Scientific Committee on Consumer Safety

SCCS

OPINION ON

the inhalation toxicity of the fragrance ingredient Acetylated Vetiver Oil – AVO

(CAS No 84082-84-8, EC No 282-031-1)

in sprayable cosmetic products

- Submission IV -

The SCCS adopted this Opinion
during the plenary meeting on 25 October 2024

ACKNOWLEDGMENTS

Members of the Working Group are acknowledged for their valuable contribution to this Opinion. The members of the Working Group are:

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This Opinion has been subject to a commenting period of 8 weeks after its publication (from 28 February 2024 to 3 May 2024). Comments received during this period were considered by the SCCS. For this Opinion, main changes occurred in the following sections: 3.1.1.4 SCCS comment, 3.3.11.1, 3.4, and inhalation exposure discussion section. Additional calculations have been updated. Exposure model: the SCCS Opinion provides the information now separately for each product, together with the Table. References/ numbering of Tables have been revised accordingly.

All Declarations of Working Group members are available on the following webpage:
http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm

1. ABSTRACT

The SCCS concludes the following:

(1) In light of the data provided concerning inhalation toxicity, does the SCCS consider Acetylated Vetiver Oil (AVO) safe when used in sprayable cosmetic products with intended maximum concentrations (IMCs) of 0.9% (w/w) in fragrance pump sprays, 0.05% (w/w) in deodorant sprays and 0.1% (w/w) in hairsprays and body lotion sprays?

Having considered the data provided concerning inhalation toxicity and aggregate exposure, the SCCS considers Acetylated Vetiver Oil (AVO) (with 1% alpha-tocopherol) safe when used at the intended maximum concentrations (IMCs) of 0.9% (w/w) in fragrance pump sprays, 0.05% (w/w) in deodorant sprays and 0.1% (w/w) in hairsprays and body lotion sprays. The findings of an *in vitro* study using Mucilair™ also support this conclusion.

(2) Does the SCCS have any further scientific concerns regarding the use of Acetylated Vetiver Oil (AVO) in cosmetic products?

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Keywords: SCCS, scientific opinion, Acetylated Vetiver Oil (AVO), Regulation 1223/2009, Acetylated Vetiver oil – AVO, CAS No 84082-84-8, EC No 282-031-1, SCCS/1663/24

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Vetiver oil is produced for the fragrance industry by distillation of fresh or dried roots of Vetiveria (Chrysopogon) zizanioides originating from different geographical areas. The Vetiver oil is subject to further processing to obtain Acetylated Vetiver oil – AVO (CAS No 84082-84-8, EC No 282-031-1).

In June 2019, the Scientific Committee on Consumer Safety (SCCS) adopted a corrigendum to its opinion on Acetylated Vetiver Oil – AVO (SCCS/1599/18)[1]. More specifically, the SCCS considered the use of Acetylated Vetiver Oil with 1% alpha-tocopherol as a fragrance ingredient in cosmetic leave-on and rinse-off type products as safe (at the concentrations proposed by IFRA). However, the SCCS noted that '*Inhalation toxicity of Acetylated Vetiver Oil (AVO) was not assessed in this Opinion because no data were provided. Assessment of the inhalation risk would be needed if AVO was intended to be used in sprayable products*'.

On 31 March 2023, industry submitted a new safety dossier focusing on the inhalation toxicity of AVO in sprayable cosmetic products to address the SCCS concerns. According to industry, typical cosmetic applications of AVO that may lead to inhalation exposure include fine fragrance pump sprays, deodorant sprays, hairsprays, and body lotion sprays with Intended Maximum Concentrations (IMCs) of AVO being up to 0.9% (w/w) in fine fragrance sprays, 0.05% (w/w) in deodorant sprays and 0.1% (w/w) in hairsprays and body lotion sprays. The Commission requests the SCCS to carry out a safety assessment of AVO in sprayable cosmetic products in view of the new information provided for inhalation toxicity.

Terms of reference

(1) In light of the data provided concerning inhalation toxicity, does the SCCS consider Acetylated Vetiver Oil (AVO) safe when used in sprayable cosmetic products with intended maximum concentrations (IMCs) of 0.9% (w/w) in fragrance pump sprays, 0.05% (w/w) in deodorant sprays and 0.1% (w/w) in hairsprays and body lotion sprays?

(2) Does the SCCS have any further scientific concerns regarding the use of Acetylated Vetiver Oil (AVO) in cosmetic products?

[1] https://health.ec.europa.eu/system/files/2021-08/sccs_o_221_0.pdf

3. OPINION

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

Vetiveryl acetate or Acetylated Vetiver Oil (AVO) is the commonly used name to refer to a complex natural substance. The starting material, Vetiver oil, is a UVCB substance (Unknown or Variable composition, Complex reaction products or Biological materials). The oil is then subjected to further processing.

A) repeated distillation (rectification) to yield 'Vetiverol' (Vetiver oil fraction rich in sesquiterpene alcohols), which is then followed by acetylation, purification and rectification,
B) acetylation (the generally applied method requiring acetic anhydride and phosphoric acid as process materials plus a temperature of 100–120 °C) to yield raw Acetylated Vetiver oil, which is then purified by neutralisation, washing steps and rectification(s)

Previously, a third manufacturing process was also used:

C) extraction of Vetiver alcohols using boric acid or phthalic anhydride to yield Vetiverol alcohols, followed by acetylation and rectification.

IFRA Standard (44th Amendment) describes the principles of three methods for the acetylation of Vetiver Oil.

3.1.1.1 Primary name and/or INCI name

Acetylated Vetiver Oil (AVO)
INCI name: Not applicable (mixture of many constituents, see 3.1.4)

3.1.1.2 Chemical names

SCCS comment (from SCCS/1599/18)
According to the Applicant, 'Vetiveryl acetate' would be better described as AVO. A description of the production method used by fragrance industry was provided, according to which Vetiver oil is produced by distillation of fresh or dried roots of Vetiveria (Chrysopogen) zizanoides originating from various geographical areas as a UVCB substance (Unknown or Variable composition, Complex reaction products or Biological materials). The oil is then subjected to further processing (see 3.1.1 above).

According to the Applicant, the final product from both processes is Acetylated Vetiver Oil (AVO), which is described by the fragrance industry using the following identifiers:

- Vetiveria zizanioides, ext, acetylated CAS number 84082-84-8, EINECS number 282-031-1
- Oils, vetiver, acetylated CAS number 68917-34-0

3.1.1.3 Trade names and abbreviations

Acetylated Vetiver Oil (AVO)

As for Submission II, the Applicant has agreed to use CAS 84082-84-8 to represent the product in Europe that is associated with the name Acetylated Vetiver Oil (AVO).

Vetiver acetate

Vetivert acetate
Vetyvenyl acetate
Vetiverol acetate, dist, CAS number 73246-97-6
Vetiveryl acetate CAS number 117-98-6
Vetiveria zizanioides, ext., acetylated, CAS number 84082-84-8, EINECS number 282-031-1
Acetyver
Vetiveryl acetate 112 Extra Aetivenol
Oils, vetiver, acetylated, CAS number 68917-34-0

In the text of the Opinion, Acetylated Vetiver Oil (AVO) associated with CAS 84082-84-8 registered under REACH has always been used. Other related CAS numbers, *e.g.* 62563-80-8, 68917-34-0, and 73246-97-6, were used to describe the exact same material in other regions of the world.

Ref. 33 and 36

3.1.1.4 CAS / EC number

Acetylated Vetiver Oil - AVO
Vetiveria zizanioides root extract acetylated
CAS 84082-84-8
EINECS: 282-031-1

CAS: 62563-80-8
EINECS: 263-597-9

CAS: 68917-34-0

CAS: 73246-97-6

SCCS comment (from SCCS/1599/18)
The Applicant agreed that the available CAS numbers for substances derived from natural sources such as Acetylated Vetiver Oil (AVO) is highly confusing, and that registrations within the Chemical Abstract Survey register relate to global differences in requirements for assigning specificity around UVCB regarding plant sections in certain regions of the world, such as the USA.

According to the Applicant, in the EU, at least two CAS numbers for Acetylated Vetiver Oil (AVO) exist:

CAS number 84082-84-8, Vetiveria zizanioides, ext. acetylated, EINECS nr 282-031-1.

CAS number 62563-80-8 Vetiverol acetate, EINECS nr 263-597-9
According to the Applicant, the SCCS remark on the IFRA Standard would be taken into consideration updating the upcoming 48th Amendment but the global scope of IFRA regulations for the fragrance industry necessitated the inclusion of CAS numbers for Acetylated Vetiver Oil (AVO) from other regions of the world besides the EU. For the sake of relevance to this particular EU situation, however, the Applicant would only refer to the EU CAS number 84082-84-8 Vetiveria zizanioides ext. acetylated for this dossier. The Applicant also agreed that the CAS number 117-98-6 refers to a specific chemical (2,6-Dimethyl-9-isopropylidenbicyclo (5.3.0) dec-2-en-4-yl-acetate) and not to Acetylated Vetiver Oil (AVO) (as supported by the fragrance industry for this dossier) and would agree to remove this CAS number from the dossier. According to the Applicant, this referred to database information that the Applicant can no longer access but it is superseded by the information presented in the response above.

It was also noted by the SCCS that the test substances used in different toxicological studies had been described in terms of more than one CAS number. These included CAS 84082-84-8, 68917-34-0, 62563-80-8 and 117-98-6.
Two of the CAS numbers (62563-80-8 and 117-98-6) have been associated with Vetiveryl acetate/vetiverol acetate with the IUPAC name 1,2,3,3a,4,5,6,8a-octahydro-2-isopropylidene-4,8-dimethylazulen-6-yl acetate. (CosIng database: https://ec.europa.eu/growth/tools-databases/cosing/details/41524) EChA Substance Information: https://echa.europa.eu/substance-information/-/substanceinfo/100.003.842).

The Applicant explained that different CAS numbers had been incorrectly used in the past to describe the same commercial fragrance material, *i.e*. Acetylated Vetiver Oil (AVO), for which a single CAS 84082-84-8 is now proposed and used by the industry. The Applicant also confirmed that all the tests presented in Submission II Dossier of 11 June 2013 (Ref 1) had been conducted on Acetylated Vetiver Oil (AVO), and although some reports stated Vetiveryl acetate (CAS 117-98-6), the test article used in the studies was in fact what is now known as Acetylated Vetiver Oil (AVO) (CAS 84082-84-8).

Based on the Applicant's explanation, the SCCS is willing to accept that the studies referring to CAS 117-98-6 can be regarded as applicable to the Acetylated Vetiver Oil (AVO) (acetylated extract of Vetiveria zizanoides, CAS 84082-84-8) for the purpose of this assessment. However, the SCCS is also aware of the limitations placed by the GLP system on making any corrections/additions to a final report in the form of amendments which also need to be signed and dated by the Study Director. The SCCS considers it to be the sole responsibility of the Applicant to clarify/amend the CAS number in the study reports through relevant institutions/authorities. The SCCS also advises the Applicant to get the relevant CosIng entries amended so that the material in question is correctly defined in terms of a single identifiable CAS number.

3.1.1.5 Structural formula

SCCS comment (from SCCS/1599/18)
According to the Applicant, supply of structural formulas for AVO, being a complex natural substance, is not appropriate. However, structural information is supplied where available for the 129 constituents of AVO recorded during an analysis in 2015 (Ref. 19 and 3.1.4 below).

3.1.1.6 Empirical formula

SCCS comment (from SCCS/1599/18)
According to the Applicant, this will be addressed in the next Amendment to the IFRA Standard. It is not possible to provide an empirical formula for a complex natural substance like Acetylated Vetiver Oil (AVO). In this respect, reference is made to the Industry dossier (mixture of many constituents, see 3.1.4).

3.1.2 Physical form

Almost colourless or pale-straw coloured, sometimes pale-olive green, slightly viscous liquid. Sweet and dry, fresh-woody and exceptionally tenacious odour. Poorer grades display conspicuous notes of vetiver oil (green earthy, rooty notes etc.)

Ref. 1

3.1.3 Molecular weight

Not applicable (mixture of many constituents, see 3.1.4)

3.1.4 Purity, composition and substance codes

SCCS comment (from SCCS/1599/18)
The Applicant provided an overview of constituents from an analysis of Acetylated Vetiver Oil (AVO) dating from 2015 (Table 1). In addition, full details of constituents identified during analyses of AVO conducted in 2007 and 2015 were provided separately.

Ref: 2

Table 1: Constituents of Acetylated Vetiver Oil (AVO)

Percentage of constituents				
		Average %	Max %	Min %
Acetate (AC)	AC°	65.41	89.75	42.06
	AC identified*	49.20	71.46	31.34
Sesquiterpene (SQ)	SQ°	13.94	38.51	0.00
	SQ identified*	12.05	32.21	0.00
Ketone (KT)	KT°	16.80	24.89	7.85
	KT identified*	12.63	19.85	5.03
Aldehyde (RCHO)	RCHO°	1.39	2.87	0.00
	RCHO identified*	1.05	2.87	0.00
Alcohol (ROH)	ROH°	0.01	0.13	0.00
	Constituents identified*	74.93		
	Chemical class identified°	97.55		

Eighteen representative samples of AVO were analysed in 2015. The samples were manufactured by processing of AVO from Haiti, Java, Madagascar, Indonesia and Brazil and represented Process A (2 samples) and Process B (16 samples). Sample analysis was performed via GC-MS.

A multi-constituent substance has, as a general rule in accordance with Regulation EC 1907/2006 (REACH), a composition in which several main constituents are present at a concentration ≥ 10 % (w/w) and < 80 % (w/w). It is considered normal by the Applicant for

constituents present at ≥ 1% to be specified, together with any known impurities present at lower concentration that contribute to the Classification and Labelling according to Regulation EC 1272/2008 (CLP) of the material.
Each of the 129 listed constituents has a determined concentration range, 97.55 % of AVO composition is known in terms of chemical class, and 74.93 % of AVO constituents have been identified.
According to the Applicant, consideration of minimum, maximum and percentage range values relating to the 18 samples analysed in 2015, plus ECHA guidance on REACH registration, leads to the conclusion that it is correct to consider the AVO submitted for analysis as one multi-constituent substance, *i.e.* geographical origin of the AVO and use of production processes A or B do not affect the range of constituents present. A total of 22 constituents were listed as present at an average concentration ≥ 1 % during the 2015 analytical procedure (Table 2).

Table 2: Constituents of Acetylated Vetiver Oil (AVO) present at ≥ 1 % in 2015

ID	Constituent	Class	Av %	Min %	Max %
97	Khusimyl acetate	Acetate	13.99	9.57	24.01
105	(E)-Isovalencenyl acetate	Acetate	13.84	1.81	24.29
94	Vetiselinenyl acetate	Acetate	6.99	2.89	11.98
89	beta-Vetivone	Ketone	4.78	3.20	6.58
37	beta-Vetivenene	Sesquiterpene	2.99	0.00	8.52
83	Khusian-2-yl acetate	Acetate	2.90	2.10	4.29
82	Cyclocopacamphanyl acetate B	Acetate	2.69	1.75	3.98
95	alpha-Vetivone	Ketone	2.42	0.00	4.87
86	Ziza-6(13)-en-3a-yl acetate	Acetate	2.29	1.78	3.32
78	Ester SQ m/z 159(100), 91(40), 105(40), 131(35), 187(35), 202(30), 262(5)	Acetate	2.09	1.10	7.97
79	Cyclocopacamphanyl acetate A	Acetate	1.99	1.31	3.26
98	Unknown structure MW 262 & 264	Acetate	1.89	1.34	2.91
52	Unknown mixture MW 200, 202	Ketone	1.66	0.00	4.08
93	Isokhusimyl acetate	Acetate	1.58	0.00	5.20
58	13-nor-7,8-Epoxyeremophil-1(10)en- 11-one	Ketone	1.55	0.00	4.25
92	Unknown structure m/z 159(100), 218(20), 202(20)	Ketone	1.30	0.00	2.52
103	Unknown structure MW 262 m/z 187(100), 202(90)	Acetate	1.29	0.00	4.03
81	Ester SQ m/z 187(100), 159(70), 105(30), 174(30), 202(30)	Acetate	1.11	0.00	4.77
108	Unknown structure 218(100), 203(60),	Acetate	1.10	0.00	5.17
60	Unknown / Mixture	Unidentified	1.03	0.09	1.78
25	beta-Vetispirene	Sesquiterpene	1.00	0.00	2.79
28	delta-Amorphene	Sesquiterpene	1.00	0.00	4.11

The Applicant has concluded that the processed materials referred to collectively by the fragrance industry as AVO can be considered equivalent and should be treated as one multi-constituent substance during the discussion of the toxicological profile.
Results of the 2015 analytical procedure were compared with data from seventeen representative samples of AVO analysed during 2007. Chemical constituents were considered to be characteristic of AVO, notably the main constituents Khusimyl acetate and (E)-Isovalencenyl acetate. Although the groups of companies submitting samples of AVO for

analysis were different in 2007 and 2015, three of the samples refer to the same commercial qualities (Sample 1 and 12 used for testing of sensitisation, and 18 used for several endpoints). Expansion of the data review to include all samples from 2007 and 2015 showed twelve constituents present at an average concentration of ≥ 1% in 17 samples analysed during 2007 (Ref. 2). The same twelve constituents were present in 18 samples characterised during 2015 (Table 3).

Table 3: Comparison of Acetylated Vetiver Oil (AVO) constituents present at ≥ 1% in 2007 and 2015

ID	Constituent	Average from all	Average from all 2015
97	Khusimyl acetate	15.37	13.99
105	(E)-Isovalencenyl acetate	14.80	13.84
94	Vetiselinenyl acetate	4.44	6.99
89	beta-Vetivone	4.24	4.78
82	Cyclocopacamphanyl acetate B	4.06	2.69
79	Cyclocopacamphanyl acetate A	3.08	1.99
83	Khusian-2-yl acetate	2.29	2.90
93	Isokhusimyl acetate	2.23	1.58
37	beta-Vetivenene	1.87	2.99
101	Isonootkatyl acetate	1.71	0.40
59	Ziza-6(13)-en-3-one	1.69	0.72
95	alpha-Vetivone	1.48	2.42

In summary, following detailed analysis of the compositional data, the Applicant found no relationship between either the geographical origin of the Vetiver Oil or the order in which the acetylation and distillation process were performed and the composition of the final AVO. In common with many other substances derived from natural sources, such variations in composition are to be expected as factors such as time of harvest, soil composition in the fields and variations in weather conditions from growing season to growing season will affect the composition of the Vetiver oil used as the starting material.
Three additional qualities of AVO (no longer produced by Givaudan) have been analysed in 2007 (origins: Java, Haiti and combined origins) and compared with Givaudan's quality of AVO (Vetiveryl acetate 112 Extra) (Table 4). These qualities were all produced following "Process B", acetylation of vetiver oil and subsequent purification.

Table 4: Analysis of 17 samples of Acetylated Vetiver Oil (AVO) in 2007 compared to 2015

Substances	Vetiveryl acetate Haïti	Vetiveryl acetate Bourbon	Vetiveryl acetate Java DM	Vetiveryl acetate 112 Extra
Year of analysis	2007	2007	2007	Current quality
Sesquiterpenes	16%	10%	12%	16.04% (13.94%)
Ketones	24%	15%	21%	14.74% (16.80%)
Acetates	54%	65%	57%	65.45% (65.41%)
Unknowns	6%	10%	10%	3.77%

Ref: 2

SCCS comment (from SCCS/1599/18)
AVO is the acetylated form of a natural fragrance (vetiver oil), which is composed of around 129 constituents. Data presented by Industry (13 May 2015) (Ref 2) concerned the analysis of 18 samples of different AVO batches produced by 10 manufacturers comparing analytical data from 2007 and 2015, and shows the range of variability of the constituents of Acetylated Vetiver, considered during an extended period of time. The SCCS has considered this variation acceptable for a plant-derived material of natural origin and, on the basis of this presumption, the SCCS considered AVO as a single entity on which to base the safety assessment.

3.1.5 Impurities / accompanying contaminants

Presence of residual process chemicals was investigated during analysis of 18 samples in 2015.

According to the Applicant, Acetic anhydride, acetic acid or any other residual solvents were not detected. The post process, likely fractionation, is the main parameter which contributes to the elimination of such potential residual traces. Water content was not measured but no evidence of cyclohexane, hexane or citric acid was detected in the samples. As such, it can be concluded that residual process chemicals are absent from Acetylated Vetiver Oil (AVO) supplied to the fragrance industry.

Analytical investigations performed on 18 commercial samples were free of these impurities. Acetic anhydride, acetic acid or any other residual solvents were not detected. The post process, likely fractionation, is the main parameter which contributes to the elimination of such potential residual traces.

3.1.6 Solubility

Not applicable. (Mixture of many substances, see 3.1.4)

3.1.7 Partition coefficient (Log P_{ow})

Partition coefficients n-octanol/water of Vetiveryl Acetate 112 Extra, for the 17 compounds that had relative areas of >1%, were: logPow in the range of 2.6 to 7.1.

SCCS comment (from SCCS/1599/18)
Providing a measure of logK_{ow} for a complex multi-constituent substance such as Acetylated Vetiver Oil (AVO) is not meaningful, given the wide range of different structures and moieties. This could only result in a log Kow spanning several digits.

LogP values have been provided. However, the SCCS notes that chemical characterisation of the compounds that correspond to these seventeen logP values has not been provided.

3.1.8 Additional physical and chemical specifications

Boiling point: 285 °C
Specific gravity: 1

Ref. 5

3.1.9 Homogeneity and Stability

The stability and homogeneity of Acetylated Vetiver Oil (AVO) (batch VE00085543) in corn oil was assessed as part of the seven-day repeated dose oral (gavage) range-finding study performed prior to the full 28-day study. Homogeneity was assessed by visual inspection of the test item formulations. Stability was determined by GC analysis of the test item formulations initially and then after storage at approximately 4 °C in the dark for 23 days. The test item formulations were deemed to be homogenous by visual inspection. Results of the GC analysis are presented in Table 5 below and show the formulations to be stable for at least 23 days. It should be noted that the same batch of AVO was used in the 28-day study, where formulations were prepared twice during the treatment period and stored at approximately 4 °C in the dark.

Table 5: Results of GC analysis from seven day repeated dose oral (gavage) range- finding study

Nominal concentration (mg/mL)	Concentration found initially (mg/mL)	Concentration found after storage for 23 days	
		(mg/mL)	(expressed as % of initial)
3.75	4.098	4.812	117
250	284	288	101

Stability of the test solutions was not assessed in any of the other studies where a solvent was used. However, based on the functional groups identified in AVO, the nature of the solvents used and the short time period between preparation and use of the solutions it is expected that they would be stable.
The shelf life of AVO claimed by manufacturers varies between one and two years when stored in full, sealed containers.
Typically, product shelf-life is determined after a series of analytical investigations over the time period claimed. Samples are checked regularly following the same initial control plan used for reception/manufacture.
The main investigations concern the physicochemical and organoleptic measurements (specific gravity, refractive index, colour, odour) and GC comparison.
As an example, GC profiles from the same batch of AVO (Sample 1; not stabilised with antioxidant) measured at 0 and 14 months (a 12-month shelf-life is claimed) showed no significant change over this time period.

Ref. 6

SCCS comment (from SCCS/1599/18)
Stability data provided by the Applicant contain only raw data without any interpretation of the results. Based on the SCCS Notes of Guidance (SCCS/1647/22), more details on stability should have been provided.

3.2 FUNCTION AND USES

Acetylated Vetiver Oil (AVO), as used, is a mixture of many constituents, resulting from acetylation of crude vetiver oil. AVO is used as a fragrance in perfumes and in cosmetics.
Maximum use concentration of AVO in various types of cosmetic products is described in the following Table below (provided by the Applicant).
According to the Applicant, in Table 6 are listed the maximum concentrations they would like to defend in different cosmetic product categories. They have incorporated the product category of hydroalcoholic based fragrances/perfumes, which is of critical importance for them

but not yet part of the systemic exposure calculation table as contained in the SCCS Notes of Guidance (SCCS/1647/22) to derive the Margin of Safety.

Ref: Acetylated Vetiver Oil – Updated use levels for review by the SCCS, letter from IFRA to DG GROW – EU Commission, November 2016 (Ref. 4)

Table 6. Maximum concentrations proposed by Applicant in different cosmetic product categories.

Hydroalcoholic-based fragrances (e.g. Eau de Toilette, Perfume, Aftershave, Cologne)	0,90%
Deodorants	0,05%
Make up products (e.g. eye make-up, make-up remover, liquid foundation, mascara, eyeliner, lipstick)	0,05%
Face cream	0,10%
Hand cream	0,10%
Body lotion	0,10%
Hair styling	0,10%
Bath cleansing products (e.g. soaps, shower gel, rinse-off conditioner, shampoo)	0,20%

3.3 TOXICOLOGICAL EVALUATION

3.3.1 Acute toxicity

3.3.1.1 Acute oral toxicity

SCCS comment (from SCCS/1599/18)
The SCCS has noted the analyses of the different samples of AVO and has considered that the range of this variability can be accepted because the samples are of natural origin. Therefore, the SCCS accepts the outcome of the acute oral toxicity studies. In view of the data provided, AVO can be regarded as acutely orally nontoxic.

Ref. 7, 9 and 13

3.3.1.2 Acute dermal toxicity

SCCS overall comment on acute dermal toxicity (from SCCS/1541/14)

The study could not be evaluated by the SCCS as the submitted original report only consisted of two pages in addition to the front page. The composition of the test substance is not known to the SCCS.

Ref. 7

3.3.1.3 Acute inhalation toxicity

/

3.3.2 Irritation and corrosivity

3.3.2.1 Skin irritation

SCCS comment (from SCCS/1599/18)
The SCCS has noted the analyses of the different samples of AVO and has considered that the range of this variability is acceptable because the samples are of natural origin. Therefore, the SCCS has accepted the outcome of the irritation studies. In view of the data provided, AVO can be regarded as mildly irritating to rabbit skin. The SCCS agrees that the concentrations to be used in consumer products are not expected to carry a risk of skin irritation to the consumer.

Ref. 10, 14

3.3.2.2 Mucous membrane irritation / eye irritation

SCCS comment (from SCCS/1599/18)
The SCCS has noted the analyses of the different samples and has considered that the range of this variability can be accepted for samples of natural origin. Therefore, the SCCS has accepted the outcome of the irritation studies. In view of the data provided, AVO can be regarded as mildly irritating to the eye. The SCCS agrees that the concentrations to be used in consumer products are not expected to carry a risk of eye irritation to the consumer.

Ref. 11, 12, 15 and 17

3.3.3 Skin sensitisation

SCCS comment (from SCCS/1599/18)
The SCCS has noted the analyses of the different samples and has considered that the range of this variability is acceptable for samples of natural origin. Therefore, the SCCS has accepted the outcome of the different LLNA's that show that the EC3 value of AVO is in the range of 9.3% - 13.3%. In view of the data provided, AVO can be regarded as a moderate skin sensitiser.

Ref. 22, 23, 24 and 29

3.3.4 Toxicokinetics

/

3.3.5 Repeated dose toxicity

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

SCCS comment (from SCCS/1599/18)
The SCCS has noted the analyses of the different samples and has considered that the range of this variability can be accepted for samples of natural origin. Therefore, the SCCS has accepted the outcome of the 28-day oral toxicity study. In view of the data provided, the

SCCS confirms the evaluation performed in Submission II, which considers as adverse effects the variations of cholesterol, total protein and alanine transferase concentrations in females treated with 1000 mg/kg bw and the increase of absolute and relative liver weights identifying a NOAEL of 350 mg / kg bw for AVO.
The SCCS noted that the NOAEL value was incorrectly reported as 300 mg/kg bw in Submission II instead of 350 mg/kg bw.

Ref. 27

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

/

3.3.5.3 Chronic (> 12 months) toxicity

/

3.3.6 Reproductive toxicity

/

3.3.7 Mutagenicity / genotoxicity

3.3.7.1 Mutagenicity / genotoxicity *in vitro*

SCCS overall comment on *in vitro* mutagenicity/genotoxicity testing (from SCCS/1599/18)
Based on available data and additional explanations provided by the Applicant, the SCCS is of the following opinion:

1. Review of analytical data from 2007 and 2015 shows the constituents of AVO to be comparable over an extended period of time. As such, the composition of the 2003 test item can be considered equivalent to analytical data associated with 'Sample n' (2007) and 'Sample 18' (2015), all three samples coming from the same producer, with no intentional changes to the manufacturing process having taken place during this period.
2. AVO was tested in 4 GLP-compliant bacterial gene mutation studies with negative results (ref. 18,-19,-20,21 Submission II). The Applicant stated that another study reported in Submission II under ref. 16 showing a negative result was conducted with AVO with 1% alpha- tocopherol (TP).
3. AVO with 1% TP was tested in one GLP-compliant mammalian cells gene mutation study with negative result, which confirms the lack of gene mutation capability of AVO with 1% TP. Ref 34
4. The Applicant did not provide any micronucleus test, even though the SCCS Notes of Guidance (SCCS/1647/22) state that this would be preferrable. Although equivocal result was observed in chromosomal aberration test on CHO cells with AVO with 1% TP (Ref. 26), the chromosomal aberration test on human lymphocytes was negative (Ref. 28).
5. Based on all data provided, the SCCS considers that AVO added with 1% TP, as used in the final products, is not likely to pose a risk of mutagenicity.

3.3.7.2 Mutagenicity / genotoxicity *in vivo*

/

3.3.8 Carcinogenicity

/

3.3.9 Photo-induced toxicity

3.3.9.1 Phototoxicity / photo-irritation and photosensitisation

In vitro

The Applicant agrees that these data are of limited value and were supplied mainly for sake of completeness and to aid an overall weight-of-evidence conclusion.

SCCS comment on phototoxicity (from SCCS/1599/18)
The SCCS noted the absence of a positive control in the second *in vitro* study with reconstructed human skin but has also taken note of the internal validation with a positive control. The submitted data do not point towards phototoxicity.

Ref. 8, 31, 33

3.3.9.2 Photomutagenicity / photoclastogenicity

/

3.3.10 Human data

SCCS comment on human data (from SCCS/1599/18)
The SCCS has noted the analyses of the different samples of AVO and has considered that the range of this variability can be accepted for samples of natural origin. Therefore, the SCCS has accepted the results of the studies, indicating no sensitisation or phototoxic potential.
Furthermore, no report on phototoxicity or photosensitisation could be identified in the public literature.

Ref. 25, 30

3.3.11 Special investigations

3.3.11.1 Data from new approach methodology (NAM)

From SCCS/1599/18

3.3.11.1.1 Threshold of Toxicological Concern

Further assessment of toxicological hazard was carried out by the Applicant using *in silico* methods to provide additional supporting evidence for the safety of the identified components by dividing them into four chemical groups, which account for 93.1% of the total AVO constituents, acetates (44.2%), sesquiterpenes (32.6%), ketones (13.2%) and aldehydes (3.10%). The remaining 9 constituents represent <6% AVO. All constituents were treated as TTC Cramer Class III (worst case) using the Class III threshold value of 1.5 µg/kg/day. The Skin Absorption Model and the Skin Perm Model were used to calculate the maximum skin absorption over 24 hours exposure (worst case) for the three highest average percentage identified constituents from each of the four chemical groups. The resulting MOS for each product type alone, or when used together, indicated that the use of AVO at the intended

concentrations in different product types as proposed by the Applicant is not likely to pose a health risk to the consumer.

Ref. 3

SCCS comment (from SCCS/1599/18)
The Applicant assessed AVO components according to TTC approach. However, a higher (7.9 µg/kg/day) than agreed threshold value (1.5 µg/kg/day) was proposed by the Applicant. The SCCS did not agree to the use of the higher threshold value in accordance with the SCCS Notes of Guidance (SCCS/1647/22) and hence the TTC assessment provided by the Applicant was not taken into consideration by the SCCS.

Submission IV (March 2020)

The Applicant proposed the use of Threshold of Toxicological concern tool for local respiratory effects. In 2009, was published an exposure based waiving approach that included the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products (Ref. 37). Their evaluation resulted in a TTC for local effects upon inhalation exposure for a material belonging to either Cramer Class I (1.4 mg/day) or III (0.47 mg/day) assuming a human lung weight of 650g. In order to derive these values, a group of 92 chemicals used primarily in consumer products was evaluated for both systemic and site of contact effects. The authors established NOAECs for site contact effects and assigned a Cramer class for each chemical. Over the years other authors have also reported separate values to address inhalation TTC (Ref 38) and later publication by the same group, (Ref 39). A summary of strengths and weakness of both approaches is presented in ANNEX 1 Inhalation TTC for Local Effects: Strengths and Weaknesses. The Research Institute for Fragrance Material (RIFM) applies the values reported by Carthew et al. (2009) in the risk assessment of fragrance materials (Ref 36)), following a review and acceptance by their Expert Panel of Fragrance Safety of these values in preference to those by the other authors. In order to apply a worst-case scenario in the application of the TTC for respiratory local effects to the assessment of AVO, it is assumed that all components in AVO are of Cramer Class III structure. Therefore, the TTC value of 470 µg/d or 7.8 µg/kg/d (for 60 kg body weight) is used.

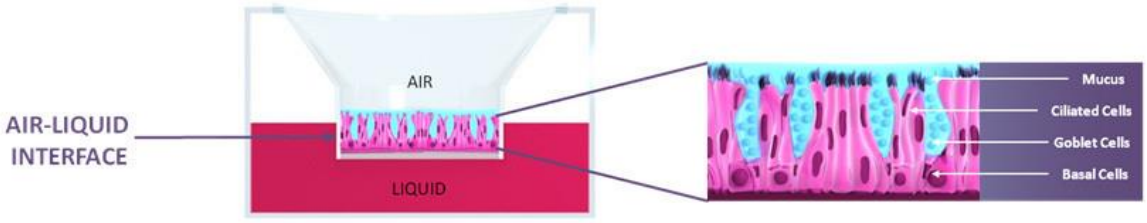
Ref 36,37,38 and 39

SCCS comment
The SCCS is of the view that the proposal is not acceptable as it is based either on an insufficiently robust dataset (92 compounds), or on the definition of thresholds NOEC values covering a very wide range from 0.001 to 100,000 ppm.

3.3.11.1.2 *In vitro* respiratory assessment.

According to the Applicant, for AVO no *in vivo* inhalation study is available, and there are no OECD approved or validated *in vitro* inhalation toxicity models available.
Based on previous SCCS Opinion, AVO has been shown to be mildly irritant or irritating to the skin and eye depending on the method used, including to rabbit eyes. In addition, it is classified as a moderate sensitiser (EC3 value of AVO is in the range of 9.3%-13.3%).
MucilAir™ is an *in vitro* cell model of the human airway epithelium cultured at the air liquid interface. It is a 3-D *in vitro* model comprising human basal, goblet and ciliated cells, represents a fully differentiated respiratory epithelium. This model reflects the upper respiratory tract (morphology and functions mirroring the tracheo-bronchial epithelium), being characterised by:

- Production of mucus
- Active cilia-beating



The model shows active ion transport, tight junctions, metabolic activity, cytokines, chemokines, metalloproteinases release.
The model does not reflect the lower respiratory tract of the lung. However, study showed a good predictive capacity of respiratory toxicity of inhaled drugs, with data showing that in vivo toxicity can be predicted in vitro by studying cell barrier integrity by transepithelial electrical resistance (TEER), and cell viability determined by the Resazurin method (88% sensitivity and 100% specificity). MucilAirTM tissues were exposed to 3 concentrations of AVO (0.1, 1 and 5%) for 6 and 24 h. SDS (1 and 2.5 mM) was used as positive control, beta-lactose (3 mg/ml) as negative control, and mineral oil as vehicle control. AVO at all concentrations did not reduce TEER or increase LDH leakage or IL-6 release compared to vehicle and untreated groups. There was a dose- and time-dependent increase in IL-8 release, which was also observed with the negative control. Histology showed some microscopic findings at 5% AVO which were absent or minimal in vehicle, negative and untreated tissues. Overall results show a minor injurious effect at the concentration of 5%. This result is consistent with the mild ocular irritation (eye irritation is believed to be closer analogue to respiratory irritation). Compared to total local inhalation exposure from sprayable products, the doses applied to the MucilAirTM is considerable higher: for the 1%, the dose applied *in vitro* (10 µl) is 330.000 higher of the expected total local inhalation exposure.

Ref. 40 and 41

SCCS comment
The SCCS has considered that AVO has a relatively low volatility, and that the respiratory exposure would mostly result from sprayed droplets that are likely to deposit in the nose, mouth and throat with a minimal exposure of the consumer's lung. Therefore, AVO used in the cosmetic sprayable products at concentrations <1% can be considered of no concern regarding local respiratory irritation.

3.4 EXPOSURE ASSESSMENT

3.4.1 General considerations

According to the Applicant, the SCCS concluded in the corrigendum to its Opinion on the fragrance ingredient Acetylated Vetiver Oil – AVO (SCCS/1599/18) dated 20-21 June 2019, that on the basis of the safety assessment carried out using a conservative approach, the use of AVO with 1% alpha-tocopherol as a fragrance ingredient in cosmetic leave-on and rinse-off type products safe at the concentrations proposed by IFRA. In the same Opinion, the SCCS also added this comment "Inhalation toxicity of Acetylated Vetiver Oil (AVO) was not assessed in this Opinion because no data were provided. Assessment of the inhalation risk would be needed if AVO was intended to be used in sprayable products." The current dossier specifically

addresses this point by presenting the inhalation safety assessment for AVO in cosmetic sprayable products.
The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation 11th revision states (SCCS/1628/21) that 'The term 'spray' or 'sprayable' means that a formulation is either dispensed by the use of propellant gas as defined in Directive 75/324 (propellant spray), or by a spray bottle with a pump dispenser that forces a liquid through a nozzle generating a spray stream or a mist of a liquid (pump spray)'. In this report, the safety assessment of AVO in typical cosmetic applications that may lead to inhalation exposure such as fine fragrance sprays, deodorant sprays, and hairsprays is addressed.

The intended maximum concentrations of AVO are 0.9% (w/w) in fragrance spray, 0.05% (w/w) in deodorant sprays, 0.1% (w/w) in hairsprays and 0.1% (w/w) in body lotion sprays.

This is an updated version of the assessment submitted by the Applicant in March 2020 (submission IV) and considers the potential systemic (through inhalation and dermal routes of exposure) and local effects (via the inhalation route only), and it demonstrates that the presence of AVO at the intended maximum concentrations in the above-mentioned products is safe to the consumer. The inhalation exposure assessment included in this dossier is based on the most recent version of the 12th SCCS Notes of Guidance (SCCS/1647/22 Corrigendum 2). The dossier has also been updated to present in vitro data from a recently completed study showing the concentrations of AVO proposed should not have significant irritancy effects on the human respiratory tract when used in sprayed products.

According to the Applicant, for AVO used in sprayable products, the potential for exposure to the respiratory tract can be via either volatilization of AVO or via inhalation of an aerosol of sprayable products that contains AVO.

Fragrance materials by their nature can volatilize, however this does not imply that such substances have high volatility. Indeed, the opposite is usually the case, a lot of fragrance substances have low volatility, so that they can generate an odour for an extended period of time. AVO has a vapour pressure in the range of 0.01-0.1 Pa (0.1 Pa at 20°C in the REACH dossier: (https://echa.europa.eu/registration-dossier/-/registered-dossier/22147/4/7) placing it amongst materials of low volatility (ECHA Guidance on Information Requirements and chemical safety assessment Chapter 15: Consumer exposure assessment Version 3.0 – _July 2019). Consequently, rapid volatilization of AVO after spraying the product is not likely to occur and respiratory exposure would mostly result from sprayed droplets. In this context, it is worth noting that smelling an ingredient should not be associated with a high volatilisation rate, as the odour threshold for fragrance ingredients is typically very low (Ref 51).

SCCS comment
With the described vapour pressure, AVO can be considered as a semi-volatile substance.

3.4.2. Choice of model and parameters

Based on the vapor pressure of AVO, inhalation exposure through excessive volatilisation is not expected. Therefore, the systemic exposure through inhalation will be performed for the sprayed fraction of finished products as below.

A systemic exposure dose (SED) from the potential for inhalation (SEDinh) from spray products can be calculated by assuming instant release of the ingredient in a defined box (1-Box model) or by applying a 2-Box model based on principles in (Ref 51). In Section 3-3.5.4.1 and Appendix 11 of the 11th Notes of Guidance (SCCS/1628/21), a deterministic approach

for 2-box modeling was presented for propellant and pump spray products according to the generic equations and associated parameters in the box below:

$SED_{inh} = (IA_1 + IA_2) \times G \times RF \times DA/BW$

Where:

SED_{inh} = Systemic Exposure Dose from the inhalation route (mg/kg/day)

IA_1 = the potential amount inhaled during the first 2 min (in mg)

$$IA_1 = (EA/V_1 \times BR \times t_1)$$

IA_2 = the potential amount inhaled during the subsequent 10-20 min (in mg)

$$IA_2 = (EA/V_2 \times BR \times t_2)$$

EA = potential amount to be inhaled:

$$EA = (A \times C \times P \times AF)/100$$

A = Amount of product by application (mg/application) (user defined or default SCCS (2021))*

C = Percentage concentration of ingredient in product (%) (user defined)*

P = Proportion of non-propellant in formulation (no units) (user defined)* or default 60% (propellant, 100% pump spray) (Bremmer *et al*., 2006)

AF = airborne fraction (no units); 1 (propellant spray); 0.2 (pump spray) (Bremmer *et al*., 2006)

V_1 = First step: near-field, 1 m^3 (SCCS, 2021)

V_2 = Second step: far-field, 10 m^3 (SCCS, 2021)

BR = breathing rate, 13 L/min (SCCS, 2021; US EPA 2011)**

t_1 = 2 min in near field (SCCS, 2021; Rothe *et al.,* 2011)

t_2 = 10-20 min in far field (SCCS, 2021; Rothe *et al.,* 2011)

G = default factor substance lung retention 0.75 (25% is exhaled) (Rothe *et al.,* 2011; SCCS, 2021)

RF = respirable fraction: propellant & pump spray specific (user defined experimental value*)

DA = Daily frequency of application (user defined* or SCCS, 2021)

BW = body weight = adult 60 kg (SCCS, 2021)

* Product-dependent parameter value

** highest median among several adult age categories

Ref 42,48

Calculation of SED_{inh} for AVO in four main spray products (hydroalcoholic fragrance spray, deodorant/antiperspirant spray, hair spray and body lotion spray) are presented in Tables 7 , 8 , 9 and 10 , respectively.

According to the Applicant, regarding the daily amount use (g/day) for fine fragrance spray, this is taken from AVO Opinion (SCCS/1599/18), that is 0.28 g/day reported as the product weight loss after use (Ref 50).

Table 7. Deterministic systemic exposure dose (SED), expressed as µg/kg/day, after inhalation exposure (SED_{inh}) to 0.9% AVO in a hydroalcoholic fragrance spray formulation

Description	Parameter	Pump spray	Unit
Amount by application*	A	280*	mg/application
Fraction of AVO in non-propellant	C	0.9	(% w/w)
Proportion of non-propellant in formulation	P	1	-
Airborne fraction	AF	0.2#	-
Potential amount to be inhaled	EA = (A x C x P x AF)/100	0.504	mg
First step: near-field, 1 m^3	V_1	1000	L
Breathing rate	BR	13	L/min
2 min in near field	t_1	2	min
Potential amount inhaled during t_1	$IA_1 = (EA/V_1 \times BR \times t_1)$	**0.013**	**mg**
Second step: far-field 10 m^3	V_2	10000	L
Breathing rate	BR	13	L/min
20 min in far-field	t_2	20 §	min
Potential amount inhaled during t_2	$IA_2 = (EA/V_2 \times BR \times t_2)$	**0.013**	**mg**
Substance availability fraction	G	0.75	-
Respirable fraction	RF	0.01 α	-
Frequency of application$	F	1	day^{-1}
Default body weight	BW	60	kg
SED_{inh}	$(IA_1+IA_2) \times G \times RF \times F/BW$	**0.0033**	**µg/kg/day**

*Based on the daily amount used reported by Ficheux and Roudot (2017) and corrected by the frequency of use. #Bremmer *et al*. (2006). § According to Rothe *et al.,* 2011, duration of inhalation exposure may be assumed to be 20 min as a worst-case conservative value - an alternative value of 10 min according to the SCCS Notes of Guidance (SCCS, 2021) could also be used. α Delmaar and Bremmer (2009). $Table 4 of the SCCS Notes of Guidance (SCCS, 2021).

Ref 50,42, 48

SCCS comment

The amount of 280 mg/application refers to the arithmetic mean for the use amounts. Therefore, the SCCS has recalculated the presented exposure with the P95 of 618 mg/application reported by Reference 50. This results in an exposure of **0.00723 µg/kg/d** to hydroalcoholic fragrance spray (pump spray).

According to the Applicant, for deodorant sprays, the amount that is used in the assessment is 6.1 g/day, described as the weight loss after use of spray by Reference 45.

Table 8. Deterministic systemic exposure dose (SED), expressed as µg/kg/day, after inhalation exposure (SEDinh) to 0.05% AVO in a deodorant/antiperspirant spray formulation

Description	Parameter	Propellant spray	Unit
Amount by application*	A	3050*	mg/application
Fraction of AVO in non-propellant	C	0.05	(% w/w)
Proportion of non-propellant in formulation	P	0.6#	-
Airborne fraction	AF	0.886**	-
Potential amount to be inhaled	EA = (A x C x P x AF)/100	0.81	mg
First step: near-field, 1 m^3	V_1	1000	L
Breathing rate	BR	13	L/min
2 min in near field	t_1	2	min
Potential amount inhaled during t_1	$IA_1 = (EA/V_1 \times BR \times t_1)$	**0.021**	**mg**
Second step: far-field 10 m^3	V_2	10000	L
Breathing rate	BR	13	L/min
20 min in far-field	t_2	20 §	min
Potential amount inhaled during t_2	$IA_2 = (EA/V_2 \times BR \times t_2)$	**0.021**	**mg**
Substance availability fraction	G	0.75	-
Respirable fraction	RF	0.2 α	-
Frequency of application$	F	2	day^{-1}
Default body weight	BW	60	kg
SED_{inh}	$(IA_1+IA_2) \times G \times RF \times F/BW$	**0.21**	**µg/kg/day**

*Based on daily amount used reported by Hall *et al.* (2007) and corrected by the frequency of use. #Bremmer *et al.* (2006). **From Table 2 in Steiling *et al.* (2012) based on 11.4% deposited. § According to Rothe *et al.* (2011), duration of inhalation exposure may be assumed to be 20 min as a worst-case conservative value - an alternative value of 10 min according to the SCCS Notes of Guidance (SCCS, 2021) could also be used. α Delmaar & Bremmer (2009). $Table 4 of the SCCS Notes of Guidance (SCCS, 2021).

Ref 45, 42. 44, 48, 49

SCCS comment

The value of 0.886 for the airborne fraction is based on an experiment (Ref 43) that derives a worst case of 11.4% product available for dermal exposure. This is therefore not a worst case for inhalation exposure, and in the absence of other data, 100% of the applied amount should be assumed to be available for inhalation. In addition, the amount of application taken by the Applicant was derived by Reference 48 for product underarm use. For its calculations, the SCCS has used instead the P95 value for underarms and torso use (7839/day, fig 4 from Reference 45. Furthermore, the Applicant has used a respirable fraction of 0.2, which the cited Reference 49 suggests for hairspray, but not for deodorant. For deodorant they suggest instead an RF of 0.9, which was used by SCCS in a recalculation. With these considerations, the resulting exposure is 1.15 µg/kg/d instead of 0.21 µg/kg/d.

According to the Applicant, regarding the daily amount of product use for hairspray, (Ref. 43) reported 6.8 g/day for hairspray (aerosol) according to Reference 43 and 3.6 g/day for hairspray (pump spray) according to Reference 47.

Table 9. Deterministic systemic exposure dose (SED), expressed as µg/kg/day, after inhalation exposure (SED_{inh}) to 0.1% AVO in hair spray formulations

Description	Parameter	Propellant spray	Pump spray	Unit
Amount by application	A	5965*	3158**	mg/application
Fraction of AVO in non-propellant	C	0.1	0.1	(% w/w)
Proportion of non-propellant in formulation	P	0.6#	1#	-
Airborne fraction#	AF	1	0.2	-
Potential amount to be inhaled	EA = (A x C x P x AF)/100	3.579	0.6316	mg
First step: near-field, 1 m^3	V_1	1000	1000	L
Breathing rate	BR	13	13	L/min
2 min in near field	t_1	2	2	min
Potential amount inhaled during t_1	$IA_1 = (EA/V_1 \times BR \times t_1)$	**0.093**	**0.016**	**mg**
Second step: far-field 10 m^3	V_2	10000	10000	L
Breathing rate	BR	13	13	L/min
20 min in far-field	t_2	20 §	20	min
Potential amount inhaled during t_2	$IA_2 = (EA/V_2 \times BR \times t_2)$	**0.093**	**0.016**	**mg**
Substance availability fraction	G	0.75	0.75	-
Respirable fraction	RF	0.2 α	0.01 α	-
Frequency of application$	F	1.14	1.14	day^{-1}
Default body weight	BW	60	60	kg
SED_{inh}	$(IA_1+IA_2) \times G \times RF \times F/BW$	**0.530**	**0.0047**	**µg/kg/day**

* Based on daily amount used reported by Steiling *et al.* (2014) and corrected by the frequency of use; **Loretz *et al.* (2006). #Bremmer *et al.* (2006). § According to Rothe *et al.* (2011), duration of inhalation exposure may be assumed to be 20 min as a worst-case conservative value - an alternative value of 10 min according to the SCCS Notes of Guidance (SCCS, 2021) could also be used. α Delmaar & Bremmer (2009). $Table 4 of the SCCS Notes of Guidance (SCCS, 2021).

Ref. 43, 47, 42, 48

SCCS comment

The use amount derived from Steiling *et al.*, 2014 (Ref 43) goes back to Bremmer *et al.*, 2006 (Ref 42), and is a P75. Therefore, for propellant spray, the SCCS has used the P95 (9890 mg/day) of Loretz *et al.*, 2006 (Ref 47) for daily use combined with a frequency of 1, which is more conservative than the P90 derived for French citizens (4900 mg/application). Neither value represents the European population but are the best proxies available. This results in an exposure value of **0.77 µg/kg/d for propellant spray**. The amount for pump spray used by the Applicant is close to a P50 derived from Loretz *et al.*, 2006 (Ref 47) (3740 mg/day). The SCCS has therefore used the P95 from Loretz *et al.*, 2006 (Ref 47) for daily use (15620

mg/day) in combination with a frequency of 1. This results in an exposure value **of 0.023 µg/kg/d for pump spray.**

According to the Applicant, for Body lotion spray, the amount used is based on the daily amount (SCCS/1647/22) and corrected by the frequency of use. Propellant spray was adjusted to yield the same 'on body' amount of 3430 mg/application.

Table 10. Deterministic systemic exposure dose (SED), expressed as µg/kg/day, after inhalation exposure (SED_{inh}) to 0.1% AVO in body lotion spray formulations

Description	Parameter	Propellant spray	Pump spray	Unit
Amount by application	A	5720*	3430*	mg/application
Fraction of AVO in non-propellant	C	0.1	0.1	(% w/w)
Proportion of non-propellant in formulation	P	0.6#	1#	-
Airborne fraction#	AF	1	0.2	-
Potential amount to be inhaled	EA = (A x C x P x AF)/100	3.4	0.69	mg
First step: near-field, 1 m^3	V_1	1000	1000	L
Breathing rate	BR	13	13	L/min
2 min in near field	t_1	2	2	min
Potential amount inhaled during t_1	$IA_1 = (EA/V_1 \times BR \times t_1)$	**0.089**	**0.018**	**mg**
Second step: far-field 10 m^3	V_2	10000	10000	L
Breathing rate	BR	13	13	L/min
20 min in far-field	t_2	20 §	20	min
Potential amount inhaled during t_2	$IA_2 = (EA/V_2 \times BR \times t_2)$	**0.089**	**0.018**	**mg**
Substance availability fraction	G	0.75	0.75	-
Respirable fraction	RF	0.2 α	0.01 α	-
Frequency of application$	F	2.28	2.28	day^{-1}
Default body weight	BW	60	60	kg
SED_{inh}	$(IA_1+IA_2) \times G \times RF \times F/BW$	**1.017**	**0.01**	**µg/kg/day**

*Based on daily amount of SCCS Notes of Guidance (SCCS, 2021) and corrected by the frequency of use. Propellant spray adjusted to yield the same 'on body' amount of 3430 mg/application. #Bremmer *et al.* (2006). § According to Rothe *et al.* (2011), duration of inhalation exposure may be assumed to be 20 min as a worst-case conservative value - an alternative value of 10 min according to the SCCS Notes of Guidance (SCCS, 2021) could also be used. α Delmaar & Bremmer (2009). $Table 4 of the SCCS Notes of Guidance 11th (SCCS, 2021).

Ref. 42, 48, 49

SCCS comment
The calculations for body lotion spray are accepted.

SCCS overall comment on exposure
The SCCS has noted that the Applicant also provided local respiratory tract exposure estimates.

3.4.4 Systemic exposure estimates (SEDs)

To evaluate the total aggregated SED to AVO, all sprayed and non-sprayed products should be considered. The aggregated SED from all dermally applied products is described in AVO Opinion (SCCS/1599/18) and shown in the Table 11 (140.1 µg/kg/day).

Table 11 . Systemic exposure dose (SED) from all non-spray products (from AVO Opinion (SCCS/1599/18)

Categories of non-spray products	Concentration of Acetate Vetiver Oil (%)	SED (µg/kg bw/day)
Fine fragrances (non-spray) (e.g. Eau de Toilette, perfume, Aftershave, Cologne)	0.90%	21.0
Deodorants (non spray)	0.05%	6.3
Make up products (e.g. eye make-up, make-up remover, liquid foundation, mascara, eyeliner, lipstick)	0.05%	4.7
Face cream	0.10%	12.8
Hand cream	0.10%	18.0
Body lotion	0.10%	65.2
Hair styling (non spray)	0.10%	3.3
Bath cleansing products (e.g. soaps, shower gel, rinse-off conditioner, shampoo)	0.20%	9
TOTAL		**140.1**

For sprayed products, this exposure includes the sum of dermal and inhaled exposure of AVO (cf. Table 11). For the assessment of dermal exposure of AVO, the assumption made in Ref 42, that 85% is retained on the skin is used in our calculations except for deodorant spray. For this product category, the experimental study conducted in Ref 44, showing that 11.4% of dose is retained on the skin, is used.

SCCS comment
The Applicant provided new calculations for consumer exposure via inhalation.
As described above, the SCCS has recalculated the inhalation exposure estimates with a more conservative 2-Box-Model and adjusted parameters as discussed above. The resulting inhalation exposure estimates are listed in Table 12.

Table 12. Inhalation exposure estimates

	Fine Fragrances	Deodorants	Hairstylings	Bodylotion spray
Weight fractions (w%)	0.9	0.05	0.1	0.1
Pump spray (µg/kg bw/d)	0.007		0.023	0.010
Propellant spray (µg/kg bw/d)		1.15	0.77	1.02

The SCCS has further applied a conservative worst-case for calculating the dermal exposure from deodorant spray, which according to Ref. 43 can be up to 23.5% deposited on the skin (instead of 11.4% reported in Table 9). The resulting dermal exposure has been estimated at 6.4 µg/kg bw /d, with this resulting in an overall dermal exposure of 140.2 µg/kg bw/d.

3.5 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS)

The SCCS applied a conservative approach to determine SED by applying a default 50% dermal absorption value as shown in Table 11 Notes of Guidance (SCCS/1647/22 Corrigendum 2).

To calculate the MOS, the deterministic aggregated systemic exposure dose for consumers was compared to the $NOAEL_{sys}$ of 58.33 mg/kg bw derived in SCCS/1559/2018.
The exposure estimates presented in the new submission only refer to selected sprayable products. However, the exposure from sprayable products needs to be aggregated with other dermally applied products. For the dermally applied products, the SCCS considers the values used in SCCS/1559/2018. The aggregation was done using either the sprayable or the non-sprayable version of a product category, whichever resulted in higher exposure estimates. The comparison of sprayable and non-sprayable products is presented in Table 13. The product form selected for aggregation is marked in bold.

Table 13 : SED calculation

Categories of products	Concentration AVO (%) (%)	SED dermal (µg/kg bw/d)	SED inhalation (µg/kg bw/d)	SED dermal+inhal (µg/kg bw/d)
Fine fragrances non-spray	**0.9**	**21**		**21.0**
Fine fragrances pump spray	0.9	17.9	0.007	17.9
Deodorants non-spray	0.05	6.3		6.35
Deodorants propellant spray	**0.05**	**6.4**	**1.15**	**7.6**
Hair styling non-spray	0.1	3.3		3.3
Hair styling propellant spray	**0.1**	**4.82**	**0.77**	**5.59**
Body lotion non-spray	**0.1**	**65.2**		**65.2**
Body lotion propellant spray	0.1	55.4	1.02	56.4

The product forms fragrance non-spray, deodorant spray, hair styling spray and body lotion non-spray, are used for the calculation of aggregate SED (by products category and route) and MOS (Table 14 below).

Table 14. Margin of Safety calculation

Categories of products	Concentration of Vetiver Oil % (w/w)	SED (µg/kg bw/d)	$NOAEL_{sys}$ (µg/kg bw/day)	MoS
fragrance non-spray	0.9	21.0	58,330	2778
deodorant sprays	0.05	7.6	58,330	7675
hairsprays	0.1	5.59	58,330	10435
Make-up products	0.05	4.7	58,330	12411
Face cream	0.1	12.8	58,330	4557
Hand Cream	0.1	18	58,330	3241
Body lotion non-spray	0.1	65.2	58,330	895
Bath cleansing*	0.2	9	58,330	6481
Aggregated SED for consumer		143.9	58,330	405

*soaps, shower gels, rinse-off conditioners, shampoo

The resulting MOS for each product types alone, or when used together, indicated that the use of AVO at the intended concentrations in different product types as proposed by the Applicant is not likely to pose a health risk to the consumer.

3.6 DISCUSSION

Physicochemical properties
AVO is the acetylated form of a natural fragrance (vetiver oil), which is composed of around 129 constituents. Data presented by Industry (13 May 2015) (Ref 2) concerned the analysis of 18 samples of different AVO batches produced by 10 manufacturers comparing analytical data from 2007 and 2015 shows that the range of variability of the constituents of Acetylated Vetiver, considered during an extended period of time, can be accepted for samples of natural origin. The SCCS has considered this variation acceptable for a plant-derived material of natural origin and, on the basis of this presumption, considered AVO as a single entity on which to assess the toxicity.

General toxicological evaluation
In view of the data provided, the SCCS confirms the evaluation performed in Submission II considering as adverse effects the variations of cholesterol, total protein and alanine transferase concentrations in females treated with 1000 mg/kg bw and the increase of absolute and relative liver weights. Based on these data, the NOAEL is set at 350 mg/kg bw.

Skin sensitisation
Based on the animal studies, AVO can be regarded as a moderate skin sensitiser. AVO did not induce skin sensitisation in human RIPT study. In the public literature there are no reports on sensitisation from AVO in humans.
Considering the results of the HRIPT study and the fact that AVO has been used for years in cosmetics without evidence of sensitising potential, it is unlikely that AVO would cause contact allergy in humans.

Inhalation exposure
As part of the submission on safety of AVO, the Applicant provided estimates for local respiratory tract exposure to address the concerns raised in the SCCS Preliminary Opinion on the use of AVO in sprayable products.
The SCCS assessed the information and recalculated the dermal exposure from the use of deodorant sprays by applying a conservative worst-case approach. The resulting dermal exposure was estimated at 6.4 µg/kg bw /d, which results in an overall dermal exposure of 140.2 µg/kg bw/d.
The SCCS also recalculated inhalation exposure with a more conservative 2-Box-Model and adjusted some of the parameters.
To evaluate the total aggregated inhalation SED to AVO, all sprayed and non-sprayed were considered. The estimated exposure from sprayable products therefore includes the sum of dermal and inhaled exposure of AVO.
As the exposure estimates show, the contribution of exposure from the inhalation route to the overall exposure to AVO is only marginal, and as a result the overall conclusions relating to safety of the proposed use of AVO remains unchanged.

Exposure assessment
Acetylated Vetiver Oil (AVO), as used, is a mixture of many constituents, resulting from acetylation of crude vetiver oil. AVO is used as a fragrance in perfumes and in cosmetics.
The SCCS applied a conservative approach to determine SED by applying a default 50% dermal absorption value. This value is used for the calculation of the MoS.
Based on the available data, the SCCS considers that an absorption value by oral route of 50% can be used in the risk assessment.
In the absence of data, 100% of the applied amount should be assumed to be available for inhalation.

Mutagenicity / genotoxicity

AVO added with 1% Alpha-tocopherol (TP) was tested in 4 GLP-compliant bacterial gene mutation studies with negative results. Additionally, AVO without Alpha-tocopherol was tested in one GLP-compliant study also with negative result. AVO added with 1% Alpha- tocopherol (TP) was tested in 1 GLP-compliant mammalian cells gene mutation study with negative result.

The Applicant did not provide any micronucleus test as preferred in the SCCS Notes of Guidance. Although equivocal result was observed in chromosomal aberration test on CHO cells with AVO added with 1% TP, the chromosomal aberration test on human lymphocytes was negative.

The concentrations of AVO intended to be used in cosmetic products are very low. Additionally, in view of the likely low bioavailability of different AVO components, the SCCS considers that AVO added with 1% TP, as used in the final products, is not likely to pose a risk of mutagenicity.

Photo-induced toxicity

The submitted data do not point towards phototoxicity. In the public literature, there are no reports on phototoxicity from AVO in humans.

4. CONCLUSION

(1) In light of the data provided concerning inhalation toxicity, does the SCCS consider Acetylated Vetiver Oil (AVO) safe when used in sprayable cosmetic products with intended maximum concentrations (IMCs) of 0.9% (w/w) in fragrance pump sprays, 0.05% (w/w) in deodorant sprays and 0.1% (w/w) in hairsprays and body lotion sprays?

Having considered the data provided concerning inhalation toxicity and aggregate exposure, the SCCS considers Acetylated Vetiver Oil (AVO) (with 1% alpha-tocopherol) safe when used at the intended maximum concentrations (IMCs) of 0.9% (w/w) in fragrance pump sprays, 0.05% (w/w) in deodorant sprays and 0.1% (w/w) in hairsprays and body lotion sprays. The findings of an *in vitro* study using Mucilair™ also support this conclusion.

(2) Does the SCCS have any further scientific concerns regarding the use of Acetylated Vetiver Oil (AVO) in cosmetic products?

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5. MINORITY OPINION

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SCCS/1674/22: SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation 12 th revision.

7. GLOSSARY OF TERMS

See SCCS/1647/22, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – Appendix 15 - from page 158.

8. LIST OF ABBREVIATIONS

See SCCS/1647/22, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – Appendix 15 - from page 158.

And the following additional Abbreviation:

AVO: Acetylated Vetiver Oil