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SCIENTIFIC OPINION

Safety and efficacy of a feed additive consisting of an essential oil derived from the flowering stems of *Salvia sclarea* L. (clary sage oil) for use in all animal species (FEFANA asbl)

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The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch

Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of an essential oil from the fresh or dried flowering stems of *Salvia sclarea* L. (clary sage oil) when used as a sensory additive in feed and in water for drinking for all animal species. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concluded that the additive under assessment is considered safe up to the maximum use level in complete feed of 15 mg/kg for veal calves (milk replacers), cattle for fattening, sheep/goats, 10 mg/kg for horses, 20 mg/kg for dogs, salmonids and ornamental fish. For the other target species, the calculated safe concentrations were 5 mg/kg for chickens for fattening, 8 mg/kg for laying hens, 7 mg/kg for turkeys for fattening, 9 mg/kg for piglets, 11 mg/kg for pigs for fattening, 14 mg/kg for sows, 13 mg/kg for dairy cows, 8 mg/kg for rabbits and 4 mg/kg for cats. These conclusions were extrapolated to other physiologically related species. For any other species, the additive is safe at 4 mg/kg complete feed. The FEEDAP Panel considered that the use level in water of clary sage oil is safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed. The use of clary sage oil in animal feed under the proposed conditions of use is safe for the consumer and the environment. Regarding user safety, the essential oil under assessment should be considered as an irritant to skin and eyes and as a dermal and respiratory sensitiser. Since the oil of the flowering stems of *S. sclarea* is recognised to flavour food and its function in feed would be essentially the same as that in food, no further demonstration of efficacy was considered necessary.

KEYWORDS

clary sage oil, flavouring compounds, linalool, linalyl acetate, *Salvia sclarea* L., sensory additives

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1 | INTRODUCTION

1.1 | Background and Terms of Reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of a feed additive shall submit an application in accordance with Article 7. In addition, Article 10(2) of that Regulation specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, within a maximum of seven years after the entry into force of this Regulation.

The European Commission received a request from Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)[2] for authorisation/re-evaluation of 41 additives (king of bitter extract, thyme leaved gratiola tincture, devils claw extract, devils claw tincture, lavender oil, lavender tincture, spike lavender oil, melissa oil, balm leaves extract, mentha arvensis/corn mint oil, pennyroyal oil, spearmint oil, peppermint oil, peppermint tincture, basil oil, basil tincture, olive extract, marjoram oil, oregano oil, oregano tincture, patchouli oil, rosemary oil, rosemary oleoresin, rosemary extract, rosemary tincture, Spanish sage oil, sage oil, sage tincture, clary sage oil, savoury summer oil, savoury summer tincture, Pau darco tincture, thymus origanum oil, thyme oil, thyme oleoresin, thyme extract, thyme tincture, lilac chastetree extract, lilac chastetree tincture, Spanish marjoram oil and wild thyme tincture) belonging to botanically defined group (BDG) 01 – Lamiales, when used as a feed additive for all animal species (category: sensory additives; functional group: flavouring compounds). During the assessment, the applicant withdrew the applications for nine additives.[3] These additives were deleted from the register of feed additives.[4] In addition, during the course of the assessment, the application was split and the present opinion covers only one out of the remaining 32 additives under application: clary sage oil from *S. sclarea*[5] for use in all animal species.

The remaining 31 additives belonging to botanically defined group (BDG) 01 – Lamiales, under application are assessed in separate opinions.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority deleted (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 1 June 2011.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the feed additive consisting of clary sage oil from the fresh or dried flowering stems of *S. sclarea*, when used under the proposed conditions of use (see **Section 3.3.3**).

1.2 | Additional information

Clary sage oil from *Salvia sclarea* L. is currently authorised as a feed additive according to the entry in the European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003 (2b natural products – botanically defined). It has not been assessed as a feed additive in the EU.

2 | DATA AND METHODOLOGIES

2.1 | Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[6] in support of the authorisation request for the use of clary sage oil from *S. sclarea* as a feed additive. The dossier was received on 22 May 2024 and the general information and supporting documentation are available at https://open.efsa.europa.eu/questions/EFSA-Q-2024-00304.[7]

[1]Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2]On 13/03/2013, EFSA was informed by the applicant that the applicant company changed to FEFANA asbl, Avenue Louise 130 A, Box 1, 1050 Brussels, Belgium.
[3]Thyme leaves gratiola tincture, spike lavender oil, melissa oil, pennyroyal oil, basil oil and savoury summer oil (27 February 2019); Spanish majoram oil (28 September 2023); lilac chastetree extract and savoury summer tincture (8 July 2024).
[4]Register of feed additives, Annex II, withdrawn by OJ L162, 10.05.2021, p. 5.
[5]Accepted name: *Salvia sclarea* L.
[6]Dossier reference: FAD-2010-0137.
[7]The original application EFSA-Q-2010-01307 was split on 22/05/2024 and a new EFSA-Q-2024-00304 was generated.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers, other scientific reports and experts' knowledge, to deliver the present output.

Many of the components of the essential oil under assessment have been already evaluated by the FEEDAP Panel as chemically defined flavourings (CDGs). The applicant submitted a written agreement to reuse the data submitted for the assessment of chemically defined flavourings (dossiers, publications and unpublished reports) for the risk assessment of additives belonging to BDG 01, including the current one under assessment.[8]

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the of the phytochemical markers in the additive. The evaluation report is related to the methods of analysis for each feed additive included in BDG 01 – Lamiales. During the assessment, upon request of EFSA, the EURL issued a partial report,[9] which included the additive under assessment. In particular, the EURL recommended a method based on gas chromatography with flame ionisation detection (GC-FID) for the quantification of the phytochemical markers *linalyl acetate* and *linalool* in *clary sage oil*.[10]

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of clary sage oil from *S. sclarea* is in line with the principles laid down in Regulation (EC) No 429/2008[11] and the relevant guidance documents: Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA Scientific Committee, 2009), Compendium of botanicals that have been reported to contain toxic, addictive, psychotropic or other substances of concern (EFSA, 2012), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a), Guidance on the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017c), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019a), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018), Guidance on the assessment of the safety of feed additives for the users (EFSA FEEDAP Panel, 2023), Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019a), Statement on the genotoxicity assessment of chemical mixtures (EFSA Scientific Committee, 2019b), Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (EFSA Scientific Committee, 2019c).

3 | ASSESSMENT

The additive under assessment, clary sage oil, is an essential oil obtained from the fresh or dried flowering stems of *Salvia sclarea* L. and is intended for use as a sensory additive (functional group: flavouring compounds) in feed and in water for drinking for all animal species.

3.1 | Origin and extraction

Salvia sclarea L., commonly called clary or clary sage, is a biennial or short-lived perennial shrub belonging to the family Lamiaceae. In common with other members of the genus, it is characterised by its many-branched panicle with whorls of pale blue flowers and large papery purple bracts. The species is native to the Mediterranean region (southern Europe, central Asia and northern Africa). The plant can be used as an alternative to the common sage (*Salvia officinalis* L.) as a herbal flavouring for foods and alcoholic beverages and the flowers are sometimes used to make a herbal tea. The essential oil (clary sage oil) is used as an additive to soaps, perfumes and cosmetics.

The additive is extracted from the fresh or dried flowering stems of *Salvia sclarea* L. by steam distillation. The volatile constituents are condensed and then separated from the aqueous phase by decantation.

[8]Technical dossier/Supplementary information August 2024/Letter dated 27/08/2024.

[9]Additives included in the partial report: Spanish sage oil, peppermint oil, thymus origanum oil, patchouli oil, clary sage oil, lavender oil and sage oil.

[10]Evaluation report available on the EU Science Hub https://joint-research-centre.ec.europa.eu/eurl-fa-eurl-feed-additives/eurl-fa-authorisation/eurl-fa-evaluation-reports_en.

[11]Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

3.2 | Uses other than feed flavouring

While there is no specific EU authorisation for any *S. sclarea* preparation when used to provide flavour in food, according to Regulation (EC) No 1334/2008[12] flavouring preparations produced from food, may be used without an evaluation and approval as long as 'they do not, on the basis of the scientific evidence available, pose a safety risk to the health of the consumer, and their use does not mislead the consumer'.

'Clary sage oil (Salviae sclareae aetheroleum)' is described in a monograph of the European Pharmacopoeia 11.4 (PhEur, 2024) for medicinal uses.

3.3 | Characterisation

3.3.1 | Characterisation of clary sage oil

The essential oil is obtained from *S. sclarea* sourced from France or Russia and is a yellow to very pale-yellow liquid with a characteristic odour. Clary sage oil is identified with the single Chemical Abstracts Service (CAS) number 8016-63-5, the European Inventory of Existing Commercial Chemical Substances (EINECS) number 283-911-8, the Flavor Extract Manufacturers Association (FEMA) number 2321 and the Council of Europe (CoE) number 415. In six batches of the additive, the refractive index (20°C) ranged between 1.4572 and 1.4698. In three batches the specific gravity (20°C) ranged between 0.895 and 0.900 and the optical rotation (20°C) between –17.48 and –14.16.[13]

For clary sage oil, the specifications used by the applicant are based on the monograph in the European Pharmacopeia for clary sage oil (PhEur, 2024),[14] which were adapted to reflect the concentrations of selected volatile components. Four components contribute to the specifications as shown in Table 1, with linalyl acetate and linalool selected as the phytochemical markers. The analysis of three batches of the additive showed compliance with these specifications when analysed by GC-FID and expressed as percentage of gas chromatographic peak area (% GC area).[15]

TABLE 1 Constituents of clary sage oil, as defined by specifications and batch to batch variation based on the analysis of three batches by gas chromatography with flame ionisation detector (GC-FID). The content of each constituent is expressed as the area per cent of the corresponding chromatographic peak (% GC area), assuming the sum of chromatographic areas of all detected peaks as 100%.

Constituent			% GC area		
EU register name	**CAS No**	**FLAVIS No**	**Specifications[1]**	**Mean**	**Range**
Linalyl acetate[2]	115-95-7	09.013	55–78	68.28	61.87–74.84
Linalool[2]	78-70-6	02.013	6.5–25	14.81	10.88–17.91
Germacra-1(10),4(14),5-triene	23986-74-5	01.042	1–12	4.12	3.57–4.50
α-Terpineol	98-55-5	02.014	0–5	1.68	0.55–2.64
Total				88.89[3]	86.72–90.77[4]

Abbreviations: CAS No: Chemical Abstracts Service number; EU: European Union; FLAVIS No: EU Flavour Information System numbers.

[1]Specifications defined based on GC-FID analysis.

[2]Ratio between *R*-(–)- and *S*-(+)-stereoisomers not given.

[3]The value given for the Total (mean) is the mean of the sum of the constituents in the individual batches analysed.

[4]The values given for the Total (range) are the lowest and the highest values of the sum of the constituents in the individual batches analysed.

The applicant provided a full analysis of the volatile constituents in six batches obtained by gas chromatography–mass spectrometry (GC–MS).[16] In total, up to 84 peaks were detected in the chromatogram, which were all identified and accounted on average for 98.9% (98.3%–99.4%) of the % GC area. The four compounds indicated in the product specifications accounted for about 84.8% on average (range 79.9%–87.8%) of % GC area. Besides the four compounds indicated in the product specifications, eight other compounds were detected at individual levels > 0.5% and are listed in Table 2. These 12 compounds account on average for 93.5% (90.3%–96.7%) of the % GC area. The remaining 72 compounds (ranging

[12]Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Regulation (EC) No 1601/91 of the Council, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34.

[13]Technical dossier/Supplementary information January 2024/Annex_II_SIn_reply_Clary_sage_oil_COA_Chrom.

[14]Technical dossier/Supplementary information January 2024/ Annex_III_SIn_reply_Clary_sage_oil _Eur.Ph.01-2008-1850.

[15]Technical dossier/Supplementary information January 2024/Annex V SIn_reply_Clary_sage_oil_raw_data.

[16]Technical dossier/Supplementary information January 2024/Annex_II_SIn_reply_Clary_sage_oil_COA_Chrom.

between 0.006% and 0.46%) and accounting on average for 5.4% (2.6%–8.0%) of the % GC area are listed in the footnote.[17] Based on these data, clary sage oil is considered a fully defined mixture (EFSA Scientific Committee, 2019a).

TABLE 2 Constituents of clary sage oil, accounting for > 0.5% of the composition: Batch to batch variation based on the analysis of six batches by gas chromatography–mass spectrometry (GC–MS). The content of each constituent is expressed as the area per cent of the corresponding chromatographic peak (% GC area), assuming the sum of chromatographic areas of all detected peaks as 100%.

Constituent			% GC area	
EU register name	**CAS No**	**FLAVIS No**	**Mean**	**Range**
Linalyl acetate[1]	115-95-7	09.013	59.38	51.71–64.22
Linalool[1]	78-70-6	02.013	18.15	13.46–20.68
Germacra-1(10),4(14),5-triene	23986-74-5	01.042	4.43	2.21–6.46
α-Terpineol	98-55-5	02.014	2.27	0.87–3.85
β-Caryophyllene	87-44-5	01.007	1.99	2.00–2.66
Geranyl acetate	105-87-3	09.011	1.04	0.77–2.61
Neryl acetate	141-12-8	09.213	0.77	0.40–1.37
α-Copaene	3856-25-5	–	0.75	0.48–1.15
Bicyclogermacrene	67650-90-2	–	0.72	0.35–1.20
Myrcene	123-35-3	01.008	0.65	0.48–1.10
Sclareol	515-03-7	02.206	0.51	0.32–1.18
(E)-β-Ocimene[2]	3779-61-1	–	2.27	0.06–0.83
Total			93.51[3]	90.31–96.72[4]

Abbreviations: CAS No, Chemical Abstracts Service number; EU, European Union; FLAVIS No, EU Flavour Information System number.

[1]Ratio between *R*-(−)- and *S*-(+)-stereoisomers not given.

[2]Synonym: *(E)*-3,7-dimethyl-1,3,6-octatriene.

[3]The value given for the Total (mean) is the mean of the sum of the constituents in the individual batches analysed.

[4]The values given for the Total (range) are the lowest and the highest values of the sum of the constituents in the individual batches analysed.

The applicant carried out an extensive database search (no time limits) to identify data related to the chemical composition to identify the presence of any recognised substances of concern, and the safety of preparations obtained from *S. sclarea*.[18] Four cumulative databases (LIVIVO, PubChem OVID and ToxInfo), 12 single databases including PubMed and Web of Science and 12 publishers' search facilities including Elsevier, Ingenta, Springer and Wiley were used. The keywords used covered different aspects of safety and the inclusion and exclusion criteria were provided by the applicant. The literature search on the chemical composition of *S. sclarea* and its preparations was aimed at identifying the presence of any recognised substances of concern. Apart from the presence of 1,8-cineole (3.23%) and camphor (1%) in the essential oil from the aerial parts of *S. sclarea* reported in the EFSA Compendium of botanicals (EFSA, 2012),[19] thujones are limited in the PhEur because of concerns related to adulterations (Comments on the PhEur, 2019; PhEur, 2024). Thujones were not detected by GC–MS in the essential oil under assessment (limit of detection, LOD 0.001%). No other substances of concern were identified in the literature provided by the applicant.

3.3.1.1 | *Impurities*

The applicant referred to the 'periodic testing' of some representative flavourings premixtures for mercury, cadmium, lead, arsenic, fluoride, dioxins and polychlorinated biphenyls (PCBs), organo-chlorine pesticides, organo-phosphorous pesticides, aflatoxins (B1, B2, G1, G2) and ochratoxin A. However, no data were provided on the presence of these impurities.

[17]Additional constituents: constituents ($n = 23$) between < 0.5% and ≥ 0.1%: linalyl formate, eremophilene, limonene, geraniol, *(Z)*-nerol, *(Z)*-3,7-dimethyl-1,3,6-octatriene (*(Z)*-β-ocimene), β-caryophyllene epoxide, β-bourbonene, (+)-δ-cadinene, β-cubebene, sclareol oxide, β-pinene, spathulenol, *trans*-β-farnesene, α-farnesene, terpinolene, α-pinene, α-bulnesene, *(E)*-2-hexen-1-ol, β-elemene, 3,7,10-humulatriene, α-eudesmol, and α-cubebene; constituents ($n = 37$) between < 0.1% and ≥ 0.02%: *(E,E)*-7,11,15-trimethyl-3-methylene-hexadeca-1,6,10,14-tetraene, 1,6-octadiene-1,3-diol, 3,7-dimethyl-, geranyl formate, benzaldehyde, octane, *d,l*-borneol, *trans*-3,7-dimethylocta-2,6-dienal, acorenone B, hex-2*(trans)*-enal, *(Z)*-dehydroxylinalool oxide, 3,7-dimethylocta-1,5,7-trien-3-ol, β-eudesmol, bornyl acetate, β-copaene, neryl formate, *(E)*-dehydroxylinalool oxide, methyl salicylate, *(2R,5E)*-caryophyll-5-en-12-al, hexan-1-ol, hex-3*(cis)*-en-1-ol, *(E)*-1-(6,10-dimethylundeca-5,9-dien-2-yl)-4-methylbenzene, epoxylinalyl acetate, camphene, sabinene, isocaryophyllene, 5,6-epoxide, γ-muurolene, 6,10-epoxy-7(14)-isodaucane, 4-(4-methyl phenyl) pentanal, 4-terpinenol, β-dihydroagarofuran, 4-hydroxy-4-methylpentan-2-one, *p*-cymene, 3,6-dihydro-4-methyl-2-(2-methylprop-1-en-1-yl)-2H-pyran, isopentyl curcumene, 5,6-dehydrohydroxylinalyl acetate, 2-(4-methylphenyl)propan-2-ol, and tridecane; constituents ($n = 12$) between < 0.02% and ≥ 0.005%: γ-terpinene, linalool oxide, alloaromadendrene, aromadendrene, 6-methylhept-5-en-2-one, 1,8-cineole, phenyl-acetaldehyde, cis-p-2-menthen-1-ol, nonane, 3-methylnonane, α-terpinene, and α-thujene.

[18]Technical dossier/Supplementary information January 2024/Literature search_Clary sage oil.

[19]https://www.efsa.europa.eu/en/data-report/compendium-botanicals.

3.3.2 | Shelf-life

The typical shelf-life of clary sage oil is stated to be at least 12 months, when stored in tightly closed containers under standard conditions (in a cool, dry place protected from light).[20] However, no data supporting this statement were provided.

3.3.3 | Conditions of use

Clary sage oil is intended to be added to feed and water for drinking for all animal species without a withdrawal period. The maximum proposed use levels in complete feed for all animal species and categories are listed in Table 3. No use level has been proposed by the applicant for the use in water for drinking.

TABLE 3 Maximum proposed use levels of clary sage oil in complete feed.

Animal category	Maximum use level (mg/kg complete feed)
Chickens for fattening	10
Laying hens	10
Turkeys for fattening	10
Piglets	15
Pigs for fattening	15
Sows	15
Veal calves (milk replacers)	15
Cattle for fattening	15
Dairy cows	15
Sheep/goats	15
Horses	20
Rabbits	20
Salmon and other fin fish	20
Dogs	20
Cats	20
Ornamental fish	20
Other species	10

3.4 | Safety

The assessment of the safety of clary sage oil is based in the maximum use levels in complete feed proposed by the applicant (Table 3).

No studies to support the safety for target animals, consumers and users were performed with the additive under assessment.

Many of the individual components of the essential oil have been already assessed as chemically defined flavourings for use in feed and food by the FEEDAP Panel, the EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) and the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). The flavouring compounds currently authorised for food[21] and/or feed[22] use, together with the EU Flavour Information System (FLAVIS) number, the chemical group as defined in Commission Regulation (EC) No 1565/2000[23] and the corresponding EFSA opinion are listed in Table 4.

[20]Technical dossier/Section II.

[21]Commission Implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012, p. 1.

[22]European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. Available online: https://ec.europa.eu/food/sites/food/files/safety/docs/animal-feed-eu-reg-comm_register_feed_additives_1831-03.pdf.

[23]Commission Regulation (EC) No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council. OJ L 1 80, 19.7.2000, p. 8.

TABLE 4 Flavouring compounds already assessed by EFSA as chemically defined flavourings, grouped according to the chemical group (CG) as defined in Commission Regulation (EC) No 1565/2000, with indication of the EU Flavour Information System (FLAVIS) number and the corresponding EFSA opinion.

CG	Chemical group	Product (EU register name)	FLAVIS No.	EFSA* opinion, year
01	Straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters with esters containing saturated alcohols and acetals containing saturated aldehydes	Hexan-1-ol	02.005	2013
03	a, ß-Unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	Geraniol	02.012	2016a
		(Z)-Nerol	02.058	
		trans-3,7-Dimethylocta-2,6-dienal (geranial)	05.188	
		Geranyl acetate	09.011	
		Geranyl formate	09.076	
		Neryl formate	09.212	
		Neryl acetate	09.213	
		Hex-2(*trans*)-enal	05.073	2019b
04	Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols, aldehydes, acids, acetals and esters	Hex-3(*cis*)-en-1-ol	02.056	2016b
05	Saturated and unsaturated aliphatic secondary alcohols, ketones and esters with esters containing secondary alcohols	6-Methylhept-5-en-2-one	07.015	2015a
06	Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters with esters containing tertiary alcohols ethers	Linalool	02.013	2012a, 2020
		α-Terpineol	02.014	2012a
		2-(4-Methylphenyl)propan-2-ol	02.042	
		4-Terpinenol	02.072	
		Linalyl acetate	09.013	
		Linalyl formate	09.080	
		Sclareol[1]	02.206	2011a, CEF
08	Secondary alicyclic saturated and unsaturated alcohols, ketones, ketals and esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols	*d,l*-Borneol	02.016	2016c
		d,l-Bornyl acetate	09.017	
10	Secondary aliphatic saturated or unsaturated alcohols, ketones, ketals and esters with a second secondary or tertiary oxygenated functional group	4-Hydroxy-4-methylpentan-2-one[1]	07.165	2008, AFC
13	Furanones and tetrahydrofurfuryl derivatives	Linalool oxide[2]	13.140	2012b
15	Phenyl ethyl alcohols, phenylacetic acids, related esters, phenoxyacetic acids and related esters	Phenylacetaldehyde	05.030	2012c
16	Aliphatic and alicyclic ethers	1,8-Cineole	03.001	2012d, 2021
		3,6-Dihydro-4-methyl-2-(2-methylprop-1-en-1-yl)-2H-pyran[1]	13.088	2011b, CEF
23	Benzyl alcohols, aldehydes, acids, esters and acetals	Benzaldehyde	05.013	2012e
		Methyl salycilate	09.749	
31	Aliphatic and aromatic hydrocarbons and acetals containing saturated aldehydes	1-Isopropyl-4-methylbenzene (*p*-cymene)	01.002	2015b
		Terpinolene	01.005	
		α-Terpinene	01.019	
		γ-Terpinene	01.020	
		d-Limonene	01.045	
		Pin-2(10)-ene (β-pinene)	01.003	2016d
		Pin-2(3)-ene (α-pinene)	01.004	
		β-Caryophyllene	01.007	
		Myrcene	01.008	
		Camphene	01.009	

TABLE 4 (Continued)

CG	Chemical group	Product (EU register name)	FLAVIS No.	EFSA* opinion, year
		β-Cubebene[1,3]	01.030	2011c, CEF
		Germacra-1(10),4(14),5-triene δ-Germacrene[1,3]	01.042	
		3,7,10-Humulatriene[1,3]	01.043	
		4(10)-Thujene (sabinene)[1]	01.059	2015a, CEF
		cis-3,7-Dimethyl-1,3,6-octatriene *(Z)*-β-Ocimene[1]	01.064	
		β-Bourbonene[1]	01.024	
		α-Farnesene[1]	01.040	
32	Epoxides	β-Caryophyllene epoxide[1]	16.043	2014, CEF

*FEEDAP opinion unless otherwise indicated.

[1]Evaluated for use in food. According to Regulation (EC) 1565/2000, flavourings evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) before 2000 are not required to be re-evaluated by EFSA.

[2]Linalool oxide [13.140]: A mixture of *cis*- and *trans*-linalool oxide (5-ring) was evaluated [13.140] (EFSA FEEDAP Panel, 2012b).

[3]Evaluated applying the 'Procedure' described in the Guidance on the data required for the risk assessment of flavourings to be used in or on food (EFSA CEF Panel, 2010). No longer authorised for use as flavours in food.

As shown in Table 4, a number of components of clary sage oil, accounting on average for about 96% of the % GC peak areas, have been previously assessed by EFSA and considered safe for use as flavourings. They are currently authorised for use in food[24] without limitations and for use in feed[25] at individual use levels higher than those resulting from the intended use in feed of the essential oil under assessment. Subsequently, linalool [02.013] was considered safe at 30 mg/kg complete feed for all animal species based on the results of tolerance studies with a mixture of flavourings referred to as 'TuttiFrutti mixture' in chickens for fattening, piglets and cattle for fattening (EFSA FEEDAP Panel, 2020). The FEEDAP Panel considers that the conclusions reached for linalool can be extrapolated to linalyl acetate [09.013] and linalyl formate [09.080].

Three compounds, listed in Table 4, β-cubebene [01.030], germacra-1(10),4(14),5-triene [01.042] and 3,7,10-humulatriene [01.043] have been evaluated in Flavouring Group Evaluations 25 Revision 2 (FGE.25Rev2) by applying the procedure described in the Guidance on the data required for the risk assessment of flavourings to be used in or on foods (EFSA CEF Panel, 2010). For these compounds, for which there is no concern for genotoxicity, EFSA requested additional subchronic toxicity data (EFSA CEF Panel, 2011c). In the absence of such toxicological data, the CEF Panel was unable to complete its assessment (EFSA CEF Panel, 2015a). As a result, these compounds are no longer authorised for use as flavours in food. For these compounds, in the absence of toxicity data, the FEEDAP Panel applies the threshold of toxicological concern (TTC) approach or read-across from structurally related substances, as recommended in the Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019a).

Thirty-nine volatile compounds have not been previously assessed for use as flavourings. The FEEDAP Panel notes that 26 of them[26] accounting for 3.9% of the GC–MS area are aliphatic monoterpenes or sesquiterpenes structurally related to flavourings already assessed in CG 6 and 31 and a similar metabolic and toxicological profile is expected. Because of their lipophilic nature, they are expected to be rapidly absorbed from the gastro-intestinal tract, oxidised to polar oxygenated metabolites, conjugated and excreted, and no significant accumulation in animal tissues and products is expected (EFSA FEEDAP Panel, 2012a, 2015b, 2016d). Isocaryophyllene, 5,6-epoxide is structurally related to β-caryophyllene epoxide and a similar behaviour is expected.

The genotoxic potential for 12 compounds ((*E*)-2-hexen-1-ol, *cis-p*-2-menthen-1-ol, *(2R,5E)*-caryophyll-5-en-12-al, acorenone B, 1,6-octadiene-1,3-diol, 3,7-dimethyl-, *(Z)*-dehydroxylinalool oxide, *(E)*-dehydroxylinalool oxide, β-dihydroagarofuran, sclareol oxide, 4-(4-methyl phenyl) pentanal, epoxylinalyl acetate and 6,10-epoxy-7(14)-isodaucane) was predicted with the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure–Activity relationship (QSAR)

[24]Commission Implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012, p. 1.

[25]European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. https://ec.europa.eu/food/sites/food/files/safety/docs/animal-feed-eu-reg-comm_register_feed_additives_1831-03.pdf.

[26]3,7-Dimethylocta-1,5,7-trien-3-ol, spathulenol, β-eudesmol, 5,6-dehydrohydroxylinalyl acetate and α-eudesmol (CG 6); octane, nonane, 3-methylnonane, tridecane, *trans*-3,7-dimethyl-1,3,6-octatriene, *trans*-β-farnesene, *(E,E)*-7,11,15-trimethyl-3-methylene-hexadeca-1,6,10,14-tetraene, β-elemene, *(E)*-1-(6,10-dimethylundeca-5,9-dien-2-yl)-4-methylbenzene, isopentyl curcumene, α-thujene, α-cubebene, α-copaene, β-copaene, aromadendrene, alloaromadendrene, eremophilene, bicyclogermacrene, (+)-δ-cadinene, α-bulnesene and γ-muurolene (CG 31).

Toolbox. Structural alerts were identified for all compounds.[27] In all cases, predictions of mutagenicity by Ames test (with and without S9 mix) were made by 'read-across' analyses of data available for substances similar to the target compounds (i.e. analogues obtained by categorisation). Categories were defined using general mechanistic and endpoint profilers as well as empirical profilers. Subcategorisation was performed in order to exclude analogues less similar to the target compounds. For all compounds, mutagenicity read-across-based predictions were found negative.[28] On this basis, the alerts raised were discounted by the FEEDAP Panel.

3.4.1 | Safety for the target species

Tolerance studies in the target species and/or toxicological studies in laboratory animals made with the essential oil under application were not submitted.

In the absence of these data, the approach to the safety assessment of a mixture whose individual components are known is based on the safety assessment of each individual component (component-based approach). This approach requires that the mixture is sufficiently characterised and that the individual components can be grouped into assessment groups, based on structural and metabolic similarity. The combined toxicity can be predicted using the dose addition assumption within an assessment group, taking into account the relative toxic potency of each component (EFSA Scientific Committee, 2019a).

As the additive under assessment is a fully defined mixture (the identified components represent 98.9% of the % GC area, see Section 3.3.1), the FEEDAP Panel applied a component-based approach to assess the safety for target species of the essential oil. Linalool, which was included in tolerance studies with the mixture of flavourings 'TuttiFrutti' (EFSA FEEDAP Panel, 2020) is assessed separately together with linalyl acetate [09.013] and linalyl formate [09.080].

Linalool, linalyl acetate and linalyl formate

For linalool [02.013], the applicant provided evidence in the form of tolerance trials in chickens for fattening, piglets and cattle for fattening, which showed that linalool was safe up to 30 mg/kg complete feed for all animal species with a margin of safety of 10 (EFSA FEEDAP Panel, 2020). The highest concentration in feed of the sum of linalool, linalyl acetate and linalyl formate resulting from the use of the additive would be 17.2 mg/kg complete feed, which is considered safe for the target species.[29]

Components other than linalool, linalyl acetate and linalyl formate

Based on considerations related to structural and metabolic similarities, the components were allocated to 10 assessment groups, corresponding to the chemical groups (CGs) 1, 3, 4, 5, 6, 7, 8, 9, 10, 13, 16, 21, 23, 31 and 32, as defined in Annex I of Regulation (EC) No 1565/2000. For CG 31 ('aliphatic and aromatic hydrocarbons'), subassessment groups as defined in Flavouring Group Evaluation 25 (FGE.25) and FGE.78 were established (EFSA CEF Panel, 2015a, 2015b). The allocation of the components to the (sub-)assessment groups is shown in Table 5 and in the corresponding footnote.

For each component in the assessment group, exposure in target animals was estimated considering the use levels in feed, the percentage of the component in the oil and the default values for feed intake according to the guidance on the safety of feed additives for target species (EFSA FEEDAP Panel, 2017b). Default values on body weight (bw) are used to express exposure in terms of mg/kg bw per day. The intake levels of the individual components are calculated for chickens for fattening, the species with the highest ratio of feed intake/body weight per day, are shown in Table 5.

For hazard characterisation, each component of an assessment group was first assigned to the structural class according to Cramer classification using Toxtree (version 3.1.0, May 2018[30]). For some components in the assessment group, toxicological data were available to derive no observed adverse effect levels (NOAEL) values. Structural and metabolic similarity among the components in the assessment groups were evaluated to explore the application of read-across. If justified, extrapolation can be made from a known NOAEL of a component in an assessment group to the other components of the group with no available NOAEL. If sufficient evidence is available for the components of a (sub-)assessment group, a (sub-) assessment group NOAEL can be derived.

Toxicological data from subchronic studies, from which NOAEL values could be derived, were available for several compounds in CG 1 (EFSA FEEDAP Panel, 2013), for the representative compound citral [05.020] and for hex-2(*trans*)-enal [05.073]

[27]Structural alerts were identified were due to the presence of: (i) the aldehyde group for *(2R,5E)*-caryophyll-5-en-12-al and 4-(4-methyl phenyl) pentanal; (ii) α,β-unsaturated ketones/vinyl/allyl ketones/α,β-unsaturated carbonyls for acorenone B; (iii) the oxolane group for *(Z)*-dehydroxylinalool oxide, *(E)*-dehydroxylinalool oxide, β-dihydroagarofuran and 6,10-epoxy-7(14)-isodaucane; (iv) the epoxide/aziridine group for epoxylinalyl acetate; (v) the vinyl/allyl group for *(E)*-2-hexen-1-ol, *cis-p*-2-menthen-1-ol, 1,6-octadiene-1,3-diol, 3,7-dimethyl-, *(Z)*-dehydroxylinalool oxide, *(E)*-dehydroxylinalool oxide, sclareol oxide and 6,10-epoxy-7(14)-isodaucane.

[28]Technical dossier/Supplementary information January 2024/Annex VII_SIn_reply_Clary_sage_oil_QSAR.

[29]Calculated considering the maximum proposed use level of 20 mg/kg complete feed and the highest concentration of linalool (20.58%), linalyl acetate (64.2%) and linalyl formate (1.12%) in the six batches.

[30]Toxtree includes both the original Cramer rule base with the 33 structural rules (Cramer et al., 1978) and an extended rule base with five additional rules which were introduced to overcome misclassification (in Class I or Class II) of several substances with low NOAELs. https://toxtree.sourceforge.net/.

in CG 3 (EFSA FEEDAP Panel, 2016a, 2019b), hex-3(cis)-en-1-ol [02.056] in CG 4 (EFSA FEEDAP Panel, 2016b), 6-methylhept-5-en-2-one [07.015] in CG 5 (EFSA FEEDAP Panel, 2015a), sclareol [02.206] and terpineol [02.230][31] in CG 6 (EFSA CEF Panel, 2011a; EFSA FEEDAP Panel, 2012a), *d,l*-isobornyl acetate [09.218] in CG 8 (EFSA FEEDAP Panel, 2016c), 1,8-cineole [03.001] in CG 16 (EFSA FEEDAP Panel, 2012d; 2021), benzaldehyde [05.013] and methyl salicylate [09.749] in CG 23 (EFSA FEEDAP Panel, 2012e), myrcene [01.008], *d*-limonene [01.045] and β-caryophyllene [01.007] in CG 31 (EFSA FEEDAP Panel, 2015b, 2016d), and β-caryophyllene epoxide [16.043] for CG 32 (EFSA CEF Panel, 2014).

For α-terpinene [01.019], the FEEDAP Panel identified a NOAEL of 60 mg/kg bw per day based on maternal toxicity (reduced body weight gain) in a teratogenicity study in rats (Araujo et al., 1996; also reported in ECHA, 2018). An uncertainty factor (UF) of 2 was applied to the NOAEL of 60 mg/kg bw per day to take into account the nature of the study.

For CG 1, a group NOAEL of 120 mg/kg was derived from the toxicological data available and was extrapolated to hexan-1-ol [02.005]. The NOAEL of 345 mg/kg bw per day for citral [05.020] was used as a group NOAEL for all geranyl and neryl derivatives in CG 3.

For the subgroup of terpinyl derivatives in CG 6, i.e. α-terpineol [02.072] and 4-terpinenol [02.072], and for α-eudesmol, β-eudesmol and *cis-p*-2-menthen-1-ol, the reference point was selected based on the NOAEL of 250 mg/kg bw per day available for terpineol [02.230]. An uncertainty factor (UF) of 2 was applied to the NOAEL of 250 mg/kg bw per day to take into account the short duration (35 days) of the study with terpineol (EFSA FEEDAP Panel, 2012a). For sclareol [02.206], no adverse effects were observed in a subacute toxicity study lasting 32 days, when sclareol (8.8 mg/kg bw per day, the only dose tested) was administered to rats by gavage (IOFI, 2006, as referenced in EFSA CEF Panel, 2011a; Bhatia et al., 2008). An uncertainty factor of 2 was applied to the NOAEL of 8.8 mg/kg bw per day because of the short duration of the study.

For *d,l-borneol [02.016] and d,l*-bornyl acetate [09.218] in CG 8, a NOAEL of 15 mg/kg bw per day was taken from a study with *d,l*-isobornyl acetate [09.218].

The NOAELs of 44, 250 and 222 mg/kg bw per day for the representative compounds of CG 31, myrcene [01.008], limonene [01.001] and β-caryophyllene [01.007] were applied, respectively, using read-across to the compounds within subassessment groups II (*trans*-3,7-dimethyl-1,3,6-octatriene, *cis*-3,7-dimethyl-1,3,6-octatriene, trans-β-farnesene and α-farnesene), III (terpinolene [01.055], γ-terpinene [01.020] and β-elemene) and V (α-pinene [01.004], β-pinene [01.003], β-cubebene [01.030], β-bourbonene [01.024], sabinene [01.059], camphene [01.009], bicyclogermacrene, α-copaene, eremophilene, (+)-δ-cadinene, α-bulsenene, α-cubebene, β-copaene, γ-muurolene, aromadendrene, alloaromadendrene and α-thujene),[32] respectively (EFSA CEF Panel, 2015a, 2015b). Read-across was also applied from β-caryophyllene [01.007] to 3,7,10-humulatriene [01.043] in CG 31,VI but not to and germacra-1(10),4(14),5-triene [01.042], which has two exocyclic double bonds, one of which is conjugated with an endocyclic double bonds. For 3,7,10-humulatriene, an UF of 2 was applied to the NOAEL of 222 mg/kg bw per day for β-caryophyllene [01.007] to take into account the uncertainty in read-across due to differences in the structure (extrapolation from a tricyclic to a macrocyclic non-aromatic compound) (EFSA FEEDAP Panel, 2023).

The NOAEL of 109 mg/kg bw per day for β-caryophyllene epoxide [16.043] was applied to isocaryophyllene, 5,6-epoxide in CG 32.

For the remaining compounds,[33] toxicity studies performed with the compounds under assessment and NOAEL values derived from toxicity studies were not available and read-across was not possible. Therefore, the threshold of toxicological concern (TTC) approach was applied (EFSA FEEDAP Panel, 2017b; EFSA Scientific Committee, 2019c).

As the result of the hazard characterisation, a reference point was identified for each component in the assessment group based on the toxicity data available (NOAEL from in vivo toxicity study or read-across) or from the 5th percentile of the distribution of NOAELs of the corresponding Cramer Class (i.e. 3, 0.91 and 0.15 mg/kg bw per day, respectively, for Cramer Class I, II and III compounds, Munro et al., 1996). Reference points selected for each compound are shown in Table 5.

For risk characterisation, the margin of exposure (MOE) was calculated for each component as the ratio between the reference point and the exposure. For each assessment group, the combined (total) margin of exposure (MOET) was calculated as the reciprocal of the sum of the reciprocals of the MOE of the individual substances (EFSA Scientific Committee, 2019a). A MOET > 100 allowed for interspecies- and intra-individual variability (as in the default 10 × 10 uncertainty factor). The compounds resulting individually in an MOE > 50,000 were not further considered in the assessment group as their contribution to the MOE(T) is negligible. They are listed in the footnote.[34]

The approach to the safety assessment of clary sage oil for the target species is summarised in Table 5. The calculations were done for chickens for fattening, the species with the highest ratio of feed intake/body weight and represent the worst-case scenario at the use level of 10 mg/kg complete feed.

[31]Terpineol is a mixture of four structural isomers: α-terpineol [02.014], β-terpineol, γ-terpineol and 4-terpinenol [02.072]. α-terpineol [02.014], is defined as a mixture of *(R)*-(+)-α-terpineol and *(S)*-(−)-α-terpineol.

[32]Some of these compounds are not listed in Table 5 because their individual margin of exposure (MOE) was >50,000.

[33]CC I (3 mg/kg bw per day): *(E)*-2-hexen-1-ol, sclareol, spathulenol, 2-(4-methylphenyl)propan-2-ol, (2R,5E)-caryophyll-5-en-12-al, 4-hydroxy-4-methylpentan-2-one, phenyl-acetaldehyde, octane, tridecane, nonane, 3-methylnonane, (E,E)-7,11,15-trimethyl-3-methylene-hexadeca-1,6,10,14-tetraene, isopentyl curcumene, *(E)*-1-(6,10-dimethylundeca-5,9-dien-2-yl)-4-methylbenzene; CC II (0.91 mg/kg bw per day): acorenone B, linalool oxide, *(Z)*-dehydroxylinalool oxide, *(E)*-dehydroxylinalool oxide, sclareol oxide, 3,6-dihydro-4-methyl-2-(2-methylprop-1-en-1-yl)-2H-pyran; CC III (0.15 mg/kg bw per day): 1,6-octadiene-1,3-diol, 3,7-dimethyl-; β-dihydroagarofuran, epoxylinalyl acetate, 6,10-epoxy-7(14)-isodaucane.

[34]Compounds included in the assessment groups but not reported in the table: hexan-1-ol (CG 1); *(Z)*-nerol, geraniol, geranyl formate, hex-2*(trans)*enal, neryl formate and geranial (CG 3); hex-3(*cis*)-en-1-ol (CG 4); 6-methylhept-5-en-2-one (CG 5); α-eudesmol, β-eudesmol, 4-terpinenol, 5,6-dehydrohydroxylinalyl acetate and *cis-p*-2-menthen-1-ol (CG 6); 1,8-cineole (CG 16); benzaldehyde and methyl salicylate (CG 23); limonene, terpinolene, β-elemene, α-terpinene and γ-terpinene (CG 31, III); *p*-cymene (CG 31,IV); eremophilene, β-cubebene, α-pinene, β-pinene, δ-cadinene, β-bourbonene, α-bulsenene, α-cubebene, sabinene, β-copaene, γ-muurolene, camphene, aromadendrene, allooaromadenderene, α-thujene; 3,7,10-humulatriene (CG 31, VI); isocaryophyllene 5,6-epoxide (CG 32).

TABLE 5 Compositional data, intake values (calculated for chickens for fattening at 10 mg/kg complete feed), reference points, margin of exposure (MOE) for the individual components of clary sage oil classified according to assessment groups, and combined margin of exposure (MOET) for each assessment group.

Essential oil composition			Exposure		Hazard characterisation		Risk characterisation	
Assessment group	**FLAVIS-No**	**Highest conc. in the oil**	**Highest feed conc.**	**Daily intake[1]**	**Cramer class[2]**	**NOAEL[3]**	**MOE[4]**	**MOET[5]**
Constituent	**–**	**%**	**mg/kg**	**mg/kg bw/day**	**–**	**mg/kg bw/day**	**–**	**–**
CG 3								
Geranyl acetate	09.011	2.61	0.261	0.0234	(I)	345	14,730	
Neryl acetate	09.213	1.37	0.137	0.0123	(I)	345	28,134	
(E)-2-Hexen-1-ol	–	0.22	0.022	0.0020	I	*3*	1526	
MOET CG 3								1318
CG 6								
α-Terpineol	02.014	3.85	0.385	0.0346	(I)	125[6]	3615	
Sclareol	02.206	1.18	0.118	0.0106	(I)	**4.4**[7]	414	
Spathulenol	–	0.31	0.031	0.0028	I	*3*	1089	
3,7-Dimethylocta-1,5,7-trien-3-ol	–	0.07	0.007	0.0006	II	*0.91*	1513	
2-(4-Methylphenyl) propan-2-ol	02.042	0.03	0.003	0.0003	I	*3*	10,780	
MOET CG 6								229
CG 7								
(2R,5E)-Caryophyll-5-en-12-al	–	0.05	0.005	0.0005	I	*3*	6305	
CG 8								
d,l-Borneol	02.016	0.13	0.013	0.0012	(I)	15	12,469	
d,l-Bornyl acetate	09.218	0.07	0.007	0.0006	(I)	15	23,207	
Acorenone B	–	1.38	0.007	0.0006	II	*0.91*	1428	
MOET CG 8								1214
CG 9								
1,6-Octadiene-1,3-diol, 3,7-dimethyl-	–	0.12	0.012	0.0011	III	*0.15*	137	
CG 10								
4-Hydroxy-4-methylpentan-2-one	07.165	0.04	0.004	0.0004	I	*3*	8569	
CG 13								
Linalool oxide	13.140	0.03	0.003	0.0002	II	*0.91*	3899	
CG 15								
Phenyl acetaldehyde	05.030	0.02	0.002	0.0002	I	*3*	15,913	
CG 16								
Sclareol oxide	–	0.30	0.030	0.0027	II	*0.91*	337	
(Z)-Dehydroxylinalool oxide	–	0.06	0.006	0.0006	II	*0.91*	1609	
(E)-Dehydroxylinalool oxide	–	0.05	0.005	0.0004	II	*0.91*	2027	
β-Dihydroagarofuran	–	0.04	0.004	0.0006	III	*0.15*	398	
3,6-Dihydro-4-methyl-2-(2-methylprop-1-en-1-yl)-2H-pyran	13.088	0.03	0.003	0.0002	II	*0.91*	3270	
MOET CG 16								145
CG 21								
4-(4-Methyl phenyl) pentanal	–	0.04	0.004	0.0004	I	*3*	7595	

TABLE 5 (Continued)

Essential oil composition			Exposure		Hazard characterisation		Risk characterisation	
Assessment group	**FLAVIS-No**	**Highest conc. in the oil**	**Highest feed conc.**	**Daily intake[1]**	**Cramer class[2]**	**NOAEL[3]**	**MOE[4]**	**MOET[5]**
Constituent	**–**	**%**	**mg/kg**	**mg/kg bw/day**	**–**	**mg/kg bw/day**	**–**	**–**
CG 31, I								
Octane	–	0.08	0.008	0.0007	I	*3*	4126	
Tridecane	–	0.03	0.003	0.0003	I	*3*	11,523	
Nonane	–	0.01	0.001	0.0001	I	*3*	27,848	
3-Methylnonane	–	0.01	0.001	0.0001	I	*3*	30,380	
MOET CG 31, I								2513
CG 31, II (Acyclic alkanes)								
Myrcene	01.008	1.10	0.110	0.0098	(I)	**44**	4468	
(E)-β-Ocimene	–	0.83	0.083	0.0074	(I)	44	5912	
(Z)-β-Ocimene	01.064	0.54	0.054	0.0049	(I)	44	9060	
trans-β-Farnesene	–	0.40	0.040	0.0036	(I)	44	12,346	
α-Farnesene	01.040	0.23	0.023	0.0010	(I)	44	21,591	
(E,E)-7,11,15-Trimethyl-3-methylene-hexadeca-1,6,10,14-tetraene	–	0.11	0.011	0.0010	I	*3*	2984	
MOET CG 31, II								1035
CG 31, IV (Benzene hydrocarbons, alkyl)								
(E)-1-(6,10-Dimethylundeca-5,9-dien-2-yl)-4-methylbenzene	–	0.05	0.005	0.0004	I	*3*	6305	
Isopentyl curcumene	–	0.06	0.003	0.0003	I	*3*	10,780	
MOET CG 31, IV								3978
CG 31, V (Bi-, tricyclic, non-aromatic hydrocarbons)								
β-Caryophyllene	01.007	2.66	0.266	0.0210	(I)	**222**	9283	
Bicyclogermacrene	–	1.20	0.120	0.0095	(I)	222	20,608	
α-Copaene	–	1.15	0.115	0.0091	(I)	222	21,504	
MOET CG 31, V								4932
CG 31, VI (macrocyclic non-aromatic hydrocarbons)								
Germacra-1(10),4(14),5-triene	01.042	6.46	0.646	0.0580	I	*3*	52	
CG 32								
β-Caryophyllene epoxide	16.043	0.36	0.036	0.0032	(III)	**109**	33,634	
Epoxylinalyl acetate	–	0.05	0.005	0.0005	III	*0.15*	321	
6,10-Epoxy-7(14)-isodaucane	–	0.04	0.004	0.0004	III	*0.15*	389	
								19,975

[1]Intake calculations for the individual components are based on the use level of 10 mg/kg in feed for chickens for fattening, the species with the highest ratio of feed intake/body weight.

[2]When a NOAEL value is available or read-across is applied, the allocation to the Cramer class is put into parentheses.

[3]Values **in bold** refer to those components for which the NOAEL value was available, values *in italics* are the 5th percentile of the distribution of NOAELs of the corresponding Cramer Class, other values (plain text) are NOAELs extrapolated by using read-across.

[4]The MOE for each component is calculated as the ratio of the reference point (no observed adverse effect level, NOAEL) to the intake.

[5]The combined margin of exposure (MOET) is calculated for each assessment group as the reciprocal of the sum of the reciprocals of the MOE of the individual substances.

[6]An uncertainty factor of 2 was applied to the NOAEL of 250 mg/kg bw per day for terpineol (short duration of the study).

[7]An uncertainty factor of 2 was applied to the NOAEL of 8.8 mg/kg bw per day for sclareol (short duration of the study).

As shown in Table 5, for all assessment groups except for CG 31,VI, the MOET was > 100 at the proposed use levels of the additive. From the lowest MOET of 52 for chickens for fattening, the MOET for CG 31,VI was calculated for the other target species considering the respective daily feed intake/kg bw and conditions of use. The results are summarised in Table 6.

TABLE 6 Combined margin of exposure (MOET) for the assessment group CG 31,VI calculated for the different target animal categories at the proposed use levels in feed and maximum safe use levels in feed calculated to ensure a MOET ≥ 100 (500 for cats).

Animal category	Daily feed intake mg DM/kg bw)	Proposed use level (mg/kg complete feed)[1]	Lowest MOET CG 31,VI	Maximum safe use level (mg/kg complete feed)[1]
Chickens for fattening	79	10	52	5
Laying hens	53	10	78	8
Turkeys for fattening	59	10	70	7
Piglets	44	15	62	9
Pigs for fattening	37	15	74	11
Sows lactating	30	15	91	14
Veal calves (milk replacer)	19	15	154	-[2]
Cattle for fattening	20	15	137	-
Dairy cows	31	15	88	13
Sheep/goats	20	15	137	-
Horses	20	10	205	-
Rabbits	50	20	41	8
Salmonids	18	20	114	-
Dogs	17	20	121	-
Cats[3]	20	20	103	4
Ornamental fish	5	20	411	-

[1]Complete feed containing 88% dry matter (DM), milk replacer 94.5% DM.

[2]For the species for which the MOET is > 100, the proposed use level is considered safe.

[3]The MOET for cats is increased to 500 because of the reduced capacity of glucuronidation.

At the proposed use levels in complete feed, the MOET exceeds the value of 100 for veal calves, cattle for fattening, sheep/goats, horses, salmon, dogs, cats and ornamental fish. For the other species, the maximum safe use levels in feed were calculated to ensure an MOET ≥ 100. Because glucuronidation is an important metabolic reaction to facilitate the excretion of the components of the essential oil and considering that cats have an unusually low capacity for glucuronidation, particularly of aromatic compounds (Court & Greenblatt, 1997; Lautz et al., 2021), the use of clary sage oil as additive in cat feed needs a wider margin of exposure. A MOET of 500 is considered adequate. The maximum use levels in complete feed proposed by the applicant of 15 mg/kg for veal calves, cattle for fattening, sheep/goats, 10 mg/kg for horses, 20 mg/kg for salmonids, dogs and ornamental fish are safe. For the other species, the resulting maximum safe levels in complete feed are shown in Table 6. These levels are extrapolated to physiologically related minor species. For the other species not considered, the lowest value of 4 mg/kg complete feed is applied.

Use in water for drinking

No specific proposals have been made by the applicant for the use level in water for drinking. The FEEDAP Panel considers that the use in water for drinking is safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed.

3.4.1.1 | *Conclusions on safety for the target species*

The FEEDAP Panel considers that the levels of clary sage oil summarised in Table 7 are safe for the respective target species.

TABLE 7 Safe concentrations of clary sage oil in complete feed (mg/kg) for all animal species and categories.

Animal categories	Safe concentration (mg/kg complete feed)[1]
Turkeys for fattening	7
Chickens for fattening, other poultry for fattening or reared for laying/reproduction and ornamental birds	5
Laying hens and other laying/reproductive birds	8
Pigs for fattening	11
Piglets and other porcine species for meat production or reared for reproduction	9
Sows and other porcine species for reproduction	14
Veal calves (milk replacer)	15
Sheep/goats	15

TABLE 7 (Continued)

Animal categories	Safe concentration (mg/kg complete feed)[1]
Cattle for fattening, other ruminants for fattening or reared for milk production/reproduction, cervids and camelids at the same physiological stage	15
Dairy cows and other ruminants, cervids and camelids for milk production or reproduction	13
Horses and other equines	10
Rabbits and other leporids	8
Salmonids and minor fin fish	20
Dogs	20
Cats	4
Ornamental fish	20
Other species	4

[1]Complete feed containing 88% DM, milk replacer 94.5% DM.

The FEEDAP Panel considers that the use level in water for drinking is safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed.

3.4.2 | Safety for the consumer

Clary sage oil is added to a wide range of food categories for flavouring purposes. Although individual consumption figures are not available, the Fenaroli's handbook of flavour ingredients (Burdock, 2009) cites values of 0.0004 mg/kg bw per day for clary sage oil (FEMA 2321). Fenaroli also reports use levels in food and beverages in the range of 1 up to 100 mg/kg for clary sage oil.

Most of the individual constituents of the essential oil under assessment are currently authorised as food flavourings without limitations and have been already assessed for consumer safety when used as feed additives in animal production (see Table 4, Section 3.4).

No data on residues in products of animal origin were made available for any of the constituents of the essential oil. However, the Panel recognises that the constituents of clary sage oil are expected to be extensively metabolised and excreted in the target species. For the major components, linalyl acetate and linalool, the available data in laboratory animals and humans indicate that they are absorbed, metabolised by oxidation and excreted and are not expected to accumulate in animal tissues and products (EFSA FEEDAP Panel, 2012a). Consequently, relevant residues in food products are unlikely.

Considering the above and the reported human exposure due to the direct use of clary sage oil in food (Burdock, 2009), it is unlikely that the consumption of products from animals given clary sage oil at the proposed maximum use level would substantially increase human background exposure. The use of clary sage oil in animal nutrition under the proposed conditions of use is considered safe for human consumers of animal products.

3.4.3 | Safety for the user

No specific data were provided by the applicant regarding the safety of the additive for users.

The applicant made a literature search aimed at retrieving studies related to the safety of preparations obtained from *S. sclarea* for users.[35] None of the references retrieved were considered relevant to the safety assessment.

The applicant provided a safety data sheet[36] for clary sage oil, which identified concerns for dermal and eye irritation and dermal and respiratory sensitisation.

The FEEDAP Panel concludes that clary sage oil should be considered as irritant to skin and eyes, and as a dermal and respiratory sensitiser.

3.4.4 | Safety for the environment

S. sclarea is a species native to Europe where it is also cultivated for culinary and ornamental purposes.

The use of clary sage oil in animal feed under the proposed conditions of use is not expected to pose a risk to the environment.

[35]Technical dossier/Supplementary information January 2024/Literature search_Clary sage oil.

[36]Technical dossier/Supplementary information January 2024/Annex VIII_SIn_reply_Clary_sage_oil_MSDS. Aspiration hazard (H304, Category 1), Hazard for skin corrosion/irritation (H315, Category 2), Serious eye damage/eye irritation (H319, Category 2), Skin sensitization (H317, Category 1), in accordance with the criteria outlined in Annex I of 1272/2008/EC (CLP/EU-GHS).

3.5 | Efficacy

Clary sage oil is listed in Fenaroli's Handbook of Flavour Ingredients (Burdock, 2009) and by FEMA with the reference number 2321.

Since clary sage oil is recognised to flavour food and its function in feed would be essentially the same as that in food, no further demonstration of efficacy is considered necessary.

4 | CONCLUSIONS

The conclusions of the FEEDAP Panel on the safe levels in complete feed of clary sage oil for all animal species are summarised as follows:

Animal categories	Safe concentration (mg/kg complete feed)[1]
Turkeys for fattening	7
Chickens for fattening, other poultry for fattening or reared for laying/reproduction and ornamental birds	5
Laying hens and other laying/reproductive birds	8
Pigs for fattening	11
Piglets and other porcine species for meat production or reared for reproduction	9
Sows and other porcine species for reproduction	14
Veal calves (milk replacer)	15
Sheep/goats	15
Cattle for fattening, other ruminants for fattening or reared for milk production/reproduction, cervids and camelids at the same physiological stage	15
Dairy cows and other ruminants, cervids and camelids for milk production or reproduction	13
Horses and other equines	10
Rabbits and other leporids	8
Salmonids and minor fin fish	20
Dogs	20
Cats	4
Ornamental fish	20
Other species	4

[1]Complete feed containing 88% DM, milk replacer 94.5% DM.

The FEEDAP Panel considers that the use level in water for drinking is safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed.

The use of clary sage oil in animal feed under the proposed conditions of use is safe for the consumer and the environment.

Regarding user safety, the essential oil under assessment should be considered as irritant to skin and eyes, and as a dermal and respiratory sensitiser.

Since the oil of the flowering stems of *Salvia sclarea* L. is recognised to flavour food and its function in feed would be essentially the same as that in food, no further demonstration of efficacy is considered necessary.

5 | DOCUMENTATION PROVIDED TO EFSA/CHRONOLOGY

Date	Event
23/11/2010	Dossier received by EFSA. Botanically defined flavourings from Botanical Group 01 – Lamiales for all animal species and categories. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)
03/01/2011	Reception mandate from the European Commission
06/01/2011	Application validated by EFSA – Start of the scientific assessment
01/04/2011	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: analytical methods*
08/01/2013	Reception of supplementary information from the applicant - Scientific assessment remains suspended
26/02/2013	EFSA informed the applicant (EFSA ref. 7,150,727) that, in view of the workload, the evaluation of applications on feed flavourings would be re-organised by giving priority to the assessment of the chemically defined feed flavourings, as agreed with the European Commission

(Continued)

Date	Event
24/06/2015	Technical hearing during risk assessment with the applicant according to the "EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products": data requirement for the risk assessment of botanicals
27/02/2019	Partial withdrawal by applicant (EC was informed) for the following additives: Thyme leaves gratiola tincture, spike lavender oil, melissa oil, pennyroyal oil, basil oil and savory summer oil
30/06/2021	EFSA informed the applicant that the evaluation process restarted
08/07/2021	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterisation, safety for target species, safety for the consumer, safety for the user and environment*
28/09/2023	Partial withdrawal of the application for the following additive: Spanish majoram oil
31/01/2024	Reception of supplementary information from the applicant (partial dataset: clary sage oil) - Scientific assessment remains suspended
22/05/2024	The application was split and a new EFSA-Q-2024-00304 was assigned to the additive included in the present assessment
08/07/2024	Partial withdrawal of the application for the following additives: lilac chastetree extract and savory summer tincture
26/08/2024	Reception of a partial evaluation report of the European Union Reference Laboratory for Feed Additives. Scientific assessment re-started for the additives included in the partial report: Spanish sage oil, peppermint oil, thymus origanum oil, patchouli oil, clary sage oil, lavender oil and sage oil
27/08/2024	Reception of supplementary information from the applicant (letter of agreement)
17/09/2024	Opinion adopted by the FEEDAP Panel on Spanish sage oil (EFSA-Q-2024-00304).
16/10/2024	Opinion readopted by the FEEDAP Panel on Spanish sage oil (EFSA-Q-2024-00304). End of the Scientific assessment for the additive included in the present assessment. The assessment of other additives in BGD 01 is still ongoing

ABBREVIATIONS

AFC	EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
bw	body weight
BDG	botanically defined group
CAS	Chemical Abstracts Service
CDG	chemically defined group
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CG	chemical group
CLP	Classification, Labelling and Packaging
CoE	Council of Europe
DM	dry matter
ECHA	European Chemicals Agency
EINECS	European Inventory of Existing Chemical Substances
EURL	European Union Reference Laboratory
FAO	Food Agriculture Organization
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
FFAC	Feed Flavourings authorisation Consortium of FEFANA (EU Association of Specialty Feed Ingredients and their Mixtures)
FEMA	Flavour Extract Manufacturers Association
FGE	food group evaluation
FLAVIS	The EU Flavour Information System
FLAVIS No	FLAVIS number
GC	gas chromatography
GC-FID	gas chromatography-flame ionisation detection
GC–MS	gas chromatography–mass spectrometry
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LOD	limit of detection
MOE	Margin of Exposure
MOET	Total Margin of Exposure
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PCBs	polychlorinated biphenyls
PhEur	European Pharmacopoeia
QSAR	Quantitative Structure Activity Relationship
TTC	threshold of toxicological concern
UF	uncertainty factor
WHO	World Health Organization

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REQUESTOR

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