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SCIENTIFIC OPINION

Safety and efficacy of a feed additive consisting of an essential oil derived from the leaves of *Salvia officinalis* ssp. *lavandulifolia* (Vahl) Gams (Spanish sage oil) for use in all animal species (FEFANA asbl)

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Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of Spanish sage oil from the leaves of *Salvia officinalis* ssp. *lavandulifolia* (Vahl) Gams (Spanish 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 of 14 mg/kg complete feed for all animal species. The FEEDAP Panel considered that the use of Spanish sage oil 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 Spanish 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 leaves of *S. officinalis* ssp. *lavandulifolia* (Vahl) Gams 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

1,8-cineole, camphor, flavouring compounds, safety, *Salvia officinalis* ssp. *lavandulifolia* (Vahl) Gams, sensory additives, Spanish sage oil

CONTENTS

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 7 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, savory summer oil, savory 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: Spanish sage oil from *S. lavandulifolia*[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 Spanish sage oil from *S. lavandulifolia* (leaves), when used under the proposed conditions of use (see Section 3.3.3).

1.2 | Additional information

Spanish sage oil from *S. officinalis* ssp. *lavandulifolia* (Vahl) Gams 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 Spanish sage oil from *S. lavandulifolia* as a feed additive. The dossier was received on 19 June 2024 and the general information and supporting documentation are available at https://open.efsa.europa.eu/questions/EFSA-Q-2024-00404.[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 officinalis* ssp. *lavandulifolia* (Vahl) Gams; synonym: *S. lavandulifolia* Vahl.
[6]Dossier reference: FAD-2010-0137.
[7]The original application EFSA-Q-2010-0137 was split on 19/06/2024 and a new EFSA-Q-2024-00404 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 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, for the characterisation of Spanish sage oil, the EURL recommended a method based on gas chromatography with flame ionisation detection (GC–FID) for the quantification of the phytochemical markers *1,8-cineole* and *camphor* in *Spanish sage oil*.[10]

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of Spanish sage oil from *S. lavandulifolia* 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, 2019), 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, 2023a), 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, Spanish sage oil, is an essential oil obtained from leaves of *S. officinalis* ssp. *lavandulifolia* (Vahl) Gams 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

S. officinalis ssp. *lavandulifolia* (Vahl) Gams (basionym *Salvia lavandulifolia* Vahl) is a small perennial shrub belonging to the family Lamiaceae. It is characterised by its whitish grey leaves and its lavender-like flower. The sub-species is native to Central and Eastern Spain and, as such, it is commonly referred to as Spanish sage to distinguish it from the common sage (*S. officinalis* L.) and other sage plants, e.g. clary sage (*S. sclarea* L.). In common with other sage plants, it has a long history of use as a culinary herb.

The additive is extracted from leaves from *S. officinalis* ssp. *lavandulifolia* (Vahl) Gams 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 27/8/2024.

[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]The full report is 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

There is no specific EU authorisation for any *S. officinalis* ssp. *lavandulifolia* preparation when used to provide flavour in food. However, 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'.

'Spanish sage oil (*Salviae lavandulifoliae* 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 Spanish sage oil

The essential oil is obtained from leaves of *S. officinalis* ssp. *lavandulifolia* (Vahl) sourced from Spain and is a colourless to pale yellow liquid with a characteristic camphoraceous and herbaceous odour. Spanish sage oil is identified with the single Chemical Abstracts Service (CAS) number 8016-65-7, the European Inventory of Existing Commercial Chemical Substances (EINECS) number 290-272-9, the Flavor Extract Manufacturers Association (FEMA) number 3003 and the Council of Europe (CoE) number 413.[13] In five batches of the additive, the refractive index (20°C) ranged between 1.4674 and 1.4690 (five batches) and was compliant with the specification (1.467–1.473).[14]

For Spanish sage oil, the specifications used by the applicant are based on the standard developed by the International Organisation for Standardization (ISO) 3526:2005 for oil of sage, Spanish.[15] Four components contribute to the specifications as shown in Table 1, with 1,8-cineole and camphor[16] selected as the phytochemical markers. The analysis of five 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).[17]

TABLE 1 Constituents of Spanish sage oil, as defined by specifications and batch to batch variation based on the analysis of five batches by gas chromatography with flame ionisation detection (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**	**Specification[a]**	**Mean**	**Range**
Camphor[b]	76-22-2	–	11–36	29.5	27.3–31.2
1,8-Cineole	470-82-6	03.001	10–30	25.5	24.0–26.9
α-Pinene (pin-2(3)-ene)	80-56-8	01.004	4–11	6.2	5.6–7.6
d-Limonene[c]	5989-27-5	01.045	2–6	4.9	4.6–5.2

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

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

[b]Present in the additive as a mixture of enantiomers (*d*-camphor and *l*-camphor), the ratio between the *d*- and *l*-stereoisomers not given.

[c]Stereochemistry not given, however considering that the naturally occurring limonene is typically *d*-limonene, it is assumed that this form also occurs in Spanish sage oil.

The applicant provided a full analysis of the volatile constituents in five batches obtained by gas chromatography–mass spectrometry (GC–MS).[18] In total, up to 72 peaks were detected in the chromatogram, which were all identified and accounted on average for 99.3% (99.2%–99.4%) of the % GC area. The four compounds indicated in the product specifications accounted for about 62.1% on average (range 57.7%–65.7%) of % GC area. Besides the four compounds indicated in the product specifications, 16 other compounds were detected at individual levels > 0.5% and are listed in Table 2. These 20 compounds account on average for 95.3% (94.0%–96.4%) of the % GC area. The remaining 52 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 March 2023/BDG_01_SIn_reply_Spanish_sage_oil.

[14]Technical dossier/Supplementary information March 2023/Annex_II_SIn_reply_Spanish_sage_oil_COA_chrom.

[15]Technical dossier/Supplementary information March 2023/ Annex_III_SIn_reply_Spanish_sage_oil_ISO-3526-2005.

[16]Present in the additive as a mixture of enantiomers (*d*-camphor and *l*-camphor), the ratio between the *d*- and *l*-stereoisomers not given.

[17]Technical dossier/Supplementary information March 2023/ BDG_01_SIn_reply_Spanish_sage_oil, Table 2.

[18]Technical dossier/Supplementary information March 2023/Annex_II_SIn_reply_Spanish_sage_oil_COA_chrom.

between 0.005% and 0.40%) and accounting on average for 4.0% (2.9%–5.3%) of the % GC area are listed in the footnote.[19] Based on these data, Spanish sage oil is considered a fully defined mixture (EFSA Scientific Committee, 2019a).

TABLE 2 Constituents of Spanish sage oil, accounting for > 0.5% of the composition: batch-to-batch variation based on the analysis of five 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**
Camphor[a]	76-22-2	–	27.88	25.53–30.83
1,8-cineole	470-82-6	03.001	23.63	23.27–23.95
α-Pinene (pin-2(3)-ene)	80-56-8	01.004	5.51	4.95–6.63
d-Limonene[b]	5989-27-5	01.045	5.06	3.95–6.26
Camphene	79-92-5	01.009	5.27	4.62–6.05
β-Pinene (pin-2(10)-ene)	127-91-3	01.003	4.30	4.10–4.57
Linalyl acetate	115-95-7	09.013	3.67	3.08–4.50
α-Terpinyl acetate	80-26-2	09.015	2.97	2.46–3.40
d,l-Borneol	507-70-0	02.016	2.84	2.57–3.31
Linalool	78-70-6	02.013	2.26	2.23–2.28
Myrcene	123-35-3	01.008	2.01	1.66–2.32
Sabinyl acetate	3536-54-7	–	1.91	1.33–2.68
β-Caryophyllene	87-44-5	01.007	1.56	1.28–1.81
d,l-Isobornyl acetate	125-12-2	09.218	1.56	1.22–1.75
Sabinene (4(10)-thujene)	3387-41-5	01.059	1.29	0.76–1.88
p-Cymene (1-isopropyl-4-methylbenzene)	99-87-6	01.002	0.82	0.56–1.03
(Z)-Sabinol	3310-02-9	–	0.81	0.22–1.38
α-Terpineol	98-55-5	02.014	0.78	0.77–0.81
4-Terpinenol	562-74-3	02.072	0.64	0.47–0.74
γ-Terpinene	99-85-4	01.020	0.56	0.31–0.78
Total			95.34	93.99–96.40[c]

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

[a]Present in the additive as a mixture of enantiomers (*d*-camphor and *l*-camphor), the ratio between the *d*- and *l*-stereoisomers not given.

[b]Stereochemistry not given, however considering that the naturally occurring limonene is typically *d*-limonene, it is assumed that this form is also in Spanish sage oil.

[c]The values given for the Total are the lowest and the highest values of the sum of the components in the five batches analysed.

The applicant performed a literature search (see Section 3.4) for the chemical composition of *S. officinalis* ssp. *lavandulifolia* (Vahl) Gams and its preparations to identify the presence of any recognised substances of concern.[20] Apart from the presence of 1,8-cineole (up to 41%) and camphor (up to 39%) in the essential oil from the aerial parts of *S. officinalis* ssp. *lavandulifolia* reported in the EFSA Compendium of botanicals (EFSA, 2012),[21] the search also identified thujones as potential substances of concern. Low concentrations (< 1.5%) of thujones were reported in seven out of the 25 publications retrieved (Herraiz-Peñalver et al., 2010; Langa et al., 2009; Méndez-Tovar et al., 2015; Méndez-Tovar et al., 2016; Santana-Méridas et al., 2012; Schmiderer et al., 2008; Usano-Alemany et al., 2013). Thujones were not detected by GC–MS in the essential oil under assessment (limit of detection, LOD 0.001%).

[19]Additional constituents: constituents ($n = 15$) between < 0.5 and ≥ 0.1%: *(E)*-isoeugenol, 3,7-dimethyl-3,6-octadienal, 2,2-dimethyl-3,4-octadienal, β-ocimene, *cis*-limonene epoxide, *(Z)*-isocitral, geranyl propionate, 3,7,10-humulatriene, terpinolene, geranyl acetate, bicyclogermacrene, tricyclene, geraniol, α-terpinene, β-caryophyllene epoxide, α-phellandrene, α-thujene, δ-cadinene, *d,l*-isobornyl propionate, spathulenol and viridiflorol; constituents ($n = 22$) between <0.1 and ≥0.02%: *trans*-sabinene hydrate, *trans*-3,7-dimethyl-1,3,6-octatriene, α-gurjunene, (1R) 2,2,3-trimethylcyclopent-3-en-1-yl acetaldehyde, *d,l*-isoborneol, 2-(4-methylphenyl) propan-2-ol, *(E)*-3,7-dimethylocta-1,5,7-trien-3-ol, *d,l*-bornyl acetate, δ-terpinyl acetate, γ-cadinene, neryl acetate, myrtenal, shyobunol, α-curcumene, 2,5-bornanedione, neral, linalool oxide, *trans-p*-2-menthen-1-ol, *trans*-3,7-dimethylocta-2,6-dienal, α-muurolene, alloaromadendrene and γ-muurolene; constituents ($n = 15$) between < 0.02 and ≥0.005%: *trans*-carveol, T-muurolol, δ-3-carene, *l*-carvone, hex-3(*cis*)-enyl acetate, aromadendrene, β-elemene, 2,4-thujadiene, α-cadinol, myrtenol, geranyl butyrate, pin-2-en-4-one, linalyl isovalerate, β-bourbonene and α-funebrene.

[20]Technical dossier/Supplementary information March 2023/Literature search_Spanish_sage_oil.

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

3.3.2 | 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.

3.3.3 | Shelf-life

The typical shelf-life of Spanish 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).[22] However, no data supporting this statement were provided.

3.3.4 | Conditions of use

Spanish 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 Spanish sage oil in complete feed.

Animal category	Maximum use level (mg/kg complete feed)
Chickens for fattening	15
Laying hens	15
Turkeys for fattening	15
Piglets	30
Pigs for fattening	30
Sows	30
Veal calves (milk replacers)	20
Cattle for fattening	20
Dairy cows	20
Sheep/goats	20
Horses	35
Rabbits	25
Fish (salmon)	25
Dogs	25
Cats	25
Ornamental fish	25
Other species	15

3.4 | Safety

The assessment of the safety of Spanish sage oil is based on 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. The applicant carried out an extensive database search (no time limits) to identify data related to the chemical composition and the safety of preparations obtained from *S. officinalis*.[23] Four cumulative databases (LIVIVO, NCBI, OVID and ToxInfo), 13 single databases 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.

[22]Technical dossier/Section II.

[23]Technical dossier/Supplementary information March 2023/ Literature search_Spanish_sage_oil.

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), the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) and the EFSA Panel on Food Additives and Flavourings (FAF). The flavouring compounds currently authorised for food[24] and/or feed[25] use, together with the EU Flavour Information System (FLAVIS) number, the chemical group as defined in Commission Regulation (EC) No 1565/2000,[26] and the corresponding EFSA opinion are listed in Table 4.

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
03	α, ß-Unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters	Geraniol	02.012	2016a
		Neral	05.170	
		trans-3,7-Dimethylocta-2,6-dienal (geranial)	05.188	
		Geranyl acetate	09.011	
		Geranyl butyrate	09.048	
		Geranyl propionate	09.128	
		Neryl acetate	09.213	
04	Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols, aldehydes, acids, acetals and esters	Hex-3(cis)-enyl acetate	09.197	2016b
06	Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters with esters containing tertiary alcohols ethers	Linalool	02.013	2012a
		α-Terpineol	02.014	
		2-(4-Methylphenyl)propan-2-ol	02.042	
		4-Terpinenol	02.072	
		Linalyl acetate	09.013	
		(E)-3,7-Dimethylocta-1,5,7-trien-3-ol[a]	02.146	
07	Primary alicyclic saturated and unsaturated alcohols/aldehydes/acids/acetals/esters with esters containing alicyclic alcohols	Myrtenol[a]	02.091	2017, CEF
		Myrtenal[a]	05.106	2019, FAF
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
		l-Carvone	07.147	
		d,l-Bornyl acetate	09.017	
		d,l-Isobornyl acetate	09.218	
		d-Camphor[b]	07.215	2016c, 2023b
		Pin-2-en-4-one[a]	07.196	2011a, CEF 2012, CEF
13	Furanones and tetrahydrofurfuryl derivatives	Linalool oxide[c]	13.140	2012b
16	Aliphatic and alicyclic ethers	1,8-Cineole	03.001	2012c, 2021
31	Aliphatic and aromatic hydrocarbons and acetals containing saturated aldehydes	1-Isopropyl-4-methylbenzene (*p*-Cymene)	01.002	2015
		Terpinolene	01.005	
		α-Phellandrene	01.006	
		α-Terpinene	01.019	
		γ-Terpinene	01.020	
		d-Limonene	01.045	

[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. Available online: https://ec.europa.eu/food/sites/food/files/safety/docs/animal-feed-eu-reg-comm_register_feed_additives_1831-03.pdf.

[26]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 (Continued)

CG	Chemical group	Product (EU register name)	FLAVIS No.	EFSA* opinion, year
		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	
		Valencene	01.017	
		3,7-Dimethyl-1,3,6-octatriene (β-ocimene)[d]	01.018	
		δ-3-Carene	01.029	
		δ-Cadinene[a,e]	01.021	2011b, CEF
		3,7,10-Humulatriene[a,e]	01.043	
		α-Muurulene[a,e]	01.052	
		1,1,7-trimethyltricyclo[2.2.1.0.(2.6)] heptane (tricyclene)[a,e]	01.060	
		4(10)-Thujene (sabinene)[a]	01.059	2015a, CEF
		β-Bourbonene[a]	01.024	
32	Epoxides	β-Caryophyllene epoxide[a]	16.043	2014, CEF

*FEEDAP opinion unless otherwise indicated.

[a]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.

[b]JECFA and EFSA evaluated the enantiomer *d*-camphor [07.159] (name in the register: (1R,4R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one) for use in food (EFSA, 2008) and in feed (EFSA FEEDAP Panel, 2016c).

[c]Linalool oxide [13.140]: A mixture of *cis*- and *trans*-linalool oxide (5-ring) was evaluated [13.140].

[d]EFSA evaluated β-ocimene [01.018], a mixture of (*E*)- and (*Z*)-isomers (EFSA CEF Panel, 2015b).

[e]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 Spanish sage oil, accounting for about 67% of the GC peak areas, have been previously assessed and considered safe for use as flavourings. They are currently authorised for use in food[27] without limitations and for use in feed[28] at individual use levels higher than those resulting from the intended use in feed of the essential oil under assessment.

Four compounds listed in Table 4, δ-cadinene [01.021], 3,7,10-humulatriene [01.043], α-muurulene [01.052] and tricyclene [01.060] 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 sub-chronic toxicity data (EFSA CEF Panel, 2011b). 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).

Twenty-five volatile compounds have not been previously assessed for use as flavourings. The FEEDAP Panel notes that 17 of them[29] accounting for 3.4% of the GC–MS area are aliphatic monoterpenes or sesquiterpenes structurally related to flavourings already assessed in CG 6, 8 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 (EFSA FEEDAP Panel, 2012a, 2015, 2016c, 2016d).

Camphor (as a mixture of isomers) has not been evaluated for use as a flavouring but is closely related to the flavouring compound *d*-camphor [07.215] already assessed in CG 8 (EFSA FEEDAP Panel, 2016c). Subsequently, *d*-camphor was assessed in tolerance studies with a mixture of flavourings referred to as 'Herbal mixture' in chickens for fattening, piglets, cattle for fattening and salmons. The tolerance studies showed that *d*-camphor was safe up to 5 mg/kg complete feed for all animal species (EFSA FEEDAP Panel, 2023b).

[27]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.

[28]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.

[29]*trans*-sabinene hydrate, δ-terpinyl acetate, α-cadinol (CG 6); (*Z*)-sabinol, *trans*-carveol, sabinyl acetate (CG 8); *trans*-3,7-dimethyl-1,3,6-octatriene, β-elemene, α-thujene, α-funebrene, α-gurjunene, aromadendrene, alloaromadendrene, γ-muurolene, bicyclogermacrene, γ-cadinene, α-curcumene (CG 31).

The genotoxic potential for seven compounds (*trans-p*-2-menthen-1-ol, spathulenol, viridiflorol, T-muurolol, shyobunol, 2,5-bornanedione and 2,4-thujadiene) was predicted with the Organisation for Economic Co-operation and Development (OECD) quantitative structure–activity relationship (QSAR) Toolbox. No alerts were identified for in vitro mutagenicity by Ames test (with and without S9 mix), for genotoxic and non-genotoxic carcinogenicity and for other toxicity endpoints for the seven compounds.[30]

The FEEDAP Panel notes that several publications indicate that Spanish sage (oil) is a well-known abortifacient. A fraction of Spanish sage oil containing 50% sabinyl acetate caused abortion and maternal toxicity in mice in a dose-dependent manner starting from 15 mg oil/kg bw per day (Pages et al., 1992, as reported in Tisserand & Young, 2014; Dosoky & Setzer, 2021; Wojtunik-Kulesza, 2022). These effects were probably due to sabinyl acetate, which is present in Spanish sage oil and in other essential oils. At very high doses (close to lethal doses, 50–550 mg/kg bw), also camphor has been reported to be reprotoxic and abortifacient (as reviewed in Dosoky & Setzer, 2021). At the concentrations of sabinyl acetate and camphor resulting from the use of the Spanish sage oil under assessment at the proposed use levels in feed, these effects are not expected to occur.

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 99.3% 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. The oil under assessment contains by specification up to 36% of an isomeric mixture of camphor, which is assessed separately from the other components of the oil.

Camphor

The tolerance trials carried out in chickens for fattening, piglets, cattle for fattening and salmons with a mixture of flavourings containing *d*-camphor ('Herbal mixture') showed that *d*-camphor is safe up to 5 mg/kg complete feed for all animal species with a margin of safety of 10 (EFSA FEEDAP Panel, 2023b). The FEEDAP Panel considers that the conclusions reached for *d*-camphor can be extrapolated to *l*-camphor by applying read-across.

At the proposed conditions of use for Spanish sage oil (see Section 3.3.3), the concentration of camphor in feed would range from 5.4 mg/kg for poultry species to 12.6 mg/kg for horses, considering that camphor is present in the essential oil under assessment at the highest specification of 36% (see Table 5).

TABLE 5 Concentration of camphor (isomeric mixture) in complete feed resulting from the use of Spanish sage oil at the proposed conditions of use and calculated maximum safe concentrations of Spanish sage oil in complete feed (mg/kg) to ensure a safe level of camphor for the different target animal categories.

Animal category	Daily feed intake (g DM/kg bw)	Proposed use level (mg/kg complete feed)[a]	Concentration of camphor (mg/kg complete feed)[b]	Maximum safe use level (mg/kg complete feed)[a,c]
Chickens for fattening	79	15	5.4	14
Laying hens	53	15	5.4	14
Turkeys for fattening	59	15	5.4	14
Piglets	44	30	10.8	14
Pigs for fattening	37	30	10.8	14
Sows lactating	30	30	10.8	14
Veal calves (milk replacer)	19	20	7.2	14
Cattle for fattening	20	20	7.2	14
Dairy cows	31	20	7.2	14
Sheep/goats	20	20	7.2	14
Horses	20	35	12.6	14
Rabbits	50	25	9.0	14

[30]Technical dossier/Supplementary information March 2023/BDG-01-SIn-reply_Spanish sage oil.

TABLE 5 (Continued)

Animal category	Daily feed intake (g DM/kg bw)	Proposed use level (mg/kg complete feed)[a]	Concentration of camphor (mg/kg complete feed)[b]	Maximum safe use level (mg/kg complete feed)[a,c]
Salmonids	18	25	9.0	14
Dogs	17	25	9.0	14
Cats[d]	20	25	9.0	14
Ornamental fish	5	25	9.0	14

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

[b]Based on the highest proposed specification (36% of the GC area) of camphor in the additive.

[c]Maximum safe use level calculated to ensure a maximum concentration of ≤ 5 mg camphor/kg complete feed.

Considering that *d*-camphor is safe up to 5 mg/kg complete feed and considering a concentration of camphor (isomeric mixture) in Spanish sage oil corresponding to the highest specification of 36%, the FEEDAP Panel concludes that the use of Spanish sage oil is safe at a maximum use level of 14 mg/kg complete feed for all animal species.

Components other than camphor

Based on considerations related to structural and metabolic similarities, the components were allocated to 10 assessment groups, corresponding to the chemical groups (CGs) 3, 4, 6, 7, 8, 10, 13, 16, 31 and 32, as defined in Annex I of Regulation (EC) No 1565/2000. For CG 31 ('aliphatic and aromatic hydrocarbons'), sub-assessment 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 calculated for chickens for fattening, the species with the highest ratio of feed intake/body weight per day, are shown in Table 6.

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[31]). For some components in the assessment group, toxicological data were available to derive no observed adverse effect levels (NOAELs). 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 sub-chronic studies, from which NOAEL values could be derived, were available for citral [05.020] the representative compound in CG 3 (EFSA FEEDAP Panel, 2016a), hex-3(cis)-en-1-ol [02.056] in CG 4 (EFSA FEEDAP Panel, 2016b), terpineol [02.230][32] and linalool [02.013] in CG 6 (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, 2012c; EFSA FEEDAP Panel, 2021), myrcene [01.008], *d*-limonene [01.045] and β-caryophyllene [01.007] in CG 31 (EFSA FEEDAP, 2015, 2016d) and β-caryophyllene epoxide [16.043] in 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.

The NOAEL of 345 mg/kg bw per day for citral [05.020] was used as a group NOAEL for all compounds belonging to CG 3. For hex-3*(cis)*-enyl acetate [09.197] in CG 4, a NOAEL of 127 mg/kg bw per day was extrapolated from hex-3(*cis*)-en-1-ol [02.056] due to structural similarity.

For the subgroup of terpinyl derivatives in CG 6, i.e. α-terpineol [02.072], 4-terpinenol [02.072], α-terpinyl acetate [09.015] and δ-terpinyl acetate, and for α-cadinol, *trans-p*-2-menthen-1-ol and T-muurolol, the reference point was selected based on the NOAEL of 250 mg/kg bw per day available for terpineol [02.230]. An 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). In CG 6, the NOAEL of 117 mg/kg bw per day from linalool [02.013] was extrapolated to linalyl isovalerate [09.454] and linalyl acetate [09.013].

[31]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/.

[32]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.

For *d,l*-isoborneol [02.059], *d,l*-borneol [02.016], *d,l*-bornyl acetate [09.218] and *d,l*-isobornyl propionate [09.131] in CG 8, a NOAEL of 15 mg/kg bw per day was extrapolated from *d,l*-isobornyl acetate [09.218]. For *l*-carvone, present in the additive and structurally related to *d*-carvone [01.146], the applicant made reference to a BMD lower confidence limit for a benchmark response of 10% ($BMDL_{10}$) of 60 mg/kg bw per day for *d*-carvone (EFSA FEEDAP Panel, 2016c; EFSA Scientific Committee, 2014).

Since a compound-specific NOAEL has been identified for α-terpinene [01.019], which is lower than that of *d*-limonene [01.045], the representative compound in CG 31, III, the FEEDAP Panel considered the need to review the read-across applied within this group. The assessment group 'cyclohexene derivatives' includes compounds characterised by the presence of at least two double bonds, which can be either isolated (as in *d*-limonene) or conjugated (as in α-terpinene). For the two subgroups of compounds, a refinement in read-across is applied as follows: the NOAEL of 250 mg/kg bw per day for *d*-limonene is applied to the compounds with isolated double bonds and the NOAEL of 60 mg/kg bw per day for α-terpinene to the compounds with conjugated double bonds.

The NOAELs of 44, 250 and 222 mg/kg bw per day for the representative compounds of CG 31, myrcene [01.008], *d*-limonene [01.045] and β-caryophyllene [01.007] were applied, respectively, using read-across to the compounds within sub-assessment groups II (*trans*-3,7-dimethyl-1,3,6-octatriene), III (γ-terpinene [01.020], terpinolene [01.055] and β-elemene) and V (tricyclene [01.060], α-thujene, α-pinene [01.004], camphene [01.009], sabinene [01.059], β-pinene [01.003], δ-3-carene [01.029], β-bourbonene [01.024], α-funebrene, α-gurjunene, β-caryophyllene [01.007], aromadendrene, alloaromadendrene, γ-muurolene, bicyclogermacrene, α-muurolene [01.052], γ-cadinene and δ-cadinene [01.021]),[33] respectively (EFSA CEF Panel, 2015a, 2015b). In the current assessment, the NOAEL of 60 mg/kg bw per day for α-terpinene [01.019] is applied to α-phellandrene, with an UF of 2 to take into account the nature of the study carried out with α-terpinene.

The NOAEL of 44 mg/kg bw per day for myrcene [01.088] was also applied to *(E)*-3,7-dimethylocta-1,5,7-trien-3-ol [02.146] in CG 6 and the NOAEL of 222 mg/kg bw per day was extrapolated from β-caryophyllene [01.007] to viridiflorol in CG 6, to *trans*-sabinene hydrate, *(Z)*-sabinol and sabinyl acetate in CG 8 and to 3,7,10-humulatriene [01.043] in CG 31, VI. 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 (EFSA FEEDAP Panel, 2023c).

For the remaining compounds,[34] 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 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 6.

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.[35]

The approach to the safety assessment of Spanish sage oil for the target species is summarised in Table 6. 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 14 mg/kg complete feed.

[35]Compounds included in the assessment groups but not reported in the table: geranyl propionate [09.128], geranyl acetate [09.011], geraniol [02.012], neryl acetate [09.213], neral [05.170], geranial [05.188], geranyl butyrate [09.048] (CG 3); hex-3(*cis*)-enyl acetate [09.197] (CG 4); viridiflorol, *trans*-sabinene hydrate, δ-terpinyl acetate, (*E*)-3,7-dimethylocta-1,5,7-trien-3-ol [02.146], *trans*-*p*-2-menthen-1-ol, T-muurolol, α-cadinol, linalyl isovalerate [09.454] (CG 6); *l*-carvone [07.147] (CG 8); α-phellandrene [01.006], α-terpinene [01.019], β-elemene (CG 31 III); bicyclogermacrene, tricyclene [01.060], α-thujene, δ-cadinene [01.021], α-gurjunene, γ-cadinene, α-muurolene [01.052], alloaromadendrene, γ-muurolene, δ-3-carene [01.029], aromadendrene, β-bourbonene [01.024], α-funebrene (CG 31 V).

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

[34]CC I (3 mg/kg bw per day): 2-(4-methylphentyl)propan-2-ol [02.042], spathulenol, viridiflorol [02.215], myrtenal, myrtenol, (1R) 2,2,3-trimethylcyclopent-3-en-1-yl acetaldehyde, *trans*-carveol, *d,l*-isobornyl propionate [09.131], shyobunol, α-curcumene; CC II (0.91 mg/kg bw per day): camphor, pin-2-en-4-one [07.196] and linalool oxide [13.140]; CC III (0.15 mg/kg bw per day): 2,5-bornanedione and 2,4-thujadiene.

TABLE 6 Compositional data, intake values (calculated for chickens for fattening at 14 mg/kg complete feed), reference points, margin of exposure (MOE) for the individual components of Spanish 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 Constituent	**FLAVIS-No –**	**Highest conc. in the oil %**	**Highest feed conc. mg/kg**	**Daily Intake[a] mg/kg bw/day**	**Cramer Class[b] –**	**NOAEL[c] mg/kg bw/day**	**MOE[d] –**	**MOET[e] –**
CG 6								
Linalyl acetate	09.013	4.50	0.630	0.0565	(I)	117	2070	
α-Terpinyl acetate	09.015	3.40	0.475	0.0427	(I)	125[f]	2929	
Linalool	02.013	2.28	0.319	0.0287	(I)	**117**	4083	
α-Terpineol	02.014	0.81	0.113	0.0101	(I)	125[f]	12,324	
4-Terpinenol	02.072	0.74	0.103	0.0093	(I)	125[f]	13,458	
Spathulenol	–	0.17	0.024	0.0022	I	*3*	1388	
2-(4-Methylphenyl) propan-2-ol	02.042	0.07	0.630	0.0565	I	*3*	3617	
MOET CG 6								450
CG 7								
(1R)-2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde	05.119	0.09	0.012	0.0011	I	*3*	2712	
Myrtenal	05.106	0.07	0.010	0.0009	I	*3*	3510	
Myrtenol	02.091	0.03	0.004	0.0003	I	*3*	9181	
MOET CG 8								1312
CG 8								
d,l-Borneol	02.016	3.31	0.464	0.0416	(I)	15	360	
Sabinyl acetate		2.68	0.375	0.0337	(I)	222	6591	
d,l-Isobornyl acetate	09.218	1.75	0.246	0.0220	(I)	**15**	680	
(Z)-Sabinol	–	1.38	0.193	0.0173	(I)	222	12,837	
d,l-Isobornyl propionate	09.131	0.15	0.021	0.0019	(I)	15	8064	
d,l-Bornyl acetate	09.017	0.07	0.009	0.0008	(I)	15	17,813	
d,l-Isoborneol	02.059	0.06	0.009	0.0008	(I)	15	19,250	
Shyobunol	–	0.05	0.007	0.0007	I	*3*	4504	
trans-Carveol	–	0.03	0.004	0.0003	I	*3*	9548	
Pin-2-en-4-one	07.196	0.02	0.002	0.0002	II	*0.91*	4827	
MOET CG 8								191
CG 10								
2,5-Bornanedione	–	0.05	0.007	0.0006	III	*0.15*	249	
CG 13								
Linalool oxide	13.140	0.04	0.006	0.0005	II	*0.91*	1810	
CG 16								
1,8-Cineole	03.001	23.95	3.353	0.3010	(II)	**100**	332	
CG 31, II (Acyclic alkanes)								
Myrcene	01.008	2.322	0.325	0.0292	(I)	**44**	1508	
trans-β-Ocimene	–	0.093	0.014	0.0013	(I)	44	35,135	
MOET CG 31, II								1446
CG 31, III (Cyclohexene hydrocarbons)								
d-Limonene	01.045	6.259	0.876	0.0787	(I)	**250**	3178	
γ-Terpinene	01.020	0.777	0.109	0.0098	(I)	250	25,600	
Terpinolene	01.005	0.440	0.062	0.0055	(I)	250	45,208	
α-Phellandrene	01.006	0.200	0.028	0.0025	(I)	30[g]	11,935	

(Continues)

TABLE 6 (Continued)

Essential oil composition			Exposure		Hazard characterisation		Risk characterisation	
Assessment group Constituent	**FLAVIS-No –**	**Highest conc. in the oil %**	**Highest feed conc. mg/kg**	**Daily Intake[a] mg/kg bw/day**	**Cramer Class[b] –**	**NOAEL[c] mg/kg bw/day**	**MOE[d] –**	**MOET[e] –**
α-Terpinene	01.019	0.198	0.028	0.0025	(I)	**30**[g]	12,055	
MOET CG 31, III								1843
CG 31, IV (Benzene hydrocarbons, alkyl)								
p-Cymene	01.002	1.029	0.144	0.0129	(I)	**154**	11,908	
α-Curcumene	-	0.054	0.008	0.0007	I	*3*	4420	
MOET CG 32, IV								3224
CG 31, V (Bi-, tricyclic, non aromatic hydrocarbons)								
α-Pinene	01.004	6.634	0.929	0.0834	(I)	222	2663	
Camphene	01.009	6.048	0.847	0.0760	(I)	222	2921	
β-Pinene	01.003	4.568	0.263	0.0236	(I)	222	3867	
Sabinene	01.059	1.880	0.640	0.0574	(I)	222	9396	
β-Caryophyllene	01.007	1.810	0.253	0.0227	(I)	**222**	9759	
2,4-Thujadiene	–	0.013	0.002	0.0002	III	*0.15*	918	
MOET CG 31, V								440
CG 31, VI (macrocyclic non aromatic hydrocarbons)								
3,7,10-Humulatriene	01.043	0.482	0.067	0.0061	(I)	111[h]	18,323	
CG 32								
β-Caryophyllene epoxide	16.043	0.194	0.027	0.0024	(III)	**109**	7793	

[a]Intake calculations for the individual components are based on the use level of 14 mg/kg in feed for chickens for fattening, the species with the highest ratio of feed intake/body weight.

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

[c]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.

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

[e]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.

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

[g]An uncertainty factor of 2 was applied to the NOAEL of 60 mg/kg bw per day for α-terpinene (nature of the study).

[h]An uncertainty factor of 2 was applied to the NOAEL of 222 mg/kg bw per day for β-caryophyllene (uncertainty in read-across).

As shown in Table 6, for all assessment groups, the MOET was > 100 at the use levels of 14 mg/kg complete feed. From the lowest MOET of 191 (for CG 8) in chickens for fattening, the MOET 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 7.

TABLE 7 Combined margin of exposure (MOET) for the assessment group CG 8 calculated for the different target animal categories at the use level of 14 mg/kg complete feed.

Animal category	Daily feed intake (g DM/kg bw)	Proposed use level (mg/kg complete feed)[a]	Lowest MOET CG 8
Chickens for fattening	79	14	191
Laying hens	53	14	285
Turkeys for fattening	59	14	256
Piglets	44	14	343
Pigs for fattening	37	14	408
Sows lactating	30	14	503
Veal calves (milk replacer)	19	14	794
Cattle for fattening	20	14	754
Dairy cows	31	14	487
Sheep/goats	20	14	754

TABLE 7 (Continued)

Animal category	Daily feed intake (g DM/kg bw)	Proposed use level (mg/kg complete feed)[a]	Lowest MOET CG 8
Horses	20	14	754
Rabbits	50	14	302
Salmonids	18	14	838
Dogs	17	14	888
Cats[b]	20	14	754
Ornamental fish	5	14	3018

[a]Complete feed containing 88% DM, milk replacer 94.5% DM.
[b]The MOET for cats is increased to 500 because of the reduced capacity of glucuronidation.

Table 7 shows that for all species the MOET exceeds the value of 100, at the use level of 14 mg/kg complete feed. 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 Spanish sage oil as additive in cat feed needs a wider margin of exposure. A MOET of 500 is considered adequate. For all target species listed in Table 7, Spanish sage oil is considered safe, when used as a feed additive at 14 mg/kg complete feed. This level is extrapolated to physiologically-related minor species and applied to the other species not considered.

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 concludes that Spanish sage oil is safe for all animal species at 14 mg/kg complete feed.

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

Spanish 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 0.001892 mg/kg bw per day for Spanish sage oil (FEMA 3003). The Fenaroli handbook also reports use levels in food and beverages in the range of 3 mg/kg up to 40 mg/kg for Spanish 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 Spanish sage oil are expected to be extensively metabolised and excreted in the target species. The use of Spanish 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.

A literature search aimed at retrieving studies related to the safety of preparations obtained from *S. officinalis* ssp. *lavandulifolia* for the users did not retrieve any relevant publication.[36]

[36]Technical dossier/Supplementary information March 2023/BDG_01_Sin_reply_Spanish_sage _oil.

The applicant provided a safety data sheet[37] for Spanish sage oil, where hazards for users have been identified.

The FEEDAP Panel considers Spanish sage oil as irritant to skin and eyes and as a dermal and respiratory sensitiser.

3.4.4 | Safety for the environment

S. officinalis ssp. *lavandulifolia* is a species native to Spain and is widely cultivated in the Mediterranean area for culinary and ornamental purposes.

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

3.5 | Efficacy

Spanish sage oil from *S. officinalis* ssp. *lavandulifolia* is listed in Fenaroli's Handbook of Flavour Ingredients (Burdock, 2009) and by FEMA with the reference number 3003.

Since Spanish 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

Spanish sage oil from *S. officinalis* ssp. *lavandulifolia* (Vahl) Gams may be produced from plants of different geographical origins and by various processes resulting in preparations with different composition and toxicological profiles. Thus, the following conclusions apply only to Spanish sage oil in which thujones are not detected and for which the content of camphor is ≤ 36%.

The FEEDAP Panel concludes that Spanish sage oil is safe at 14 mg/kg complete feed for all animal species. 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 Spanish 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 leaves of *S. officinalis* ssp. *lavandulifolia* (Vahl) Gams 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
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

[37]Technical dossier/Supplementary information March 2023/Annex VII_Sin_reply_Spanish_sage_oil_MSDS. Aspiration hazard (H304, category 1), Hazards for skin corrosion/irritation (H315, category 2), serious eye damage/eye irritation (H318, category 1), skin sensitisation (H317, category 1), specific target organ toxicity (single exposure, H371, category 2) in accordance with the criteria outlined in Annex I of 1272/2008/EC (CLP/EU-GHS).

Date	Event
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*
09/03/2023	Reception of supplementary information from the applicant (partial dataset: Spanish sage oil) - Scientific assessment remains suspended
28/09/2023	Partial withdrawal of the application for the following additive: Spanish majoram oil
19/06/2024	The application was split and a new EFSA-Q-2024-00404 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-2024-00404). 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
EMA	European Medicines Agency
EURL	European Union Reference Laboratory
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–MS	gas chromatography–mass spectrometry
GC–FID	gas chromatography–flame ionisation detection
ISO	International Organisation for Standardization
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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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

European Commission

QUESTION NUMBER

EFSA-Q-2010-01307 (new EFSA-Q-2024-00404)

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