dermal penetration test has a shelf life superior to 30 months.

Ref: 14

Thermal stability (OECD 113, batch VP983050): The differential calorimetry (DSC) measurements in closed glass crucibles showed an endothermic effect in the temperature range of 70-115°C (melting) and an exothermal effect in the temperature range 120 -185°C and an exothermal decomposition in the temperature range 185-235°C with an overall energy of 955 J/g.

Ref: 11

The stability tests for three batches VL438450, VL438550, VL438650 (Purity: 99.8%, 98.9%, 98.9%) when stored at 5±3°C are presented in the following tables.

Article no:	110150	Product name:	Dihydroxyaceton extra pure for cosmetic purposes		
Batch number:	VL438450	Storage conditions:	5+-3 °C % rel.	Container:	PE-Bag

Parameter	Specification	Release	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	60 months
Appearance	white to almost white finecrystalline - free-flowing powder, eventually with granular parts	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	
Assay	98,0 -102,0 %	99,8 %	99,8 %	99,8 %	99,8 %	101,4 %	99,2 %	98,6 %	99,7 %	99,6 %	
Appearance of solution	clear	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	
Appearance of solution [color]	<= 25 Hazen	< 10	< 10	15	10	< 10	< 10	< 10	< 10	9	
pH value	4,0 – 6,0	4,8	4,8	4,8	4,8	4,7	4,7	4,7	4,8	4,7	
Methanal	<= 50 ppm	18,2 ppm	19,0 ppm	16,7 ppm	17,4 ppm	18,8 ppm	20,2 ppm	22,9 ppm	32,3 ppm	30,9 ppm	
Formic acid	<= 30 ppm	13,2 ppm	15,9 ppm	8,8 ppm	9,5 ppm	11,3 ppm	7,9 ppm	14,2 ppm	7,4 ppm	11,7 ppm	

Article no:	110150	Product name:	Dihydroxyaceton extra pure for cosmetic purposes		
Batch number:	VL438550	Storage conditions:	5+-3 °C % rel.	Container:	PE-Bag

Parameter	Specification	Release	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	60 months
Appearance	white to almost white finecrystalline - free-flowing powder, eventually with granular parts	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	
Assay	98,0 -102,0 %	98,9 %	99,7 %	99,2 %	99,8 %	100,2 %	99,5 %	99,9 %	100,2 %	99,8 %	
Appearance of solution	clear	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	
Appearance of solution [color]	<= 25 Hazen	< 10	< 10	10	< 10	< 10	< 10	< 10	< 10	6	
pH value	4,0 – 6,0	4,9	4,7	4,8	4,8	4,7	4,6	4,8	4,7	4,6	
Methanal	<= 50 ppm	18,1 pm	20,6 ppm	17,2 ppm	16,4 ppm	18,6 ppm	19,9 ppm	25,3 ppm	30,9 ppm	29,9 ppm	
Formic acid	<= 30 ppm	16,5 ppm	11,3 ppm	8,8 ppm	9,4 ppm	11,4 ppm	7,1 ppm	17,2 ppm	< 5,0 ppm	8,9 ppm	

Article no:	110150	Product name:	Dihydroxyaceton extra pure for cosmetic purposes		
Batch number:	VL 438650	Storage conditions:	5+-3 °C % rel. humidity	Container:	PE-Bag

Parameter	Specification	Release	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	60 months
Appearance	white to almost white finecrystalline - free-flowing powder, eventually with granular parts	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	
Assay	98,0 -102,0 %	98,9 %	98,9 %	98,7 %	99,5 %	100,1 %	99,1 %	100,7 %	100,3 %	99,4 %	
Appearance of solution	clear	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	Passes test	
Appearance of solution [color]	<= 25 Hazen	< 10	< 10	10	< 10	< 10	< 10	< 10	< 10	7	
pH value	4,0 – 6,0	4,9	4,8	4,8	4,8	4,8	4,7	4,8	4,8	4,7	
Methanal	<= 50 ppm	15,4 ppm	18,4 ppm	16,0ppm	14,7 ppm	17,0ppm	18,3 ppm	20,9 ppm	28,7 ppm	27,3 ppm	
Formic acid	<= 30 ppm	13,0 ppm	12,0 ppm	9,1 ppm	8,9 ppm	10,4 ppm	7,1 ppm	14,8 ppm	5,9 ppm	11,1 ppm	

Ref: 15

Taken from SCCS/1347/10

Analytical procedures (HPLC) were developed for analysis of DHA in bi-distilled water. These procedures were shown to be appropriate for measurement of the concentration of DHA in dosing solutions in the concentration range 25 - 100 mg/ml in bi-distilled water. The test item is stable in dosing solutions when kept for 4 hours at room temperature; recovery rates at the end of this period were within ± 10% of initial values.

According to the authors, the results of this study indicate the appropriate development and validation of the analytical method for the measurement of the DHA concentration in bidistilled water, as well as the appropriate stability of the dosing solutions used in the different toxicity studies.
Stability tests according to ICH-Q1A Guideline showed that DHA Batch number VL720150 stored at 2 – 8°C is stable for at least 18 months. As a general statement, the storage stability of DHA at 4 – 8 °C is declared to be at least 18 months.

Ref: 16

SCCS comment
After 18 months of storage at 5±3°C and %relative humidity (value not mentioned), the formaldehyde content increased, yet it remained below 50 ppm after 48 months of storage.

3.2 TOXICOKINETICS

3.2.1 Dermal / percutaneous absorption

Guideline:	OECD Test Guideline 428 (2004); OECD Guidance Document No. 28 (2004); SCCS/1358/10; SCCS/1564/15
Test system:	Frozen dermatomed human skin (400 µm)
Number of donors:	3 samples from 4 donors (58 – 82 years)
Membrane integrity:	Electrical resistance barrier integrity test, membranes with a resistance < 10 kΩ were excluded
Test substance:	DHA Simple test foam solution and [2-^{14}C]1,3-dihydroxyacetone
Test item:	Leave-on hair care formulation containing 6.25% w/w DHA
Batch:	1251-144-290 (non-radiolabeled); 5689DJS004-2 (radiolabeled)
Purity:	99% (non-radiolabelled, GC); >95% (radiolabelled)
Dose applied:	625 µg DHA/cm^2 (1588 µg DHA/cell)
Exposed area:	2.54 cm^2
Exposure period:	24h (unoccluded)
Sampling period:	up to 24h post dose
Receptor fluid:	physiological saline
Solubility in receptor fluid:	(at least) 0.42 mg/mL
Mass balance analysis:	Provided
Tape stripping:	Yes (max 20)
Method of Analysis:	Liquid scintillation counting
GLP:	In compliance
Date of test:	1 Feb 2018 - 27 Apr 2018

Test system
Skin sections were cut at a thickness setting of 400 µm using an electric dermatome.
The type of static glass diffusion cell used in this study has an exposed skin surface area of 2.54 cm2 and a receptor volume of approximately 4.5 mL. Discs of approximately 3.3 cm diameter of prepared skin were mounted, dermal side down, in diffusion cells held together with individually numbered clamps and placed in a water bath maintained at 32°C ± 1°C. Skin integrity was assessed by measurement of the electrical resistance across the sample. Skin with a measured resistance of <10 KΩk were regarded as having a lower integrity than normal and not used for exposure to the test substances. Cells were selected such that each application was represented by a total of twelve intact skin samples from at least four different donors.

Test procedure

The in vitro percutaneous absorption and distribution of a nominal 6.25% w/w DHA from a leave-on hair care formulation through human dermatomed skin over a 24 hour exposure period was determined. The doses were applied to the skin surface at a rate of 10 µL/cm2 (625 Mg DHA/cm2) to twelve skin diffusion cells containing skin from four different human donors. The skin surface was left unoccluded for the duration of the experiment.

Samples (0.5 mL) of physiological saline receptor fluid were taken from the receptor chambers of the static cell system at pre-treatment and at 1,2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours after application using an autosampler. The receptor fluid in the chambers was stirred continuously and the receptor volume was maintained by the replacement of a volume of fresh receptor fluid, equal to the sample volume, after each sample had been taken.

After the final receptor fluid sample had been taken at 24 hours, the remaining fluid in the receptor chamber was discarded. To remove residual receptor fluid from under the surface of the skin, the receptor chamber was again refilled with fresh receptor fluid, which was afterwards discarded. The cell was dismantled and the clamp removed before carefully removing the glass donor chamber and wiping the underside (surface contact with the membrane) with one sponge pre-wetted with 3% Teepol® L in water which was added to the container that would later house the sponges used for decontamination of the skin surface. Residual test material was washed from the donor chamber using water.

The epidermal surface of the skin was decontaminated by gently swabbing the application site with natural sponges pre-wetted with 3% Teepol® L, and with further sponges pre-wetted with water. The sponges were digested in Soluene 350® and made up to a recorded volume.

For tape stripping, the surface of the skin was allowed to dry naturally, prior to the removal of successively deeper layers of the stratum corneum by the repeated application of adhesive tape (Scotch 3M Magic Tape, 1.9 cm wide) up to a maximum of 20 strips. Tape strips 1-5 were extracted individually and the remaining 15 tape strips were combined in groups of five (6-10, 11-15 and 16-20) prior to being extracted for at least 20 hours in Soluene 350®.

The skin was carefully removed from the receptor chamber, the flange area was cut away and digested in Soluene 350®.

The epidermis on the remaining skin was separated from the dermis using a heat separation technique. The skin was placed dermis side down, on cling film. A second piece of cling film was then used to cover the epidermis side. A 200 g weight was placed in a water bath at 65°C for an hour prior to use. The weight was placed onto the epidermal surface for approximately 90 seconds. The epidermis was peeled away from the dermis using forceps. To maintain the required temperature, the weight was returned to the water bath between separations. The epidermis and dermis were separately digested in Soluene 350® prior to analysis.

Results

Between 0-6 hours, the mean absorption rate of DHA through human dermatomed skin was 0.205 µg/cm2/hour. This increased to 0.424 µg/cm2/hour between 6-12 hours and to 0.603 µg/cm2/hour between 12-24 hours. Over the 24 hour experimental period the mean rate was 0.452 µg/cm2/hour.

The amount absorbed into receptor fluid at 24 hours, following a 24 hour skin wash, was 11.0 µg/cm2 (1.67% of the dose applied).

Mean total recovery of DHA was 595 µg/cm2 (90.9%, n=12). The individual cell recovery values were very consistent and ranged from 88.2% to 93.9%.

The greatest proportion of the applied DHA (510 µg/cm2 = 77.9%) was recovered from the skin wash at 24 hours. The proportions of the dose applied that were recovered from the stratum corneum (tape strips 1-20), heat-separated epidermis after tape stripping and dermis were 11.7 µg/cm2 (1.79%), 33.5 µg/cm2 (5.12%) and 2.75 µg/cm2 0.421%), respectively. The donor chamber extracts and flange digest were 17.9 µg/cm2 (2.73%) and 7.82 µg/cm2 (1.20%), respectively.

The mean bioavailable dose (receptor fluid + epidermis + dermis) of DHA was 47.3 µg/cm2 (7.22%) of the dose applied.

Test Compartment	**µg DHA per cm²** (mean ± SD (n = 12*))			**% of applied dose** (mean ± SD (n = 12*))		
Donor chamber	17.9	±	11.6	2.73	±	1.78
Skin wash – 24 hours	510	±	29.2	77.9	±	4.47
Stratum corneum (Tape strips 1-20)	11.7	±	8.81	1.79	±	1.35
Flange	7.82	±	3.57	1.20	±	0.546
Epidermis	33.5	±	15.6	5.12	±	2.39
Dermis	2.75	±	1.02	0.421	±	0.155
Receptor fluid	11.0	±	4.58	1.67	±	0.700
Bioavailable dose#	**47.3**	±	**17.3**	**7.22**	±	**2.65**
Total recovery	595	±	12.7	90.9	±	1.94
#Bioavailable dose = Receptor fluid + Epidermis + Dermis * n =11 for tape strips 16-20						

Conclusion
The extent of DHA penetration through human dermatomed skin into the receptor fluid amounted to just 11.0 µg/cm² (1.67% of the dose applied) with a mean bioavailable dose amounting to only 47.3 µg/cm² (7.22%) of that applied to the skin. Thus, it was shown that DHA when tested under predicted use conditions has a low dermal penetration potential. Considering the current conservative SCCS procedure, a value of 64.6 µg/cm² (47.3 µg/cm² plus SD 17.3 µg/cm²) will be used for Margin of Safety (MoS) calculation.

SCCS Comment
A value of 64.6 µg/cm² or 9.87% (bioavailable dose + 1SD) will be used for Margin of Safety (MoS) calculations for DHA in hair colouring products.

Ref: 17

3.2.2 Other studies on toxicokinetics

Pharmacokinetics of DHA investigation on transdermal penetration, excretion in urine and feces in human volunteers

Taken from SCCS/1347/10

Conclusion
The low amount of radioactivity measured in urine and faeces, together with the low plasma levels of [^{14}C]-Dihydroxyacetone, indicate that no noticeable dermal absorption took place in the setting of this study.

The low recovery rate is explained by the galenic formulation (part of it evaporates and is shed off the skin immediately) and by the mechanism of reaction of Dihydroxyacetone within the skin (binds covalently with proteins/lysine residues in the upper layers). The fact that the volunteers' treated skin area was still coloured (pale brown) on the day of discharge supports this theory.

Ref: 18

3.3 EXPOSURE ASSESSMENT

3.3.1 Function and uses

DHA is intended to be used as active colouring ingredient at a concentration of up to 6.25% in leave-on hair care formulations for daily use. In addition, DHA is a self-tanning agent used in face creams and body lotions.

3.3.2 Calculation of SED/LED

The systemic exposure dose for hair dyes is calculated using a dermal absorption value of 9.61% based on the *in vitro* dermal absorption study with a DHA concentration of 6.25%. Systemic exposure doses for self-tanning lotions and spraying applications are calculated using dermal absorption values of 48.03% taken from SCCS/1347/10 based on a study with DHA concentrations of 10%.

Daily use of hair dye containing 6.25% DHA:

Amount applied	=	11 600 mg/day
Maximum concentration of DHA in formulation	=	6.25%
Dermal absorption	=	9.87%
Typical human body weight	=	60 kg
Systemic exposure dose (SED)		
(11600 mg/kg x 6.25/100 x 9.87/100) /60 kg	=	1.19 mg/kg/d

Weekly[1] application of a self-tanning lotion containing 10% DHA:

Amount applied	=	8 000 mg/day
Maximum concentration of DHA in formulation	=	10%
Dermal absorption	=	48.03%
Typical human body weight	=	60 kg
Systemic exposure dose (SED)		
(8000 mg/kg x 10/100 x 48.03/100 x 1/7) /60 kg	=	0.91 mg/kg/d

Weekly[1] of face cream containing 10% DHA:

Amount applied	=	1 600 mg/day
Maximum concentration of DHA in formulation	=	10%
Dermal absorption	=	48.03%
Typical human body weight	=	60 kg
Systemic exposure dose (SED)		
(1600 mg/kg x 10/100 x /100 x 1/7) /60 kg	=	0.18 mg/kg/d

[1]A Danish EPA report (19) takes into account that common application may occur once a month, or in more specific cases (TV-presenters, models), once per week. Therefore, the first calculation of the MoS takes into account a weekly application averaged out over 7 days, leading to the maximal frequency of application of 1/7.

3.4 TOXICOLOGICAL EVALUATION

3.4.1 Irritation and corrosivity

3.4.1.1 Skin irritation

SCCS comment SCCS/1347/10
This study is old and the description does not allow to check whether it is completely according to the current EC B.4 Guideline. A conclusion is not stated.
Nevertheless the substance does not appear to cause any severe irritation after 24h contact under occlusion, even on abraded skin.

Ref: 20

3.4.1.2 Mucous membrane irritation / eye irritation

SCCS comment SCCS/1347/10
This study is old and the description does not allow to check whether it is completely according to the current EC B.5 Guideline.
Nevertheless the substance does not appear to cause eye irritation in the rabbit.

Ref: 20

3.4.2 Skin sensitisation

Animal data

SCCS comment SCCS/1347/10
Based on the results of an LLNA study, DHA is evaluated as not sensitizing to the skin.
Another solvent than normally used in the LLNA was applied here, probably because of the high water solubility. The solvent or solvent mixture, however, might have an effect on the test outcome.

Ref: 21

Human data
/

3.4.3 Acute toxicity

3.4.3.1 Acute oral toxicity

Taken from SCCS/1347/10

Conclusion
The study authors conclude that the LD_{50}-value for Dihydroxyacetone is > 16 000 mg/kg bw.

Ref: 20

3.4.3.2 Acute dermal toxicity

/

3.4.3.3 Acute inhalation toxicity

Taken from SCCS/1347/10

Conclusion
The LC50 of DHA in rats obtained in this study was estimated to be > 5.114 mg/l/4h.

Ref: 22

3.4.3.4 Acute intraperitoneal toxicity

Taken from SCCS/1347/10 (4)
In a study of 1970, Dihydroxyacetone was administered to Wistar rats through the intraperitoneal route at dose levels of 400 - 800 – 1 600 – 3 200 – 6 400 mg/kg bw. At the highest doses, rats showed dazing, staggering, dyspnoea and temporary dragging of the hind paw immediately after injection. All effects were fully reversible.
The LD50-value for Dihydroxyacetone was considered > 6 400 mg/kg bw

Ref: 20

3.4.4 Repeated dose toxicity

3.4.4.1 Repeated dose (28 days) oral / dermal / inhalation toxicity

SCCS comment SCCS/1347/10
The above assay is a dose-range finding study for the 90-day subchronic toxicity test with a shortened administration period (14 days instead of 28 days).

Ref: 23

3.4.4.2 Sub-chronic (90 days) oral / dermal / inhalation toxicity

Taken from SCCS/1347/10

Conclusion
Treatment for 13 weeks with Dihydroxyacetone at daily oral dosage levels of 250 to 1000 mg/kg bw/day did not cause adverse effects in the Wistar rat. Based on the results of this study, the dosage level of 1000 mg/kg bw/day was chosen as the NOEL-value.

Ref: 24

3.4.4.3 Chronic (> 12 months) toxicity

/

3.4.5 Reproductive toxicity

3.4.5.1 Fertility and reproduction toxicity

/

3.4.5.2 Developmental Toxicity

Taken from SCCS/1347/10

Conclusion
Based on the results described above, 1000 mg/kg bw/day of Dihydroxyacetone is considered to be the No-Observable- Effect-Level (NOEL) for maternal and foetal organisms.

Ref: 25

3.4.6 Mutagenicity / genotoxicity

3.4.6.1 Mutagenicity / genotoxicity *in vitro*

Bacterial Reverse mutation test 1
SCCS comment SCCS/1347/10
With and without the addition of S9, DHA was mutagenic in two test strains (TA100, TA102) under the experimental conditions described in this study.

Ref: 26

Bacterial Reverse Mutation test 2
SCCS comment SCCS/1347/10
With and without the addition of S9, DHA was mutagenic in two test strains (TA100, TA102) under the experimental conditions described in this study.

Ref: 27

Reverse mutation test 3, including influence of protein on mutagenic potential of DHA in S. typhimurium TA100
SCCS comment SCCS/1347/10
Under the experimental conditions of this report the mutagenic activity of DHA in Salmonella typhimurium TA100 was only slightly affected by the addition of different protein preparations to the test system. Nevertheless, according to the study authors, this study shows that the direct acting mutagen DHA was inactivated by mammalian metabolizing enzymes.

Ref: 28

Mammalian Cell Gene Mutation Assay
SCCS comment SCCS/1347/10
DHA was, up to concentrations reaching the solubility limits of the compound, not mutagenic in this mammalian cell gene mutation test in V79 cells (hprt locus) either in the absence or presence of metabolic activation under conditions where the positive controls exerted potent mutagenic effects.

Ref: 29

Mammalian Cell Chromosomal Aberration test
SCCS comment SCCS/1347/10

DHA was not clastogenic in this test system under conditions where the positive controls exerted potent clastogenic effects.

Ref: 30

3.4.6.2 Mutagenicity / genotoxicity *in vivo*

Mammalian erythrocyte micronucleus test in mice

SCCS comment SCCS/1347/10

DHA was not mutagenic in this *in vivo* micronucleus assay in male mice under conditions where the positive controls exerted potent mutagenic effects.

The full study report of this *in vivo* micronucleus test is not available, only an extensive summary.

Ref: 31

Overall SCCS comment

The previous submission contained 3 reverse mutation tests, which all reveal a mutagenic potential of DHA in two particular Salmonella typhimurium strains (TA100 and TA102). One of them includes an investigation on the effect of different kinds of proteins or different concentrations of these proteins on the mutagenic activity of DHA. According to the study authors, the results indicated that direct acting mutagen DHA may be inactivated by mammalian metabolizing enzymes. This means that the mutation effects would not occur in an *in vivo* setting.

An *in vitro* mammalian cell gene mutation test in V79 cells shows DHA to be non-mutagenic up to concentrations reaching the solubility limits of the compound. This appears to be true as well in the absence as in the presence of metabolic activation. DHA also shows to be non-clastogenic in the presented in vitro mammalian chromosome aberration assay.

Finally, an in vivo micronucleus test in the mouse reveals no statistically significant or biologically relevant increase in the number of polychromatic erythrocytes with micronuclei in any of the DHA-treated groups compared to the negative control.

Although the in vitro mutagenicity/genotoxicity testing battery is known to yield a high rate of false positive results and even though the mammalian cell gene mutation as well as the chromosome aberration test gave negative results, the consistent positive results obtained in the reverse mutation assays cannot be denied. Therefore, the SCCS invited external experts to discuss the in vitro positive results. In first instance, the presented in vitro / in vivo testing battery was considered of good scientific quality. Subsequently, a large-scale study of the in vitro genotoxicity results obtained for known carcinogens and in vivo genotoxic compounds was presented in detail in order to help elucidating the ambiguities related to the obtained positive in vitro results for DHA. One of the key findings of this comprehensive study was that all bacterial reverse mutation positive carcinogens and the majority of bacterial reverse mutation positive in vivo genotoxins also produced positive results in one of the performed in vitro genotoxicity assays with mammalian cells (personal communication). As DHA only showed to be positive in two specific bacterial strains (S. Typhimurium TA 100 & TA 102) and was negative in an in vitro mammalian cell gene mutation test, in an in vitro mammalian chromosome aberration assay and in an in vivo micronucleus test, the experts considered it unlikely that the compound would have any in vivo genotoxic potential. Moreover, the use of the S9 mix was questioned, as DHA is expected to be quickly metabolized in the endogenous glycolytic pathway (Ref. 35), without having the opportunity to undergo extensive CYP450 metabolism. One of the experts made the comment that the DHA could have been used by the bacterial cultures as an alternative carbon source, which might then influence the test outcome.

The experts unanimously came to the conclusion that based on the presented raw data and a weight of evidence approach, there is no reason to consider DHA as an in vivo mutagenic/genotoxic substance.

The SCCS has performed additional literature search and found no new data. Therefore the SCCS overall conclusion remains the same as in the previous Opinion.

3.4.7 Carcinogenicity

Taken from SCCS/1347/10
A short publication of 1984 describes a dermal carcinogenicity study with DHA in Swiss-Webster mice. Animals were treated by topical application with aqueous solutions of DHA (5 or 40%) on the shaved dorsal regions once weekly for 80 weeks. Except for the brown coloration of application sites in DHA-treated mice, no differences in gross physical appearance or clinical signs were observed. Body weight gains were reported to be similar in all groups. Survival rate was not affected by DHA treatment. Histopathologically, there were no changes attributed to treatment with DHA. The tumours observed were typical of the type normally observed in mice of this strain and age, and they were equally distributed among control and treated groups. The authors conclude that DHA shows to be non-carcinogenic in the presented study.

Ref: 32

3.4.8 Photo-induced toxicity

3.4.8.1 Phototoxicity / photo-irritation and photosensitisation

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3.4.8.2 Photomutagenicity / photoclastogenicity

Reverse mutation test with UV irradiation 1
SCCS comment SCCS/1347/10
With and without the addition of S9, DHA was mutagenic in two test strains (TA100, TA102) under the experimental conditions described in this study. However, deliberate exposure of DHA to light did not result in a significant enhanced mutagenic response.

Ref: 33

Reverse mutation test with UV irradiation 2
SCCS comment SCCS/1347/10
DHA was not photomutagenic under conditions whereas the positive control, 8-methoxypsoralen, induced a clear UV-dependent mutagenic effect.

Ref: 34

3.4.9 Human data

/

3.4.10 Special investigations

/

3.5 SAFETY EVALUATION (including calculation of the MoS)

The Applicant defined a NOEL-value of 1000 mg/kg bw/day based on the 90-days repeated toxicity study. Since this was the highest concentration tested, the SCCS considers 1000 mg/kg bw/day to be a NOAEL. Information on bioavailability after oral intake is not known. Thus, standard procedure according to the SCCS's Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation is to use 50% bioavailability giving an adjusted NOAEL of 500 mg/kg bw/day.

Product type	SED (mg/kg/d)	MoS
Hair dye	1.19	419
Self-tanning lotion	0.91	547
Self-tanning face cream	0.18	2733
Aggregated SED (all three product types)	2.29	218

In the previous Opinion, the MoS was calculated for spray self-tanning applications as 104, based on overly conservative exposure estimates. Therefore, in the present Opinion, the SCCS is not calculating aggregate exposure for the hair colorant and spray self-tanning application.

3.6 DISCUSSION

Physicochemical properties
The storage stability of DHA at 4 to 8 °C is declared to be at least 18 months. After 18 months of storage at 5±3 °C and %relative humidity (value not mentioned), the formaldehyde content increased, yet it remained below 50 ppm after 48 months of storage.

Toxicokinetics
Based on the *in vitro* human skin percutaneous absorption study using a 6.25% w/w DHA from a leave-on hair care formulation over a 24 hour exposure period, a value of 64.6 µg/cm² or 9.87% (bioavailable dose + 1SD) will be used for Margin of Safety (MoS) calculations.

Exposure assessment

Function and uses
DHA is intended to be used as active colouring ingredient at a concentration of up to 6.25% in leave-on hair care formulations for daily use. In addition, DHA is a self-tanning agent used in face creams and body lotions.

Calculation of SED / LED
The systemic exposure dose for hair dyes is calculated using a dermal absorption value of 9.61%, whereas systemic exposure doses for self-tanning lotions are calculated using dermal absorption values of 48.03% taken from the previous Opinion SCCS/1347/10.

Toxicological Evaluation

Irritation and corrosivity
A relatively old Draize skin irritation study (1970) indicates that DHA does not appear to cause any severe irritation after 24h contact under occlusion, even on abraded skin. An analogous eye irritation study suggests that DHA is non-irritating to the eye.
Although both studies are outdated, the available raw data allow supporting the conclusion that DHA is neither a skin nor an eye irritant.

Skin sensitisation
A Local Lymph Node Assay (carried out in 2007) shows DHA to be non-sensitising to the skin in that *in vivo* model.

Acute toxicity
DHA has a low acute toxicity profile, with an acute oral LD50 value of more than 16 000 mg/kg bw and an inhalation LC50 above the limit test threshold of 5 mg/l/4h. The intraperitoneal LD50 value was determined to be above 6 400 mg/kg bw.

Repeated dose toxicity
The submission contains 14 day and 90 day oral tests with the rat with DHA dosage levels up to 1000 mg/kg bw/day, the limit dosage for this type of studies. The results reveal that treatment for 13 weeks with DHA at daily oral dosage levels of 250 to 1000 mg/kg bw/day did not cause adverse effects in the Wistar rat, wherefore the level of 1000 mg/kg bw/day can be established as the NOEL-value and used for the MoS calculation.

Reproductive toxicity
A teratogenicity study, in which DHA is tested up to 1000 mg/kg bw/day, is available and shows that the compound does not display any embryotoxic properties. The NOEL for maternal and foetal toxicity is 1000 mg/kg bw/day.
No 2-generation reproduction toxicity study is provided.

Mutagenicity / genotoxicity
The SCCS has performed additional literature search and found no new data. Therefore the SCCS overall conclusion remains the same as in the previous Opinion.

Carcinogenicity
No fully described carcinogenicity study is available. Instead, a short publication of 1984 describes a dermal carcinogenicity study with DHA in Swiss-Webster mice. No conclusion could be drawn from the study.

Photo-induced toxicity
Two photo-bacterial reverse mutation assays are presented and confirm the mutagenic potential of non-radiated DHA in Salmonella typhimurium strains TA100 and TA102.
However, exposure of DHA to light did not result in an enhanced mutagenic response.

Human data
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Special investigation
/

4. CONCLUSION

1. In light of the data provided, does the SCCS consider Dihydroxyacetone safe when used as hair colouring ingredient in leave-on applications up to a maximum concentration of 6.25 %?

On the basis of data provided, the SCCS considers Dihydroxyacetone safe when used as hair colouring ingredient in leave-on applications (non-oxidative) up to a maximum concentration of 6.25%.

2. Does the SCCS have any further scientific concerns with regard to the use of Dihydroxyacetone in cosmetic products?

The use of Dihydroxyacetone as hair colouring ingredient in leave-on applications (non-oxidative) up to a maximum concentration of 6.25% together with the use of self-tanning lotion and face cream containing up to a maximum concentration of 10% Dihydroxyacetone is considered safe.

5. MINORITY OPINION

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Database search for references

A comprehensive update data base research on the toxicological profile of DHA was carried out using various patent data bases of the data base provider TOXNET (TOXLINE) to assess relevant references published between 2009 and end of 2018. This procedure was considered as justified with regards to the available SCCS Opinion on DHA from 2010 (Reference: SCCS; 2010 (27)).

TOXNET (TOXLINE) provides access to structure and nomenclature authority files and included relevant inventories, biomedical resources and databases (TOXLINE Components: ANEUPL, BIOSIS, CIS, DART (non-PubMed), DART (PubMed: non-tox subset), EMIC, EPIDEM, FEDRIP, HEEP, HMTC, IPA, KEMI Riskline, Meeting abstracts, NIOSH, NTIS, PESTAB, PPBIB, PubMed, RePORTERTOX, TSCATS). All languages were searched.

All hits relevant for risk assessment of DHA were included in the present safety evaluation. The complete print out covering all hit is attached.

1. TOXNET-TOXLINE literature search 2009-2018 on DHA 2019-01-21

7. GLOSSARY OF TERMS

See SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 141

8. LIST OF ABBREVIATIONS

See SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 141
