Scientific Committee on Consumer Safety

SCCS

REVISION

of the scientific Opinion (SCCS/1576/16) on vitamin A (Retinol, Retinyl Acetate, Retinyl Palmitate)

The SCCS adopted this document
during the plenary meeting on 24-25 October 2022

ACKNOWLEDGMENTS

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This Opinion has been subject to a commenting period of eight weeks after its initial publication (from 13 December 2021 to 7 February 2022). Comments received during this period were considered by the SCCS. For this Opinion, main changes of the text occurred in the exposure assessment, i.e. in following sections: 3.2.4.2, 3.2.4.3, 3.4, 3.5, 4 under first conclusion, and Appendix 1.

All Declarations of Working Group members are available on the following webpage:
Register of Commission expert groups and other similar entities (europa.eu)

1. ABSTRACT

The SCCS concludes the following:

1. *In light of the data provided, does the SCCS consider that the contribution of the cosmetic products among the overall/total exposure to vitamin A is of concern?*

The SCCS is of the opinion that vitamin A in cosmetics at the concentrations of 0.05% Retinol Equivalent (RE) in body lotion, and 0.3% RE for other leave-on and rinse-off products is safe.

Regarding the contribution from cosmetics to overall/total exposure, no conclusion can be drawn due to inconsistencies in the presented model calculations. However, the probabilistic assessment regarding the contribution from food and food supplements shows that the exposure to vitamin A of the most exposed consumers (5% of the total population) may already exceed the upper limit. Compared to food, the contribution of vitamin A from cosmetics is lower. However, it will add to the overall consumer exposure and this may be of concern for consumers with the highest exposure (5% of the total population) to vitamin A from food and food supplements.

2. *SCCS is invited to update accordingly opinion SCCS/1576/16 on vitamin A notably as regards, as needed, the maximum concentration limits for the different categories of cosmetic products indicated in that Opinion.*

Since cosmetics alone do not exceed the upper limit, the allocation of contributions of different exposure sources is a risk management issue and cannot be addressed at the level of risk assessment.
Therefore, it is beyond the scope of the SCCS to suggest maximum concentration limits that take into account contributions from other sources e.g. food, food supplements.

Keywords: SCCS, revision, scientific opinion, vitamin A, Retinol, Retinyl Acetate, Retinyl Palmitate, Regulation 1223/2009

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), revision of the scientific Opinion (SCCS/1576/16) on vitamin A (Retinol, Retinyl Acetate, Retinyl Palmitate), preliminary version of 10 December 2021, final version of 24-25 October 2022, SCCS/1639/21

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.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

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

Vitamin A is currently not regulated in the Annexes to the Cosmetics Regulation (EC) No 1223/2009. In 2016, the SCCS issued the opinion SCCS/1576/16 on vitamin A concluding that its use as a cosmetic ingredient is safe at given concentrations for body lotions and face creams, leave-on (other than body lotions) and rinse-off products (see concentrations mentioned above).

However, in its opinion, SCCS recognized also that the population's overall exposure to vitamin A can be significantly higher: "The most important source of vitamin A in the population is diet, followed by food supplements and cosmetics (…) exposure to vitamin A via food may already be very close to the UL and any additional source of exposure, including cosmetic products, may exceed this UL" (UL stands for tolerable Upper intake Levels and it is used in the Risk Assessment).

Based on the SCCS opinion, intake of vitamin A via additional sources of exposure to vitamin A (in addition to exposure via food) may, therefore, exceed safe levels.

In 2020, the Commission services received additional information on a recent study that evaluated the aggregated exposure to vitamin A from cosmetics, diet and food supplements and the contribution of cosmetic products among the overall/total exposure to vitamin A.

Terms of reference

1. *In light of the data provided, does the SCCS consider that the contribution of the cosmetic products among the overall/total exposure to vitamin A is of concern?*

2. *SCCS is invited to update accordingly opinion SCCS/1576/16 on vitamin A notably as regards, as needed, the maximum concentration limits for the different categories of cosmetic products indicated in that opinion.*

3. OPINION

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

As no data were specifically reported for retinal and retinol linoleate in the dossier submitted by the applicant, these two vitamin A derivatives were not included in this Opinion.

3.1.1 Chemical identity

The term "vitamin A" refers to a group of substances, the retinoids, including retinol (vitamin A1) and substances with similar structures and the biological behaviour of retinol. This Opinion refers only to retinol, retinyl acetate and retinyl palmitate.

3.1.1.1 Primary name and/or INCI name

Retinol
Retinyl acetate
Retinyl palmitate

3.1.1.2 Chemical names

Retinol:
Chemical names:
All-trans-3, 7-dimethyl-9-(2, 6, 6-trimethyl-1-cyclohexen-1-yl)-2, 4, 6, 8-nonatetraen-1-ol;
OR
(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraen-1-ol

Retinyl acetate:
Chemical names:
All-trans-3, 7-dimethyl-9-(2, 6, 6-trimethyl-1-cyclohexen-1-yl)-2, 4, 6, 8-nonatetraene-1-yl acetate;
OR
[(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenyl] acetate

Retinyl palmitate:
Chemical names:
All-trans-3, 7-dimethyl-9-(2, 6, 6-trimethyl-1-cyclohexen-1-yl)-2, 4, 6, 8-nonatetraene-1-yl palmitate;
OR
[(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenyl] hexadecanoate

References: 18, 20, 37, 48, 49, 50, 51, 52, 76, PubChem

3.1.1.3 Trade names and abbreviations

Retinol: Acon, Afaxin, Agiolan, Alphsterol, Epiteliol, Testavol

Retinyl acetate: Vitamin Acetate

Retinyl palmitate: Arovit, Testavol S; vitamin A Palmitate

Reference: 71

3.1.1.1 Synonyms

Retinol:

Synonyms: All-trans-retinol
All-trans-retinyl-alcohol
Vitamin A alcohol
15-apo-(3-caroten-15-ol)
Axerol
Axerophthol
Axerophtholum
Biosterol
(E)-3, 7-dimethyl-9-(2, 6, 6-trimethylcyclohex-enyl)-2, 4, 6, 8-nonatetraenol
(E)-3, 7-dimethyl-9-(2, 6, 6-trimethylcyclohexen- l -yl)-2, 4, 6, 8-nonatetraenol
(E)-9-hydroxy-3, 7-dimethyl-9-(2, 6, 6-trimethylcyclo-hexenyl)-1, 3, 5, 7-Nonatetraene
OleoVitamin A
Retinol
Trans-retinol
2-trans, 4-trans
Vitamin A
Vitamin A alcohol
Vitaminum A

Retinyl acetate:

Synonyms: All-trans-Vitamin A acetate
Vitamin A acetate
Acetic acid (E) -3, 7-dimethyl-9-(2, 6, 6-trimethyl-cyclohexenyl)-2, 4, 6, 8-nonatetraenylester
Acetic acid retinyl ester
All-trans-retinyl acetate
All-trans-retinol acetate
O-acetoxy-all-trans-retinol
O-acetyl-all-trans-retinol
Retinylacetate
2-trans, 4-trans, 6-trans, 8-trans-retinolacetate
2-trans, 4-trans, 6-trans, 8-trans-retinylacetate
Rac

Retinyl palmitate:

Synonyms: All-trans-Retinyl palmitate
Retinyl palmitate
Palmitic acid (E)-3, 7-dimethyl-9-(2, 6, 6-trimethyl-cyclohexenyl)-2, 4, 6, 8-nonatetraenyl ester
Palmitic acid retinyl ester
O-palmitoyl-all-trans-retinol
O-palmitoyl-retinol
Retinylpalmitate
2-trans, 4-trans, 6-trans, 8-trans-retinylpalmitate
2-trans, 4-trans, 6-trans, 8-trans-retinol palmitate
Retinol hexadecanoate
Trans-retinol palmitate
Trans-retinyl palmitate
RP

References: 18, 20, 37, 48, 49, 50, 51, 52, 76

3.1.1.5 CAS / EC number

Vitamin A:
CAS: 11103-57-4
EC: 234-328-2

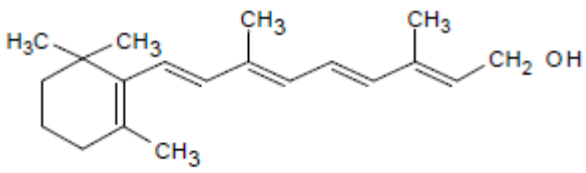
Retinol:
CAS: 68-26-8
EC: 200-683-7

Retinyl acetate:
CAS: 127-47-9
EC: 204-844-2

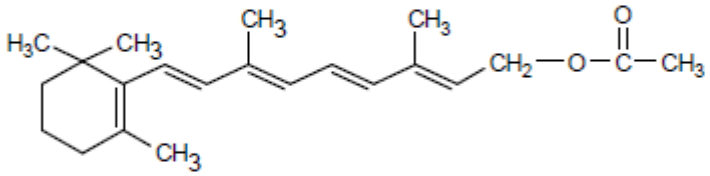
Retinyl palmitate:
CAS: 79-81-2
EC: 201-228-5

3.1.1.6 Structural formula

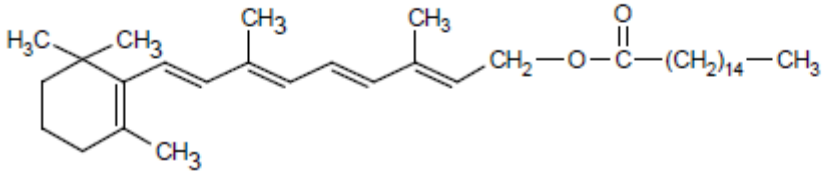
Retinol:



Retinyl Acetate:



Retinyl Palmitate:



References: 18, 20, 37, 48, 49, 50, 51, 52, 76

3.1.1.7 Empirical formula

Retinol: $C_{20}H_{30}O$

Retinyl acetate: $C_{22}H_{32}O_2$

Retinyl palmitate: $C_{36}H_{60}O_2$

References: 18, 20, 37, 48, 49, 50, 51, 52, 76

3.1.2 Physical form

Retinol:
Pale yellow oil, which may crystallise at low temperatures

Retinyl acetate:
Pale yellow prisms or yellow supercooled melt, viscous liquid

Retinyl palmitate:
Yellow, crystalline or amorphous powder

3.1.3 Molecular weight

Retinol: 286.5 g/mol

Retinyl acetate: 328.5 g/mol

Retinyl palmitate: 524.9 g/mol

References: 18, 20, 37, 48, 49, 50, 51, 52, 76

3.1.4 Purity, composition and substance codes

Representative examples of marketed products are provided in the following paragraphs.

Retinol (e.g., Retinol 10 S, 15 D, 50 C):
Purity: ≥95% (all-trans retinol)
≤5% (cis-isomers)
International units (IU): 330000–370000 IU/g (Retinol 10 S)
500000–530000 IU/g (Retinol 15 D)
1425000–1650000 IU/g (Retinol 50 C)
Stabiliser: Butylhydroxytoluol (BHT) or Butylhydroxyanisol (BHA)

Retinyl acetate (e.g., vitamin A acetate 1.5 mio IU/g):
Appearance: viscous-yellow oil, may crystallise on storage
Peroxide value: <10 meq/kg
Acid value: <2.0 mg/ KOH/g
International units (IU): 1500000 IU/g
Stabiliser: Tocopherol or BHT

Retinyl palmitate (e.g., retinyl palmitate 1.0 or 1.7 mio IU/g):
Appearance: viscous-yellow oil, may crystallise on storage
Peroxide value: <10 meq/kg
Acid value: <2.0 mg/ KOH/g
International units (IU): 1000000 or 1700000 IU/g
Stabiliser: Tocopherol, BHT, or BHA

All toxicological study data presented in section 6 (Toxicological evaluation) were checked for information on purity and composition. The respective information has been provided where available.

References: 18, 20, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 57, 58

Table 1 presents purity data for different batches of retinyl acetate, retinyl palmitate and retinol:

Compound	Batch No	Purity	Study (Ref.)
Retinyl acetate	6/17	1.53 mio IU/g USP XIX (526 mg RAc/g)	Acute toxicity (ref 7) Mucous membrane irritation (ref 6)
	805043	1.5 mio IU/g (515 mg RAc/g)	Skin irritation (Ref 129) Skin sensitisation (ref 132) Mucous membrane irritation / Eye irritation Batch (ref 130)

	/	1.0 mio IU/g (344 mg Rac/g)	Skin irritation (Ref 8)
Retinyl palmitate	710758	1.7 mio IU/g (935 mg RP/g)	Mucous membrane irritation / Eye irritation (ref 131) Skin sensitisation (ref 126)
	/	1.0 mio IU/g (550 mg Rac/g)	Skin irritation (Ref 10)
Retinol	50-2498	47.7 g/100 g	Mucous membrane irritation / Eye irritation (ref: 17)
	23-0136	47.1 g/100 g	Buehler test (a) (Ref.14), Open epicutaneous test (Ref. 16)
	Not provided	Not provided	Buehler test (c)
	82-0085-00	Not provided	Buehler test (b) (Ref.14)

3.1.5 Impurities / accompanying contaminants

Impurity data have not been provided.

SCCS comment
Data on purity determination was not submitted. According to the specification sheets, UV spectrophotometry was used to calculate the content of retinol, retinyl palmitate and retinyl acetate.

No information on the determination of impurities was provided for retinol, retinyl acetate and retinyl palmitate as the applicant refers to the exception proposal (EU Monograph No 2034).

3.1.6 Solubility

Retinol: Soluble in most organic solvents (acetone, chloroform, dimethyl sulfoxide, diethyl ether, ethanol, hexane, isopropanol, methanol) and in fats and mineral oils (2.5 mol/L).
Practically insoluble in water (water solubility: 0.06 nmol/L) and glycerol.

Retinyl acetate: Soluble in most organic solvents (acetone, chloroform, ethanol, isopropanol) and in fats or oils (750 g/100 mL).
Insoluble in water and glycerol.

Retinyl palmitate: Soluble in most organic solvents (ethanol, iso-propanol, chloroform, acetone) and in fats and oils.
Insoluble in water and glycerol.

References: 18, 37, 76

3.1.7 Partition coefficient (Log P_{ow})

Retinol:
Log P_{ow}: 5.68 (measured)
7.6 (calculated KOWIN V 1.67, 2006)

Retinyl acetate:

Log P_{ow}: 9.4 (BASF SE, unpublished results, 1989)

Retinyl palmitate:
Log P_{ow}: 15.51 (calculated: KOWIN, V 1.67, 2006)

SCCS comment on calculated value
In case of a calculated value, the method should be specified. The P_{ow} strongly depends on the pH, especially for ionisable molecules, zwitterions etc. Therefore, a single calculated value of Log P_{ow}, usually without any reference to respective pH, cannot be correlated to physiological conditions and to the pH conditions of the dermal absorption studies.

3.1.8 Additional physical and chemical specifications

Retinol:

Melting point: 62–64° C
Boiling point: 137–138°C at 1x10^{-6} mm Hg / 421.2°C at 760 mm Hg
Flash point:

Vapour pressure:	/
Density:	0.954 g/cm^3
Viscosity:	/
pKa:	/
Refractive index:	/
pH:	/
UV_Vis spectrum:	λ_{max} = 325 nm, $E^{1\%}_{1cm}$= 1820, ε=52140
UV_Vis in ethanol:	λ_{max} at 325 nm; E1%/1cm = 1835
Fluorescence:	Yellow-green at 510 nm or 470 nm after excitation at 327 nm or 325 nm, respectively.

Spectroscopy: Double-bond isomers of retinol do not show differences in their infrared spectra. The infrared (IR) and proton magnetic resonance (^{1}H-NMR) spectra of retinol can be found in the relevant Aldrich Library volumes.

Retinyl acetate:

Melting point: 57-58° C
Boiling point: 440.5 °C at 760 mm Hg
Flash point:

Vapour pressure:	/
Density:	0.968 g/cm^3
Viscosity:	/
pKa:	/
Refractive index:	/
pH:	/
UV_Vis in ethanol:	λ_{max} 326 nm (in ethanol); $A^{1\%}$ /$_{1cm}$ 1550.
Fluorescence:	Emission λ_{max} at 470 nm for excitation at 325 nm.

Retinyl palmitate:

Melting point:	27-29° C
Boiling point:	607.5 °C at 760 mm Hg

Flash point:	
Vapour pressure:	/
Density:	0.92 g/cm^3
Viscosity:	/
pKa:	/
Refractive index:	/
pH:	/
UV_Vis spectrum:	λ_{max} = 326 nm, $A^{1\%}_{1cm}$= 960, ε=50.390
UV-Vis in ethanol:	λ_{max} = 325-328 nm (in ethanol); $E^{1\%}/_{1cm}$ 940-975.
Fluorescence:	Emission λ_{max} at 470 nm for excitation at 325 nm.

References: 19, 37, 71, 76

Analytics:

Recently, a novel sensitive analytical method was reported, including reversed-phase high performance liquid chromatography (HPLC) with ultraviolet (UV) detection for the quantification of retinol, retinyl palmitate, and retinoic acid in cosmetic preparations with respective recoveries from spiked cosmetic products of 95% or higher. The author emphasised that the method may be used to quantitatively determine several retinoids and their isomers in cosmetic products.

Reference: 75

SCCS comment
It is unclear if the HPLC method has been applied to the analysis of the batches used in toxicity testing. This method does not include retinyl acetate.

3.1.9 Homogeneity and Stability

Retinol:

Photo-induced bond isomerisation from trans to cis gives the other known retinol isomers: 11-cis (neo b), 13-cis (neo a), 9, 13-di-cis (iso b), 9-cis (iso a), and 11, 13-di-cis (neo c). Bond isomerisation can be caused by heat and iodine.

Retinol is sensitive to oxygen, heat, light and heavy metals. Heat and trace metals accelerate retinol decomposition by oxygen and light. High levels of illumination can induce polymerisation. Retinol is unstable with acids, which cause bond rearrangement to retro-vitamin A, isomerisation, and dehydration to anhydro-vitamin A, sometimes followed by solvent addition. Retinol is also unstable with alkali in the presence of oxygen (unlike the palmitate ester).

Particularly in an oil solution, retinol can be protected from isomerisation by preventing exposure to UV and sunlight. It is optimally stored below 4°C under an inert gas (argon or nitrogen) or in the presence of an antioxidant (e.g. butylated hydroxytoluene, tocopherol). Stability of different retinol grades differed according to the antioxidant systems used and ranged between 6–24 months, if stored below 15–20 °C. Retinol in cosmetic formulations is stable for ≥6 months if manufactured under inert atmosphere and stored e.g., in aluminium tubes at ≤ 20 °C.

Retinol and its acetate can bind strongly to polyvinyl chloride in plastics.

Retinyl acetate:
Slightly more stable than retinol, but in general the same statements apply.

Retinyl palmitate:
Slightly more stable than retinol, but in general the same statements apply.

References: 18, 20, 37, 48, 49, 50, 51, 52, 76

SCCS comment
No data are available on the stability.
Retinol in cosmetic products needs to be stabilised.

General Comments on physicochemical characterisation
Calculations use international units (IUs) or retinol equivalents (REs). A conversion of the individual derivatives into IUs can be found in Table 2.

Retinol has a high estimated $LogK_{ow,}$ indicating that the substance has a high potential to bioaccumulate and thus potentially fulfils the B/vB criteria of REACH Annex XIII. However, no experimental bioaccumulation data are available.

In terms of persistence, based on screening criteria, Retinol can be considered as not P/vP. According to experimental data on ready biodegradability test (OECD 301B), the substance exhibited 81% degradation in 28 days.

Table 2: Conversion of the various vitamin A derivatives into international units (IUs)

Vitamin A derivative	1IU corresponds to
Retinol	0.300 µg
Retinyl acetate	0.345 µg
Retinyl palmitate	0.550 µg

Conversion factors for vitamin A weight, international units, or retinol equivalents (RE) (http://robert-forbes.com/resources/vitaminconverter)

	Vitamin A activity in International Units (IU)	Vitamin A activity in Retinol Equivalents (µg RE)
Retinol (1 mg)	3330	1000
Retinyl acetate (1 mg)	2900	870
Retinyl palmitat (1 mg)	1830	550

In this Opinion, the SCCS has chosen to express vitamin A amounts in RE.

3.2 EXPOSURE ASSESSMENT & TOXICOKINETICS

3.2.1 Function and uses

3.2.1.1 Cosmetics

Retinol, retinyl acetate and retinyl palmitate are used as cosmetic ingredients at maximum use concentrations of 0.05% (retinol equivalents) in body lotions, 0.3% (retinol equivalents) in hand and face creams as well as in other leave-on or rinse-off products (e.g. sunscreens, anti-wrinkle creams, eye cream). They induce biosynthesis of collagen in the skin and, at the same time, impede the UV-induced synthesis of collagen-reducing enzymes. As active ingredients they are expected to provide the cosmetic product with a series of specific abilities to improve and counteract skin aging and photoaging, prevent oxidative stress, and control cutaneous bacterial flora. They promise to smooth wrinkles and fine lines in skin aged by both time and sun exposure. In toothpastes, they serve to protect the gum epithelium against marginal parodontitis (Buddecke *et al.* 1981).

Although retinyl esters did not show significant anti-aging activity, retinyl palmitate is widely used in cosmetics because of its stability. With respect to sunscreen products, retinyl palmitate is extensively used because of its antioxidant, stabilising properties. However, in Europe and the USA, retinyl palmitate is not allowed to be added as UV-filter as such (VKM, 2012).

Apparently, the anti-aging effect of topical retinoids is mainly linked to the receptor-mediated gene activation induced by the ligand retinoic acid modulating epidermal cell proliferation and differentiation, extracellular matrix production, angiogenesis, oxidative stress and melanocyte function (Sorg *et al.*, 2006; Sorg and Saurat, 2014). According to the intracrine-proligand concept, the other topical retinoids have to be metabolised to retinoic acid by the skin to exert their genomic effects. This concept implies that topical application of any precursor retinoids may result in biological effects. However, the potency of the retinoid is strongly dependent on its metabolic distance to retinoic acid. Hence, the retinoid-like activity after topical application increases in the following order: retinyl esters << retinol < retinal < retinoic acid.

The maximum concentrations (in RE), of retinol, retinyl palmitate and retinyl acetate typically used in cosmetic preparations in the EU can be summarised as follows:

Product category	RE (%) [#]
Face and hand creams and other leave-on products	0.3
Body lotions	0.05
Rinse-off products	0.3

[#] RE = retinol equivalents, i.e. retinyl palmitate and retinyl acetate at corresponding retinol concentrations

References: 18, 22, 72, 92, 100, 150, 157

Retinoic acid is banned in cosmetic products in the EU, whatever the concentration (Annex 2, entry 375). Based on information provided by cosmetic industry, vitamin A and esters are not used for children in the EU.

3.2.1.2 Food and food supplements

Vitamin A and its derivatives are present in various diet components and in food supplements, respectively. Among the different substances, humans mainly take up retinol and retinyl palmitate with the normal diet.

3.2.2 Dermal / percutaneous absorption

All available studies have been discussed in SCCS/1576/16. For the calculation of the MoS, the study by Yourick *et al.* 2008 on *in vitro* dermal uptake of retinol had been selected, which is described here below. For all other studies, consult SCCS/1576/16.

In vitro

Guideline:	/
Species/strain:	Human
Test system:	Freshly biopsied human skin from abdominal surgery (split thickness skin layer: 200–320 µm)
Membrane integrity:	^{3}H water test
Group size:	2 donors – 3 replicates
Method:	Flow-through diffusion cells
Test substance:	Retinol
Batch:	No data
Purity:	>99%
Test item:	Hydroalcoholic gel or oil in water emulsion containing 0.3% [^{3}H]-retinol (specific activity: 47 Ci/mmol, radiochemical/chemical) corresponding to about 0.7 µCi/cell
Dose applied:	2 mg/cm²
Exposed area:	0.64 cm²
Exposure time:	24h
Sampling:	6-h fractions for a total of 24 or 72 h
Receptor fluid:	Hanks' balanced salt solution (HBSS) plus 4% bovine serum albumin plus 0.001 % butylhydroxytoluene (BHT)
Tape stipping:	Yes (10 times)
Method of Analysis:	Liquid scintillation counting
GLP:	Not in compliance
Study period:	/

Retinol was tested *in vitro* for dermal permeation by means of either a gel or oil-in-water emulsion with a content of 0.3% [^{3}H]-retinol. Freshly biopsied human skin from abdominal surgery of 2 volunteers was used. The subcutaneous fat was removed and the skin was cleaned with a 10% soap solution and thoroughly rinsed with distilled water. A split-thickness layer (200-320 µm) was prepared with a dermatome. Discs of dermatomed skin were obtained and mounted on the flow-through diffusion cell (exposed surface area, 0.64 cm²). The receptor fluid was HBSS + 4% bovine serum albumin + 0.001% BHT (pH 7.4). The flow rate of the receptor fluid was approximately 1.5 mL/h. The skin surface temperature was maintained at 32 °C by circulating 35 °C water through the diffusion cell holding block. The retinol dose (2 mg/cm² application amount) was applied to each diffusion cell for 24 h, and then washed off to remove any unabsorbed material. A fraction collector was used to collect receptor fluid as 6-h fractions for a total of 24 or 72 h. At the end of the study (24 or 72 h), the skin was removed from the diffusion cell and the amount of retinol remaining in the skin was determined. Skin discs were tape stripped ten times to remove the *stratum corneum*. Each tape strip was placed into a scintillation vial. Skin discs containing the viable epidermis/dermis were then frozen for later analysis. Skin discs were thawed and homogenized on ice and dissolved. The viable skin content was determined from the amount of radioactivity in the skin homogenate by liquid scintillation counting.

Results

The vast majority of the applied [3H]-retinol, applied either as hydro-alcoholic gel or as oil-in water emulsion was washed off after 24 h of exposure. The labelled [3H]-retinol penetrated into and through the human skin. The recovery rates were in an acceptable range of 87 – 96%. The amount absorbed into the receptor fluid at 24-h was 0.3% of the applied dose for the gel vehicle and 1.3% for the emulsion. The major portion of the penetrated amount was related to the *stratum corneum* (SC) and amounted between 3.5–5.9% for the gel and emulsion at 24-h. At that time, the total amount in the SC and viable skin was 5.7% of the applied dose for the gel and 8.9% for the emulsion. There was an increase in retinol absorbed in the receptor fluid with the gel and emulsion vehicles, when data from 72 h was compared to those from 24 h. The details are provided in the following Table:

Table 3 *In vitro* percutaneous absorption of [^{3}H]-retinol in human (means of 2 volunteers with each 3 replicates) skin using gel and oil-in-water emulsion vehicles after exposure of 24-h and determination after 24-h and 72-h

Recovery site	24h – gel (%)	72h – gel (%)	24h – emulsion (%)	72h – emulsion (%)
Receptor fluid	0.3 +/- 0.1	0.5 +/- 0.01	1.3 +/- 0.1	2.2 +/- 0.2
Stratum Corneum (SC)	3.5 +/- 0.4	2.8 +/- 0.8	5.9 +/- 1.4	4.8 +/- 0.8
Viable skin	2.1 +/- 1.2	1.0 +/- 0.1	3.0 +/- 0.6	2.9 +/- 0.6
Total amount in SC and viable skin	5.7 +/- 0.8	3.8 +/- 0.7	8.9 +/- 2.0	7.8 +/- 1.4
Bioavailable portion (viable skin, receptor fluid)	2.4	1.5	4.3	5.1
Recovery	87.3 +/- 6.3	95.9 +/- 0.2	94.8 +/- 2.6	96.3 +/- 5.3

Conclusion

The exposure of freshly biopsied human skin *in vitro* to cosmetic preparations in the form of either a hydro-alcoholic gel or oil-in water emulsions containing 0.3% [^{3}H]-retinol for 24 h showed that the majority of the test substance was washed off and the major portion was attached to the SC. Only small amounts remained in the viable skin (epidermis/dermis) or receptor fluid. The portion penetrated into the skin of human (SC, viable skin) amounted to 5.7% or 8.9% after 24 hours with values of 3.8% and 7.8% after 72 hours for the gel or emulsion, respectively.

The bioavailable portion amounted to 2.4% or 4.3% after 24 hours with values of 1.5% and 5.1% after 72 hours of the applied dose level for the gel or emulsion, respectively under the study conditions.

Reference: 168

SCCS conclusion
For the calculation of the MoS, in SCCS/1576/16 the SCCS used the study from Yourick *et al.* 2008 (Reference: 168) described above for dermal penetration. As in this study, standard errors (SEM) were provided instead of Standard Deviation (SD), SDs were calculated by SCCS as follows: 2 donors were used with 3 replicates per donor which results in a total number of samples (n) of 6. With viable skin penetration of 3.0 ± 0.6 % and receptor fluid penetration of 1.3 ± 0.1 %, knowing that SEM = SD/√n, SD = SEM x $\sqrt{6}$, the resulting mean values with SD for viable skin and receptor fluid are 3.0 ± 1.5 % and 1.3 ± 0.2 %, respectively. This yields a dermal absorption of 4.3 ± 1.7 %.

For the MoS calculation, because the number of donors was not according to the SCCS requirements, mean + 2SD were used, i.e. a dermal absorption percentage of 7.7 %.

3.2.3 Other studies on toxicokinetics

The pharmacokinetics of orally and dermally administered retinol, retinyl acetate and retinyl palmitate were assessed in the previous opinion. Only general information on toxicokinetics are described below.

3.2.3.1 Toxicokinetics in laboratory animals

/

3.2.3.2. Toxicokinetics in humans

Vitamin A status is best expressed in terms of total body store of retinol (i.e. as free retinol and retinyl esters) or, alternatively, as liver concentration of the vitamin. A concentration of 20µg retinol/g liver (0.07 µmol/g) in adults represents a level assumed to maintain adequate plasma retinol concentration, to prevent clinical signs of deficiency and to provide adequate stores.

In human studies, there is no evidence that topically applied retinol or retinoid metabolites induce detectable changes in their constitutive plasma levels.

Absorption, metabolism, distribution and metabolism of vitamin A are summarised here below.

Absorption

Vitamin A is readily absorbed from the intestines as retinyl esters and depends on bile and fat for optimal absorption. Retinol is the form of vitamin A that is absorbed into the intestinal mucosal cells. The absorption of retinol is around 80%. The retinyl esters are hydrolysed to retinol in the intestinal lumen by the action of pancreatic triglyceride lipase and intestinal phospholipase B. In the intestinal mucosa, retinol is re-esterified and incorporated into chylomicra. The retinyl esters in chylomicra are then transported into the blood stream and broken by serum lipases, resulting in the release of retinyl esters. Retinyl esters are stored in the liver.

Metabolism

Retinoid metabolism is complex and involves many different retinoid forms, including retinyl esters, retinal, retinoic acid and oxidized and conjugated metabolites of both retinol and

retinoic acid. In addition, retinoid metabolism involves carrier proteins and enzymes that are specific to retinoid metabolism, as well as other proteins, which may be related to triglyceride and/or cholesterol metabolism (Reference: 40).

Retinol is oxidised to retinaldehyde (retinal) by cytosolic and microsomal retinol dehydrogenases (member of alcohol dehydrogenase (ADH) families). These ADHs oxidize all-trans retinol to all-trans retinaldehyde. Retinal is oxidised irreversibly to retinoic acid through the action of the enzyme, retinaldehyde dehydrogenase. Retinoic acid is then metabolised by CYP2A6 to oxidative metabolites (Figure1).
In the liver, vitamin A can be conjugated with glucuronic acid or taurine.

Reference: 40

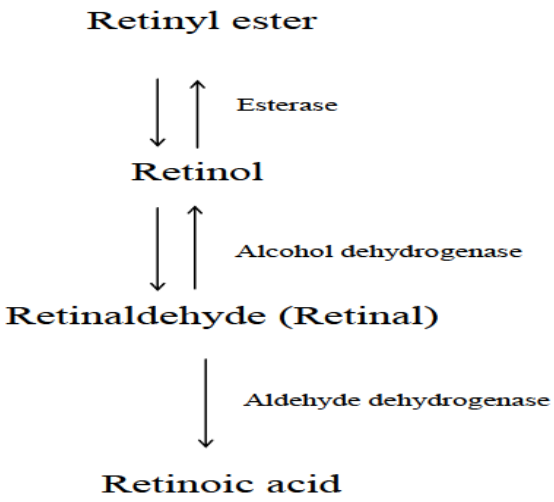


Figure 1: Metabolism of retinyl esters to retinoic acid

Distribution

In plasma, retinol circulates bound to retinol-binding protein (RBP or RBP4; molecular weight - MW -, 24 kDa), the specific vitamin A carrier protein synthetised mainly by the liver, which in turn forms a high MW complex with transthyretin (TTR, 55 kDa). In some tissues, retinol-bound RBP (holo-RBP) is specifically recognised by a receptor stimulated by retinoic acid 6 (STRA6), which transports retinol into cells. Upon delivery of retinol, RBP dissociates from TTR (becoming apo-RBP) and is rapidly eliminated by glomerular filtration followed by reabsorption and catabolism in renal tubules. The highly specific interaction between RBP and STRA6 ensures that retinol be delivered only to cells that have a means to store it, which prevents excessive uptake and random diffusion of retinol. Under fasting conditions, more than 95% of retinol in the circulation is bound to RBP (holo-RBP). Under non-fasting conditions, by contrast, approximately one third of the dietary retinoid is delivered as bound chylomicrons (i.e. as retinyl esters) and their remnants to tissues other than the liver. It has been established that about 25% of postprandial retinyl is taken up by extra-hepatic tissues, including white adipose tissue, skeletal muscle, heart, lungs, and kidneys. In the postprandial state, chylomicron retinyl ester is elevated in plasma and can quantitatively predominate over retinol-RBP.
A concentration of 20µg retinol/g liver (0.07 µmol/g) in adults represents a level assumed to maintain adequate plasma retinol concentration, to prevent clinical signs of deficiency and to provide adequate stores.

According to the adequate plasma retinol concentration, it has been estimated that approximately 50% to 85% of the total body retinol is stored in the liver. Retinol returning to the liver is re-esterified before storage in the form of retinyl esters in hepatic cells.

Excretion

The excretion of vitamin A metabolites has been reported to be about 60% in urine and 40% in faeces. The amount of excreted vitamin A compounds in bile increases if the level of vitamin A in liver exceeds a critical concentration, depending of several factors e.g. genetics factor, nutritional status.

SCCS comments
While many advances have been made in understanding the metabolism of retinol absorbed by the oral route, little is known about the metabolic fate of retinol or retinoids after skin absorption. It has also been established that the skin can metabolise retinoids and synthesise cellular retinol-binding protein (RBP), meaning that the skin has some storage capacity for retinol. By contrast, there is a complete lack of data regarding the distribution of absorbed retinol and, importantly, regarding the proportion of absorbed retinol that is not taken by the RBP-dependent transport and storage pathways.

3.2.4 Calculation of SED/LED

3.2.4.1 General approach

In its Opinion SCCS/1576/2016, the SCCS had used an upper bound deterministic approach to calculate exposure to vitamin A (retinol, retinyl palmitate and retinyl acetate) in body lotion, hand cream, face cream and rinse-off products. It has also provided an upper bound deterministic aggregate exposure to vitamin A in cosmetics with the assumptions that all cosmetic products contain maximum concentrations and are all used at the same time.

For this revision, a probabilistic assessment is considered that was submitted to the SCCS in 2020. This refinement of the exposure calculation is based on habits and practices data (e.g. of the Kantar World Panel www.kantarworldpanel.com) as implemented in the commercial software tool "Creme Care & Cosmetics model" (Comiskey *et al.*, 2015, 2017; Safford *et al.*, 2015, 2017). Two Tiers were presented that are described as follows:

Tier 1: In this scenario, the maximum concentrations defined by the SCCS are used and the refinement is achieved using real habits and practices from European consumers available in the Kantar World Panel dataset. It is assumed that vitamin A is present in 100% of cosmetic products, which represents an overestimation in exposure to vitamin A.

Tier 2: In this scenario, the maximum concentrations defined by the SCCS are used and the refinement is achieved using real habits and practices from European consumers, as well as occurrence data for vitamin A, derived from the Mintel database. The presence probability was rounded up to 10% for each product type to account for any remaining uncertainties in the approach. In the opinion of the Applicant, this is still a conservative approach, as most of the values for the probability of inclusion are well below 10% according to the Mintel dataset.

To determine total aggregate exposure to vitamin A, this study also included an assessment of exposure to vitamin A from the diet. The model used to calculate dietary exposures is Creme Global's Nutrition probabilistic model, which uses intake data for three European

countries namely France, The United Kingdom and The Netherlands for foods and supplements being representative for Europe. Finally, to calculate the total aggregate exposure to vitamin A from cosmetics, diet and food supplements, individual subjects were matched between the two models and their cosmetic and dietary exposures summed.

SCCS comment
In its 2016 Opinion, the SCCS had concluded that both as single products and taken together in an aggregate deterministic assessment, the cosmetic products as such are safe. However, it was pointed out that cosmetics add to the larger dietary exposure to vitamin A, which is already close to the Tolerable Upper Intake Level (UL) defined by EFSA. The submitted probabilistic assessment helps to further investigate the contribution of cosmetics to the overall exposure.

As laid down and explained in its Notes of Guidance (SCCS/1628/21), the SCCS accepts probabilistic aggregate assessments that are based on maximum concentrations in products and the assumption of 100% presence probability. This is a conservative approach that takes into account possible changes of occurrence in the future by using an upper bound approach.

Therefore, on principle the probabilistic assessment presented above as "Tier 1" could be used to refine the calculation of SED's. In the following, only this Tier is documented. The results of the "Tier 2" approach are given in Appendix 1. As described above, that approach uses present occurrences of vitamin A in cosmetics of around 10% combined with maximal vitamin A concentrations in the evaluated cosmetics.

Furthermore, since exposure to vitamin A may also occur from sources other than cosmetic products, the provided aggregate assessment with the most important other sources of vitamin A in the population – diet and food supplements – has also been evaluated.

3.2.4.2 Calculation of aggregate exposure to vitamin A in cosmetics

Model

The probabilistic assessment is performed with the Creme Care and Cosmetics Model CCCM (v1.5.2), which according to the Applicant currently covers 70 different product types and has the ability to include custom data for further types. Also, it is based on a large dataset of habits and practice data from six countries in Europe (Spain, France, Germany, Italy, Poland and Great Britain) and from the United States provided by the Kantar World Panel Usage Toiletries and Cosmetics Database. Habits and practices data are in the form of panellists' diaries and cover the period from the 4th quarter of 2014 to the 3rd quarter of 2015 inclusive. In this project only European subjects of age 18 and above were considered (27,157 subjects), which were from 6 different countries (France, Germany, Spain, Great Britain, Italy, Poland)). Every individual in the habits and practice database logged product use by the hour for 7 consecutive days. Usage events logged in the diary describe the day and time of a usage event, the product type used and the site(s) of application. If multiple products are used at the same time, these are listed in separate records. This provides detailed daily product co-use information. Statistical weightings are assigned to each subject according to the three stratifiers (country, sex and age) and reflect the number of people in the general population that are represented by the subjects and are used to account for imbalances in the actual survey sample.

For the purpose of this assessment the products listed in Table 4 were included in the exposure assessments. According to the Applicant, the CCCM nomenclature, leave-on category covers Hand Cream and Face Products (Toner/Astringent, FaceMoisturizer, EyeCream, LiquidMakeupFoundation). It is noted that the FaceMoisturizer product category in the Creme Care and Cosmetics Model covers anti-ageing creams and face masks.

Table 4 Cosmetics/Personal Care products included in the probabilistic assessment with the CCCM

Creme Care and Cosmetic Products	Creme Care and Cosmetic Category
BodyLotionMass	BodyLotion (Leave On)
BodyLotionOther	
BodyLotionPrestige	
FacialScrub	Rinse Off
FaceWash	
MakeupRemoverCreamRinseOff	
EyeMakeupRemoverCreamRinseOff	
Showergel	
Shampoo	
RinseoffConditioner	
BarSoap	
LiquidHandSoap	
Toner/Astringent	Face Products (Leave On)
FaceMoisturizer	Face Products (Leave On)
HandCream	Hand Cream (Leave On)
EyeCream	Face Products (Leave On)
LiquMakeupFoundation	Face Products (Leave On)

According to the Applicant, the Kantar survey that provides the habits and practice data does not include a record of subjects' bodyweight and height. As there was no available dataset on body measurements (bodyweight and skin surface area) for the European population that is both comprehensive and paired, a data-based simulation method was used to assign measurements to European subjects on the basis of gender and age. The method models height and weight as a bivariate distribution, and is based on national mean height and weight data (see the references of these data in Table 5).

Table 5 References for National Mean Body Weight and Height Data

Country	Age Group	Source
Spain	19 – 24	Carrascosa Lezcano *et al.* (2008)
Spain	11 – 23	López-Siguero *et al.* (2008)
Italy	11 – 95+	ExpoFacts[3]
Germany	11 – 59	Bergmann and Mensink, (1999)
Great Britain	16 – 85+	HSE[4]
France	11 – 71+	INCA2[5]
Poland	14 - 18	Klimek-Piotrowska *et al.* (2015)
USA	11 – 71+	NHANES[6]

According to the Applicant, amount per use data for each product was collected from consumer studies in the USA and UK and described in recent publications. Table 6 below lists the product types and indicates the corresponding source of amount data. From these data sources, probability distribution expressions were derived. Amount distributions describe the variability and range of amounts of each product consumed by the subjects, according to age, gender and country.

Table 6 References for amounts per use data for Creme Care & Cosmetics Model products

Product	Source
Make-up remover	Biesterbos et al. (2013b)[6]
FacialScrub	Ficheux et al. (2016)
Body lotion	Hall et al. (2007)
Liquid make-up foundation Hand cream Shampoo	Hall et al. (2011)
Bar soap Liquid hand soap	Larsen & Andersen (2006)
Face moisturizer	Loretz et al. (2005)
Showergel	Loretz et al. (2006)
Rinse-off conditioner	Loretz et al. (2008)
Toner/Astringent	RIFM
EyeCream EyeMakeupRemoverCreamRinseOff FaceWash	SCCS (2016)

SCCS comment
The SCCS assumes that by "gender" the Applicant means "biological sex". In other places the Applicant uses "sex" for denoting a stratifier.

Study population

The exposure is calculated for the model population based on a 7-day diary. According to the Applicant, the *chronic exposure* is then the average over the 7-day period, also called daily average, while the *acute exposure* is the maximum exposure within the 7-day period. For the purposes of this study, the chronic exposure was considered as the most relevant parameter for the exposure assessment with vitamin A.
Each subject has a value of exposure (for all exposure types described above), the final step is to aggregate and present the distribution of such exposures at a population level.
After the full simulation of all usage events for all subjects is completed, a given subject is either exposed or not exposed. Subjects are considered exposed if there is at least one usage event of a product containing the substance (i.e. at least one event during the 7-day period).
The population summary statistics can be computed:

- Over all subjects, exposed and not exposed (All population)
- Over exposed subjects only (exposed population)

According to the Applicant, not all subjects use cosmetic products. "All population" represents a realistic view as it includes every subject, is a relevant approach to evaluate a realistic exposure in daily life and allows a sound assessment of the aggregate exposure from different sources. For the reason given above, this report is based on chronic exposure in the "All population". Acute exposure estimates were not included into this report, nor were exposures based on the "exposed population".
Upon request of the SCCS the Applicant has specified that there are 6.4% and 8.8% users of body lotion and hand cream in the Kantar database, meaning that these percentages use the products once or more per week.

SCCS comment
The SCCS agrees that basing the exposure assessment on the entire population as has been done with "all population" may create a realistic estimate of the population exposure, provided that the model population is comparable to the assessed population.

However, the exposure estimate for assessing cosmetics products to be used in an SCCS opinion needs to be conservative enough to protect the European citizens. Therefore, the assessment should be based on the exposed population.

Regarding the Kantar database, the SCCS has serious concerns that the proportion of non-exposed and exposed individuals in this database does not match the respective proportion in the European population.

For a plausibility check the SCCS has compared the percent users for body lotion and hand cream in the unpublished commercial Kantar database with published data on frequency of use (Table 7).

Table 7: Use frequencies for body lotion and hand cream from public literature

	Kantar database, 2014/2015	**Biesterbos *et al.* (2013), Table 3**		**Manova *et al.* (2015), Figure 1**		**Ficheux *et al.* (2015), Table 2**
	users > once per week, according to the Applicant (%)	daily users NL (%)	users NL (%)	daily users CH (%)	User adult CH (%)	Users FR (%)
Body Lotion	6.4	25	75	35	70	61*
Hand cream	8.83	35	80	40	85	81

*Ficheux *et al.*, 2015 reports different kinds of body lotion, among them moisturizing milk

As shown in the table above, fractions of users in published studies are significantly higher in three European countries (France, The Netherlands, Switzerland). Since body lotion and hand cream are key contributors to exposure, the model's study population is considered too different from the assessed population to provide a realistic view.

Furthermore, in the publication of Comiskey *et al.*, 2015 which explains the basis of the Crème model, in Figure 2 e the number of users of body lotion mass and body lotion prestige are given. These are altogether 5'296 (body lotion mass alone 4'032). If the number of 36'447 individuals in the database is correct this would then amount to 14.5% (body lotion mass alone 11%). Both of the percentages are higher than the number of users claimed by the Applicant.

On the basis of these inconsistencies, the SCCS considers the presented results on the total population ("all population") not acceptable because it is not representative of the exposed European population. The SCCS will therefore use the deterministic exposure assessment presented with the last opinion for the assessment of vitamin A in cosmetic products.

Model parameterisation

According to the Applicant, concentration data used in the assessment of vitamin A retinol is detailed in Table 8. It should be noted that the concentrations used in cosmetic assessments are maximal concentration values. Dermal retention factors were provided by the vitamin A Consortium and derived from SCCS Notes of Guidance (SCCS, 2018). Ingestion and inhalation retention were disregarded given the products analysed (see Table 6).

Dermal absorption is the percentage of product that penetrates the skin. A value of 7.74% was used for all products analysed in this report. This value was provided by the vitamin A Consortium and was derived from an *in vitro* skin penetration study (mean + 2SD, Yourick *et al.* 2008) referred to in the dermal/percutaneous absorption section of the SCCS Opinion on vitamin A Retinol (SCCS (Scientific Committee on Consumer Safety), 2016).

Table 8 Parameter values used in the probabilistic assessment

Creme Product	Category	Retinol Equivalent Concentration (%)	Retention Factor	Dermal Absorption	Presence Probability %
BodyLotionMass	BodyLotion (Leave On)	0.05	1	7.74%	100
BodyLotionPrestige	BodyLotion (Leave On)	0.05	1	7.74%	100
BodyLotionOther	BodyLotion (Leave On)	0.05	1	7.74%	100
FacialScrub	Rinse Off	0.3	0.01	7.74%	100
EyeMakeupRemoverCreamRinse Off	Rinse Off	0.3	0.01	7.74%	100
Showergel	Rinse Off	0.3	0.01	7.74%	100
Shampoo	Rinse Off	0.3	0.01	7.74%	100
RinseoffConditioner	Rinse Off	0.3	0.01	7.74%	100
BarSoap	Rinse Off	0.3	0.01	7.74%	100
LiquidHandSoap	Rinse Off	0.3	0.01	7.74%	100
Toner/Astringent	Face Products (Leave On)	0.3	1	7.74%	100
FaceMoisturizer	Face Products (Leave On)	0.3	1	7.74%	100
HandCream	Hand Cream (Leave On)	0.3	1	7.74%	100
EyeCream	Face Products (Leave On)	0.3	1	7.74%	100
Liquid Makeup Foundation	Face Products (Leave On)	0.3	1	7.74%	100

Modelling results

According to the Applicant, this assessment assumes that vitamin A is always present in the products selected in this study, i.e. a presence probability of 100% for all products. For the purpose of this study, the retinol, retinyl palmitate, and retinyl acetate are expressed in retinol equivalent (RE).

Table 9 European population, exposure estimate by product category and aggregate cosmetics in µg RE/ day

Product	Min	Mean	P50	P90	P95	P97.5	Max
Body Lotion (Leave On)	0.00	7.15	0.00	0.00	34.48	107.28	843.68
Face Products (Leave On)	0.00	66.5	0.00	228.83	327.38	422.9	1327.16
Hand Cream (Leave On)	0.00	19.71	0.00	0.00	135.46	277.31	1555.48
Rinse Off	0.00	24.79	21.32	50.35	61.44	72.93	320.01
All Products	0.00	118.5	36.92	342.23	502.17	664.47	2308

SCCS comment
For the reasons presented above, the modelling results based on use habits of the "all population" sample in the Kantar database are considered not acceptable for this Opinion.

3.2.4.3 Comparison of Cosmetics contribution to Food and Food Supplements

In order to determine an aggregate exposure to retinol, retinyl acetate and retinyl palmitate from cosmetics, food and food supplements, the Applicant performed an assessment of exposure to retinol, retinyl acetate and retinyl palmitate from the diet.

Model

According to the Applicant, the model used to calculate dietary exposures is the Creme Global Nutrition probabilistic model, which uses intake data for three European countries namely France, The United Kingdom and The Netherlands for foods and supplements. These countries have been noted to have relatively high intakes of retinol/vitamin A (and having accessible raw data for analysis) and give a reasonable representation of retinol/ vitamin A intakes in the European population. Finally, in order to calculate the total aggregate exposure to vitamin A from cosmetics, diet and food supplements, individual subjects were matched between the two models and their cosmetic and dietary exposures were summed up together.

Study population

According to the Applicant, the Dutch National Food Consumption Survey (DNFCS) is a cross-sectional survey carried out from 2012 to 2016 to gain insight into the diet of children and adults aged 1 to 79 years living in the Netherlands. The consumption data was collected through two non-consecutive 24-hour dietary recalls (https://www.rivm.nl/publicaties/diet-of-dutch-results-of-first-two-years-of-dutch-national-food-consumption-survey-2012).

The National Diet and Nutrition Survey (NDNS) rolling programme for 2015 to 2016 is a continuous, cross-sectional survey. A detailed, quantitative information on the food consumption, nutrient intake and nutritional status of the general population aged 1.5 years and over living in private households in the United Kingdom (U.K.) was collected through a four-day diet diary (https://www.gov.uk/government/statistics).

The National Food Consumption Survey (INCA3) is a cross-sectional survey that was carried out in 2014-2015. Its main objectives were to update the data on food consumption and nutrient intakes of individuals aged from 0 to 79 years living in mainland France. The food consumption was collected through three non-consecutive 24h recalls (15-79 years old) or records (0-14 years old) (Dubuisson *et al.*, 2017).

According to the Applicant, subjects aged 18 years and older, that had statistical weightings, were used for the nutritional intake assessments. That is 4,313 subjects from the Netherlands, 2,723 subjects from the UK, 4,108 subjects from France. These national consumption surveys, except for France, also recorded data on dietary supplement intakes. Previous studies have shown that Scandinavian, German and Polish population recorded the highest retinol/vitamin A intakes (Jenab *et al*, 2009; Flynn *et al.*, 2009), however dietary surveys from these countries were not readily available for this type of analysis. The lowest retinol/vitamin A intakes were found in Spanish and Italian population. All three selected countries (Netherlands, UK and France) have been noted to have relatively high intakes of retinol/vitamin A (Jenab *et al.*, 2009; Flynn *et al.*, 2009) and give a reasonable representation of retinol intakes in the European population.

Parameterisation

Retention and dermal penetration factors are not relevant for foods and supplements, as they are ingested. Instead, the relevant concept is oral bioavailability - the proportion of the ingested chemical that enters the bloodstream through the intestinal tract. It has been reported that the oral bioavailability for retinol ranges between 75 and 100% (Sivakumar *et al.* 1972, West *et al.*, 1987, Bielalski *et al.* 1997, Reboul *et al.* 2013). An oral bioavailability factor of 90% was assumed for this study.

Nutritional intake assessments of the adult population (18 years and older) were stratified by gender and run using the Creme Food Data Science® model on Expert Models (McNamara *et al.* 2003). Retinol intakes were calculated in µg RE/kg bw/day and µg RE/day. For the purpose of this study, only Retinol intakes of total population were considered. Total Population indicates the cohort of interest such as an age group and consists of both subjects who consume and do not consume a food/supplement of interest.

Methodology – Combining Cosmetic and Dietary Exposure

According to the Applicant, separate exposure assessments were carried out for cosmetics/personal care products and for dietary exposure. The subjects in the cosmetics model were filtered by age (>= 18) and by country (France, UK, Germany) and the age, gender, country, and statistical weighting of each was determined. These variables were used to match subjects of the cosmetics assessment to similar subjects in the dietary assessment as follows.

1. Since the ages of subjects in the INCA survey are grouped in three bins (<45, 45-64, >64), the ages of all other subjects were similarly binned.

2. French subjects in the cosmetics assessment are matched with the INCA3 dietary survey (Dubuisson *et al.*, 2017), British cosmetics subjects are matched with NDNS survey subjects (NDNS, 2018); German cosmetics subjects were matched with the Dutch DNFCS dietary survey (DNFCS, 2012). As there were no food consumption surveys for some countries

recorded in the Creme Care and Cosmetics habits and practices database, namely Poland, Spain and Italy, these countries were excluded from the aggregation process.

3. Randomly select, with replacement, 100,000 cosmetics subjects. Selection is weighted according to the subjects' statistical weighting values.

4. Randomly assign a dietary subject within the matching gender, age, and country group to each cosmetics subject.

5. Add together the cosmetics and dietary exposures for each pair of subjects.

6. Calculate the population statistics for combined cosmetics and dietary exposure from this set of 100,000 subject pairs.

Results

Following the methodology outlined above, the results of the exposure to food and cosmetics are summarised in the Table below.

Table 10 Aggregate exposures to food and cosmetics in µg RE/day

Statistic	Aggregate food exposure	Aggregate cosmetics exposure	Aggregate food and cosmetics exposure
	µg RE/day	µg RE/day	µg RE/day
Min	0.18	0	0.18
Mean	533	119	724
Median (P50)	316	36.9	430
P95	1614	502	2367
P97.5	2440	664	3356
Max	27590	2308	32303

SCCS comment
The comparison of the probabilistic assessments (P95 for adults) of exposure to vitamin A via food and cosmetics shows that the contribution coming from cosmetics is around one third of the total aggregate exposure from food and cosmetics.

Overall SCCS comment on exposure
Since the presented probabilistic exposure calculations are based on a model population that may not be representative for the exposed population, the SCCS will use the deterministic exposure calculation from the preceding opinion for the risk assessment of vitamin A in cosmetic products.

3.3 TOXICOLOGICAL EVALUATION

This revision only relates to the exposure assessment. The relevant toxicological studies are discussed in detail in SCCS1576/16. The relevant parts in the discussion have been taken over below:

Acute toxicity

A more detailed elaboration is given in SCCS/1576/16. In experimental acute oral toxicity studies, vitamin A (retinol, retinyl palmitate, retinyl acetate) was found to be of low toxicity in laboratory animal species (LD50 values in rodents >2000 mg RE/kg bw).

The ranking of acute oral toxicity declines in the order of retinol > retinyl acetate > retinyl palmitate.

Local toxicity

A more detailed elaboration is given in SCCS/1576/16.
Considering that vitamin A in cosmetics is used in a variety of products at concentrations not exceeding 0.3% RE in hand/face creams and in other leave-on or rinse-off products, and up to 0.05% RE in body lotions, it can be concluded that there is no risk of skin or eye irritation for the consumer from these exposures to cosmetic products.

Sensitisation

A more detailed elaboration is given in SCCS/1576/16. In view of the sparse case reports on sensitisation in humans despite widespread exposure in cosmetics (see 3.3.11 Human data), the SCCS considers the risk of sensitisation to retinol, retinyl acetate and retinyl palmitate as negligible.

Repeated dose toxicity

Both acute and chronic excessive intake of vitamin A may result in hypervitaminosis A, which includes a number of systemic adverse effects. The teratogenic effect of excessive intake of vitamin A or specific retinoids is well documented in both animals and humans.

The SCCS considers that the teratogenic potential, effects on liver and local effects in the skin of vitamin A are the most critical toxicological endpoints. For assessing the systemic toxicity of vitamin A after cosmetic exposure, the SCCS considered the Tolerable Upper Intake Level (UL) for preformed vitamin A of:

- 3 000 µg RE/day (or 10 000 IU) for women of childbearing age and men. This UL also applies during pregnancy and lactation.
- 800 µg RE/day (2700 IU) for children aged 1–3 years,
- 1 100 µg RE/day (3700 IU) for children aged 4–6 years,
- 1 500 µg RE/day (5000 IU) for children aged 7–10 years,
- 2 000 µg RE/day (6700 IU) for children aged 11–14 years and
- 2 600 µg RE/day (8700 IU) for children aged 15–17 years.

To take into account more susceptible populations, such as women suffering from osteoporosis or children above 6 years old who may also be exposed to vitamin A *via* cosmetic products, the SCCS has used the value of 1500 µg RE/day (5000 IU) for the safety assessment of vitamin A in cosmetic products. This value is appropriate for women of childbearing age but also for middle-age and elderly women who may suffer decreasing bone density, as well as for men and children.
For children aged 1-3 years, the SCCS has used the value of 800 µg RE/day (2700 IU) for the safety assessment of vitamin A in cosmetic products. Application of vitamin A-containing baby skin care products such as body lotions and creams were considered by the SCCS as relevant for 1- and 3-year-old children.

For children aged 4-6 years, the SCCS has used the value of 1100 µg RE/day (3700 IU) for the safety assessment of vitamin A in cosmetic products.

Phototoxicity/photo-irritation and photosensitisation

Phototoxicity and photo sensitisation have been studied for retinyl palmitate. The results from the *in vitro* and *in vivo* studies do not indicate that retinyl palmitate has a phototoxic/ photo-irritant or a photosensitising potential. There are no clinical reports and other human data that indicate a phototoxic or photosensitising capacity of Retinol, Retinyl acetate, Retinyl palmitate, Retinyl linoleate or Retinal.
Although there are indications that topical retinyl palmitate could be photocarcinogenic in hairless mice, the ongoing scientific debate on this issue (which includes a challenge of the appropriateness of the test-vehicle used) precludes an extrapolation of these findings from the very susceptible mouse skin to human skin.

3.4 SAFETY EVALUATION (including calculation of the MoS)

This exposure calculation based on the probabilistic scenario for use of hand and face cream, body lotion, and rinse-off products (no lip products) was considered not acceptable to the SCCS. Therefore, the deterministic exposure values derived in the previous opinion will be maintained for this evaluation.

The SCCS was informed that the Applicant does not support the use of vitamin A in lip products. Based on the calculations above, exposure to vitamin A (retinol, retinyl palmitate, and retinyl acetate) *via* all cosmetic products (without lip products) may lead to daily systemic dose of 24.3 RE µg/kg bw/day or 70.94 IU /kg bw/day, which is equivalent to 4256 IU for an adult of 60 kg. This exposure could constitute up to **85%** of the UL of 5000 IU/day of vitamin A. This calculation is based on a worst-case scenario assuming that all the cosmetic products used (hand and face cream, body lotion, rinse-off products) contain vitamin A at the maximum concentrations.

Also, for children the deterministic exposure estimates provided in Opinion SCCS/1576/2016 remain valid. They are:

For children between 1 and 3 years old, assuming a body weight of 15 kg, based on the calculations in SCCS/1576/2016 exposure to vitamin A (retinol, retinyl palmitate, and retinyl acetate) *via* all cosmetic products (without lip products) may lead to daily systemic dose of 1064 IU (319 µg RE). This exposure could constitute up to **39%** of the UL of 2700 IU/day (800 µg RE) of vitamin A. This calculation is based on a worst-case scenario assuming that all the cosmetic products used (hand and face cream, body lotion, rinse-off products) contain vitamin A at the maximum concentrations.

For children between 4 and 6 years old, the same calculation will lead to lower exposure estimation to vitamin A compared to the UL of 3700 IU/day (1100 µg RE/day) for this subpopulation.

Aggregate exposure cosmetics and food
The Applicant's probabilistic assessment of exposure to vitamin A via food shows that for adults with high intake (95th percentile) the UL of 1500 µg RE/day is already exceeded with 1614 µg RE/day, see Table 10. Cosmetics and food together contribute 2367 µg RE/day in this high intake group (95th percentile), under the assumption that all cosmetic products used contain vitamin A at the maximum concentrations.

SCCS conclusion
Based on the maximum concentration of vitamin A in the cosmetic products and a skin penetration of 7.7 %, the calculated systemic exposure to vitamin A is below the Upper Limit for the targeted subpopulation (adults, including women suffering osteoporosis, and children). However, topical application of cosmetic products increases the total exposure to vitamin A (retinol and retinyl esters) including via food.

Compared to food, the contribution of vitamin A from cosmetics is lower. In this context, the German risk assessment authority BfR's Committee for cosmetic products had taken the view that the additional contribution of a substance from cosmetic products should not exceed 10% of the UL (BfR, 2012). Also, as an example, in Commission Regulation (EU) No 681/2013 it is mentioned that "The Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) recommended in its 2004 report that a maximum of 10% of the tolerable daily intake may be allocated to toys". In view of these suggestions, the SCCS considers that a contribution from cosmetic products of up to 10% could be acceptable.

When total exposure to vitamin A for the general population needs to be reduced, then the actual levels from food or other sources (e.g. supplements, cosmetics) could be considered for lowering. However, consideration of contributions of different exposure sources is a risk management issue and cannot be addressed at the level of risk assessment.

3.5 DISCUSSION

Physicochemical properties

The purity, impurities and stability tests have not been performed according to the SCCS Notes of Guidance:

- No raw analytical data has been provided regarding purity for the batches used in these studies. According to the specification sheets UV spectrophotometry was used to calculate the content of retinol, retinyl palmitate and retinyl acetate. It is unclear if the HPLC method mentioned as an article publication in Ref 75 was applied to the analysis of the batches used in toxicity testing. In addition, this article (ref. 75) does not include retinyl acetate.
- No information for the determination of impurities was provided for retinol, retinyl acetate or retinyl palmitate.
- SCCS reminds the Applicant that retinoic acid is banned in cosmetic products in the EU (Annex 2, entry 375) and therefore it should not be present in cosmetic products, with the exception of occurring as an unavoidable trace impurity for which a justified limit is provided.
- No data are available on the stability. Retinol in cosmetic products needs to be stabilised.

Exposure Assessment

Since the presented probabilistic exposure calculations are based on a model population that may not be representative for the exposed population, the SCCS has used the deterministic exposure calculation from the preceding opinion for the risk assessment of vitamin A in cosmetic products.

Dermal absorption

For the MoS calculation, because the number of donors did not meet SCCS requirements, mean + 2SD were used, i.e. a dermal absorption percentage of 7.7 %.

Toxicokinetics

While many advances have been made in understanding the metabolism of retinol absorbed by the oral route, little is known about the metabolic fate of retinol or retinoids after skin absorption. What has been established is that these lipophilic compounds are absorbed across the skin with estimated absorption rates in the range of 5-8%. It has also been established that the skin can metabolise retinoids and synthesise cellular RBP, meaning that the skin has some storage capacity for retinol. By contrast, there is a complete lack of data regarding the distribution of absorbed retinol and importantly, regarding the proportion of absorbed retinol that is not taken by the RBP-dependent transport and storage pathways.

The studies by Sass *et al.* (1996) and Nohynek *et al.* (2006) with retinol-based cosmetic products provide little insight into the fate of retinol after regular skin application.

Toxicological Evaluation

The SCCS considers that the teratogenic potential, effects on liver and local effects in the skin of vitamin A are the most critical toxicological endpoints. For assessing the systemic toxicity of vitamin A after cosmetic exposure, the SCCS has relied on the Tolerable Upper Intake Level (UL) for preformed vitamin A of:

- 3 000 µg RE/day (or 10 000 IU) for women of childbearing age and men. This UL also applies during pregnancy and lactation.
- 800 µg RE/day (2700 IU) for children aged 1–3 years,
- 1 100 µg RE/day (3700 IU) for children aged 4–6 years,
- 1 500 µg RE/day (5000 IU) for children aged 7–10 years,
- 2 000 µg RE/day (6700 IU) for children aged 11–14 years and
- 2 600 µg RE/day (8700 IU) for children aged 15–17 years.

To take into account more susceptible populations, such as women suffering from osteoporosis or children above 6 years old who may also be exposed to vitamin A *via* cosmetic products, the SCCS has used the value of 1500 µg RE/day (5000 IU/day) for the safety assessment of vitamin A in cosmetic products. This value is appropriate for women of childbearing age but also for middle-age and elderly women who may suffer decreasing bone density, as well as for men and children.
For children aged 1-3 years, the SCCS has used the value of 800 µg RE/day (2700 IU) for the safety assessment of vitamin A in cosmetic products. Application of vitamin A-containing baby skin care products such as body lotions and creams were considered by SCCS relevant for 1- and 3-year-old children.
For children aged 4-6 years, the SCCS has used the value of 1100 µg RE/day (3700 IU) for the safety assessment of vitamin A in cosmetic products.

In the *in vivo* studies cited above, no significant increase in plasma levels of retinoids could be detected after repeated applications of retinal, retinol or retinyl palmitate (Sass *et al.*, 1996; Nohynek *et al.*, 2006).

For the calculation of the MoS, the SCCs has used the study from Yourick *et al.* 2008 (Reference: 168) described above for dermal penetration. As in this study, standard errors (SEM) were provided instead of Standard Deviation (SD), SD were calculated by SCCS. Because the number of donors did not meet SCCS requirements, mean + 2SD were used

which resulted in an estimated value of 7.7 % skin penetration to be used for the calculation of the margin of safety.

SED calculations

Based on the maximum concentration of vitamin A in the cosmetic products and a skin penetration of 7.7 %, the calculated systemic exposure to vitamin A is below the Upper Limit for the dedicated subpopulation (adults, including women suffering osteoporosis, and children). However, topical application of cosmetic products increases the total exposure to vitamin A (retinol and retinyl esters).

By using a probabilistic scenario with maximum concentrations and presence probability of 100% (vitamin A present in all products used), the Applicant has demonstrated that the worst-case deterministic approach taken in SCCS/1576/2016 can be refined by using a probabilistic approach. The new upper bound contribution of cosmetics to the UL for adults is 33.5%. No probabilistic calculations were submitted for children, so that the value of 39% that was derived in SCCS/1576/2016 remains valid.

When total exposure to vitamin A for the general population needs to be reduced, then the actual levels from food or other sources (e.g. supplements, cosmetics) could be considered for lowering. However, consideration of contributions of different exposure sources is a risk management issue and cannot be addressed at the level of risk assessment.

4. CONCLUSION

1. *In light of the data provided, does the SCCS consider that the contribution of the cosmetic products among the overall/total exposure to vitamin A is of concern?*

The SCCS is of the opinion that vitamin A in cosmetics at the concentrations of 0.05% Retinol Equivalent (RE) in body lotion, and 0.3% RE for other leave-on and rinse-off products is safe.

Regarding the contribution from cosmetics to overall/total exposure, no conclusion can be drawn due to inconsistencies in the presented model calculations. However, the probabilistic assessment regarding the contribution from food and food supplements shows that the exposure to vitamin A of the most exposed consumers (5% of the total population) may already exceed the upper limit. Compared to food, the contribution of vitamin A from cosmetics is lower. However, it will add to the overall consumer exposure and this may be of concern for consumers with the highest exposure (5% of the total population) to vitamin A from food and food supplements.

2. *SCCS is invited to update accordingly opinion SCCS/1576/16 on vitamin A notably as regards, as needed, the maximum concentration limits for the different categories of cosmetic products indicated in that Opinion.*

Since cosmetics alone do not exceed the upper limit, the allocation of contributions of different exposure sources is a risk management issue and cannot be addressed at the level of risk assessment.
Therefore, it is beyond the scope of the SCCS to suggest maximum concentration limits that take into account contributions from other sources e.g. food, food supplements.

5. MINORITY OPINION

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7. GLOSSARY OF TERMS

See SCCS/1628/21, 11th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 181

8. LIST OF ABBREVIATIONS

See SCCS/1628/21, 11th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 181

9. APPENDIX 1

According to the Applicant, the presence probability of vitamin A in cosmetics products was defined by using market research data available in the Mintel database. This database is considered as valuable; no presence probability of vitamin A was observed above 10% in the Mintel GNPD data. Nevertheless, a conservative approach was taken by rounding values up to the 10% (Tozer *et al.*, 2015). The database is divided into categories such as_Face/Neck Care, Body_Care, Eye Care, etc... Using the site's search function returns the total number of products per category. Adding the ingredient names (Retinol; Retinyl Palmitate; Retinyl Acetate; Retinyl Propionate) gives the subset of those products containing RE. By determining the number of products within a product category that contain RE, relative to the total number of products, the presence probability can be derived, which in this model is interpreted as the likelihood that a cosmetic product contains RE as an ingredient. The Mintel product categories used in the search were then matched to the products used in the Tier 1 assessment and are summarised in the following Table.

Table A1: Tier 2 Presence probabilities for Mintel products matched to Creme Care & Cosmetics model products.

Creme Product	Mintel Search Term	Category	Presence Probability (%)	Presence Probability (% used in the study)
BodyLotionMass	Body lotion	BodyLotion (Leave On)	2.84	10.00
BodyLotionPrestige	Body lotion	BodyLotion (Leave On)	2.84	10.00
BodyLotionOther	Body lotion	BodyLotion (leave On)	2.84	10.00
FacialScrub	Face - Cleansers	Rinse Off	2.32	10.00
EyeMakeupRemoverCreamRinse Off	Eye - Cleansers	Rinse Off	1.46	10.00
Showergel	Showergel	Rinse Off	1.55	10.00
Shampoo	Shampoo	Rinse Off	1.19	10.00
RinseoffConditioner	Conditioner	Rinse Off	1.57	10.00
BarSoap	Bar soap	Rinse Off	0.25	10.00
LiquidHandSoap	Liquid Soap	Rinse Off	1.66	10.00
Toner/Astringent	Face/Neck Care	Face Products (Leave On)	6.28	10.00
FaceMoisturizer	Face/Neck Care	Face Products (Leave On)	6.28	10.00
HandCream	Hand/Nail Care	Hand Cream (Leave On)	5.44	10.00
EyeCream	Eye Care	Face Products (Leave On)	9.49	10.00
LiquMakeupFoundation	Face Colour Cosmetics - Foundations / Fluid Illuminators	Face Products (Leave On)	5.75	10.00

Table A2: Tier 2 assessment, 10% presence probability, European population, exposure estimate by product category and aggregate cosmetics in µg RE/ day

Category	Min	Mean	P50	P90	P95	P97.5	Max
Body lotion	0.00	0.65	0.00	0.00	0.00	0.00	359.24
Face Products (Leave on)	0.00	**6.39**	0.00	0.00	**18.01**	**89.56**	**779.46**
Hand Cream (Leave On)	0.00	1.99	0.00	0.00	0.00	0.00	1133.70
Rinse off	0.00	2.43	0.00	8.75	17.035	24.56	172.40
All products	0.00	11.05	0.00	19.72	54.73	128.36	1180.87

Table A3: Tier 2 Systemic Exposure Dose. Exposure given in µg RE/day

Scenario	CC&C Systemic Exposure Dose P95 (RE µg/day)	IU Retinol (IU/ day)	Percentage of UL (5000 IU/day) (%)
Aggregate Cosmetics	54.73	182	3.65
Aggregate Food	1614.00	5380	108
Aggrgate Food + Cosmetics	1615.00	5383	108