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Safety and efficacy of a feed additive consisting of an essential oil from the fruit of *Cuminum cyminum* L. (cumin 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 an essential oil obtained from the fruit of *Cuminum cyminum* L. (cumin oil), when used as a sensory additive in feed and water for drinking for all animal species. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concluded that the use of cumin oil up to the maximum proposed use levels in feed of 15 mg/kg complete feed is considered as safe for all animal species. The FEEDAP Panel considered the use in water for drinking as safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed. No concerns for consumers were identified following the use of cumin oil up to the maximum proposed use level in feed. The additive under assessment should be considered as irritant to skin and eyes, and as a dermal and respiratory sensitiser. When handling the essential oil, exposure of unprotected users to estragole (and dillapiole) cannot be excluded. Therefore, to reduce the risk, the exposure of the users should be minimised. The use of cumin oil at the proposed use level in feed is not expected to pose a risk to the environment. Since *C. cyminum* and its preparations are 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.

Keywords: sensory additives, flavouring compounds, *Cuminum cyminum* L., cumin oil, 4-isopropylbenzaldehyde (cuminaldehyde), estragole, dillapiole

Requestor: European Commission

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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 29 preparations (namely dill herb oil, dill seed extract, dill tincture, dong quai tincture, celery seed oil, celery seed extract (oleoresin), celery tincture, hares ear tincture, caraway seed oil, caraway oleoresin/extract, coriander oil, cumin oil, taiga root extract (solvent-based, sb), taiga root tincture, fennel oil, fennel tincture, common ivy extract (sb), opoponax oil, ginseng tincture, parsley oil, parsley tincture, anise oil, anise tincture, ajowan oil, Ferula Assa-foetida oil, anise star oil, anise star tincture, anise star terpenes and omicha tincture) belonging to botanically defined group (BDG) 02 – *Apiales/ Austrobaileyales* when used as feed additives for all animal species (category: sensory additives; functional group: flavourings). During the assessment, the applicant withdrew the application for nine preparations (dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, opoponax oil,[3] parsley oil, hares ear tincture, taiga root extract (sb), ajowan oil[4] and parsley tincture[5]). During the course of the assessment, this application was split and the present opinion covers only one out of the 20 remaining preparations under application: cumin oil from the fruit of *Cuminum cyminum* L. for all animal species.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (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 24 June 2019.

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 product cumin oil (*C. cyminum*), when used under the proposed conditions of use (see Section 3.2.4).

The remaining 19 preparations belonging to botanically defined group (BDG) 02 – *Apiales/ Austrobaileyales* under application are assessed in separate opinions.

1.2. Additional information

The additive 'cumin oil' from *C. yminum* 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.

EFSA issued an opinion on the safety and efficacy of cumin tincture when used in feed for all animal species (EFSA FEEDAP Panel, 2018a).

There is no specific EU authorisation for any *C. cyminum* L. preparation when used to provide flavour in food. However, according to Regulation (EC) No 1334/2008[6] flavouring preparations

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on 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, 1,050 Brussels, Belgium.

[3] On 27 February 2019, EFSA was informed by the applicant about the withdrawal of the applications on dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, and opoponax oil.

[4] On 2 April 2020, EFSA was informed by the applicant about the withdrawal of the applications on parsley oil, hares ear tincture, taiga root extract (sb), ajowan oil.

[5] On 9 December 2020, the applicant informed EFSA about the withdrawal of the application on celery tincture.

[6] 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.

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'.

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/or the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The list of flavouring compounds currently authorised for food[7] and feed[8] uses together with the EU Flavour Information System (FLAVIS) number, the chemical group as defined in Commission Regulation (EC) No 1565/2000[9] and the corresponding EFSA opinion are given in Table 1.

Table 1: 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 (common name)	FLAVIS No	EFSA* or JECFA opinion, Year
03	a, ß-Unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/ acids, acetals and esters	trans-2-Nonenal	05.072	2019a
06	Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters with esters containing tertiary alcohols ethers	Linalool	02.013	2012a
		2-(4-Methylphenyl) propan-2-ol	02.042	
		4-Terpinenol	02.072	
07	Primary alicyclic saturated and unsaturated alcohols, aldehydes, acids, acetals esters with esters containing alicyclic alcohols	1,3-*p*-Menthadien-7-al(α-terpinen-7-al)	05.133	WHO, 2010a,b (JECFA)
08	Secondary alicyclic saturated and unsaturated alcohols, ketones, ketals and esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols	Pinocarveol[(a)]	02.100	2011a, CEF 2012, CEF
16	Aliphatic and alicyclic ethers	1,8-Cineole	03.001	2012b, 2021a
23	Benzyl alcohols, aldehydes, acids, esters and acetals	4-Isopropylbenzayl alcohol	02.039	2012c
		4-Isopropylbenzaldehyde (cuminaldehyde)	05.022	
25	Phenol derivatives containing ring-alkyl, ring-alkoxy and side-chains with an oxygenated functional group	Thymol	04.006	2012d
		4-Methylphenol	04.026	
		Carvacrol	04.031	
		4-Isopropylphenol	04.073	
31	Aliphatic and aromatic hydrocarbons and acetals containing saturated aldehydes	Limonene[(a),(b)]	01.001	2008, AFC
		1-Isopropyl-4-methylbenzene(*p*-cymene)	01.002	2015
		Terpinolene	01.005	

[7] 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.

[8] 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

[9] 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 180, 19.7.2000, p. 8.

CG	Chemical Group	Product – EU register name (common name)	FLAVIS No	EFSA* or JECFA opinion, Year
		α-Phellandrene	01.006	
		1-Isopropenyl-4-methylbenzene	01.010	
		α-Terpinene	01.019	
		γ-Terpinene	01.020	
		Pin-2(10)-ene (β-pinene)	01.003	2016a
		Pin-2(3)-ene (α-pinene)	01.004	
		β-Caryophyllene	01.007	
		Myrcene	01.008	
		Camphene	01.009	
		δ-3-Carene	01.029	
		δ-Cadinene[(a),(c)]	01.021	2011b, CEF
		β-Bisabolene[(a)]	01.028	
		3,7,10-Humulatriene[(a),(c)]	01.043	
		β-Phellandrene[(a),(c)]	01.055	
		β-Farnesene[(a)]	01.041	2015a, CEF
		Sabinene (4(10)-thujene)[(a)]	01.059	2015b, CEF
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 JECFA before 2000 are not required to be re-evaluated by EFSA.
(b): JECFA and EFSA evaluated d-limonene [01.045] (EFSA, 2008). d-Limonene [01.045] and l-limonene [01.046] were also evaluated for use in feed (EFSA FEEDAP Panel, 2015).
(c): 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).

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[10] in support of the authorisation request for the use of cumin oil from *C. cyminum* as a feed additive.

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 preparations belonging to BDG 2.[11]

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 additives. The evaluation report is related to the methods of analysis for each feed additive included the group BDG 02 (Apiales and Austrobaileyales). In particular, for the determination of the phytochemical markers *α-pinene* and *cuminaldehyde* in *cumin oil* the EURL recommended a method based on gas chromatography coupled with flame ionisation detection (GC-FID).[12]

[10] FEED dossier reference: FAD-2010-0221.
[11] Technical dossier/Supplementary information/Letter dated 29/04/2021.
[12] The full report is available on the EURL website: https://joint-research-centre.ec.europa.eu/publications/fad-2010-0221_en

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of cumin oil from *C. cyminum* is in line with the principles laid down in Regulation (EC) No 429/2008[13] and the relevant guidance documents: Opinion of the Scientific Committee on harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic (EFSA, 2005), Statement on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed (EFSA SC, 2012), Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA SC, 2009), Compendium of botanicals that have been reported to contain toxic, addictive, psychotropic or other substances of concern (EFSA, 2012), Guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012e), Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012f), 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, 2019b), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018b), Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA SC, 2019a), Statement on the genotoxicity assessment of chemical mixtures (EFSA SC, 2019b), Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (EFSA SC, 2019c), General approach to assess the safety for the target species of botanical preparations which contain compounds that are genotoxic and/or carcinogenic (EFSA FEEDAP Panel, 2021b).[14]

3. Assessment

The additive under assessment, cumin oil, is obtained from the fruit of *C. cyminum* L. It 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

Cuminum cyminum L. is an annual flowering plant in the Apiaceae family, said to be native to south Asia. The species is the source of cumin fruit (commonly referred to as cumin seeds) extensively used as a spice and also as medicinal plant in several traditions outside the EU. The term 'cumin' may be loosely used to describe the whole *C. cyminum* plant, or its fruit, or fruit derived from other plants (black cumin from *Nigella sativa* and bitter cumin from *Cuminum nigrum*) used for similar purposes.

The additive is extracted from the fruit by steam distillation. The volatile constituents are condensed and then separated from the aqueous phase by decantation.

3.2. Characterisation

3.2.1. Characterisation of cumin oil

Cumin oil is a colourless to pale yellow clear mobile liquid, with a characteristic spicy earthy aroma. In seven recent batches of the additive (all originating from India, produced in 2020), the refractive index (20°C) ranged between 1.496 and 1.501, the density (20°C, five batches) between 910 and 914 kg/m^3, the optical rotation (20°C) between 3.25° and 4.68° (five batches).[15] Cumin oil is identified with the single Chemical Abstracts Service (CAS) number 8014-13-9, the European Inventory of Existing Commercial Chemical Substances (EINECS) number 283–881-7, the Flavor Extract Manufacturers Association (FEMA) number 2340 and the Council of Europe (CoE) number 161.

[13] 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.

[14] https://www.efsa.europa.eu/sites/default/files/2021-05/general-approach-assessment-botanical-preparations-containing-genotoxic-carcinogenic-compounds.pdf

[15] Technical dossier/Supplementary information July 2021/Annex_II_cumin_oil_CoA_chrom.

For cumin oil, the product specifications used by the applicant are based on those developed by the International Organization for Standardization (ISO) 9301:2003 for essential oil of 'cumin seed' (*C. cyminum*),[16] adapted to reflect the concentrations of selected volatile components of the essential oil. Four components contribute to the specifications as shown in Table 2, with 4-isopropylbenzaldehyde (hereinafter referred to as cuminaldehyde) selected as phytochemical marker. The analysis of seven batches of the additive showed compliance with these specifications when analysed by GC-FID and expressed as % of gas chromatographic peak area (% GC area).[17] The applicant provided the full characterisation of the volatile constituents in seven batches obtained by gas chromatography–mass spectrometry (GC–MS).[18] The four compounds accounted for about 64.4% on average (range 57.9–67.7%) of % GC area (Table 2).

Table 2: Selected constituents of the essential oil from the fruit of *Cuminum cyminum* L. as defined based on ISO standard (9301:2003): specifications and batch to batch variation based on the analysis of seven batches. 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	CAS No	FLAVIS No	% GC area		
EU register name			Specification	Mean	Range
Cuminaldehyde (4-isopropylbenzaldehyde)	122-03-2	05.022	14–56	32.3	29.8–34.3
γ-Terpinene	99-85-4	01.020	13–32	20.0	15.9–22.7
β-Pinene (pin-2(10)-ene)	127-91-3	01.003	7–20	11.2	10.2–12.7
α-Pinene (pin-2(3)-ene)	80-56-8	01.004	0.3–2.0	0.88	0.67–1.07
Total				64.4	57.9–67.7

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

In total, up to 70 constituents were detected, 62 of which were identified and accounted on average for 99.5% (99.1–99.9%) of the 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 3. These 12 compounds together account on average for 94.9% (93.3–96.4%) of the % GC area. The remaining 50 compounds (ranging between 0.007% and 0.5%) and accounting on average for 4.6% are listed in the footnote.[19] Based on the available data on the characterisation, cumin oil is considered a fully defined mixture.

Table 3: Other volatile constituents of the essential oil from the fruit of *Cuminum cyminum* L. accounting on average for >0.5% of the composition (based on the analysis of seven batches) not included in the specifications. 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	CAS No	FLAVIS No	% GC area	
EU register name			Mean	Range
p-Cymene (1-isopropyl-4-methylbenzene)	99-87-6	01.002	14.0	11.9–18.8
1,3-*p*-Menthadien-7-al (α-terpinen-7-al)	1197-15-5	05.133	8.31	7.18–10.9
1,4-*p*-Menthadien-7-al (γ-terpinen-7-al)	22580-90-1	–	4.07	2.77–6.66

[16] Technical dossier/Supplementary information July 2021/Annex_III_SIn_reply_cumin_oil_ ISO.
[17] Technical dossier/Supplementary information July 2021/SIn reply_cumin oil. GC-FID analysis: cuminaldehyde (27.2–32.3%), γ-terpinene (16.6–26.5%), β-pinene (11.5–15.7%) and α-pinene (0.6–1.1%).
[18] Technical dossier/Supplementary information July 2021/Annex_II_ cumin_oil_CoA_chromatogram.
[19] Additional constituents: constituents (n = 21) between < 0.5% and > 0.1%: carvotan acetone, limonene, α-neocallitropsene, p-1,4-menthadien-7-ol, 4(10)-thujene (sabinene), carvacrol, phellandral, α-thujene, β-phellandrene, 1-isopropenyl-4-methylbenzene, β-farnesene, β-caryophyllene, daucene, 2-(4-methylphenyl)propan-2-ol, 4-terpinenol, carotol, α-curcumene, α-terpinene, p-mentha-1(7),5-dien-2-ol, 1,8-cineol and p-mentha-3,8-diene; constituents (n = 29) between < 0.1 and ≥ 0.009%: 4-isopropylphenol, (E)-α-bergamotene, terpinolene, p-menth-4(8)-en-7-ol, β-bisabolene, 1,8-p-menthadien-4-ol, o-cymene, α-alaskene, thymol, β-caryophyllene epoxide, fenchone, trans-2-nonenal, carvenone, 3,7,10-humulatriene, δ-3-carene, pinocarveol, δ-cadinene, linalool, α-copaene, p-1-menthene, m-cymene, dillapiole, camphene, estragole, 3-methylphenol, cumene, 2,3-dihydro-1,8-cineole, trans-sabinene hydrate and α-fenchene.

Constituent EU register name	CAS No	FLAVIS No	% GC area	
			Mean	Range
β-Acoradiene	28477-64-7	–	2.65	2.31–3.34
α-Phellandrene	99-83-2	01.06	0.74	0.36–1.14
4-Isopropylbenzyl alcohol	526-60-7	02.039	0.70	0.59–0.82
3-p-Menthen-7-al	27841-22-1	–	0.69	0.37–0.93
Myrcene	125-35-3	01.008	0.57	0.51–0.74
Total			30.5	27.2–38.4

EU: European Union; CAS no. Chemical Abstracts Service number; FLAVIS number: EU Flavour Information System number.

The applicant performed a literature search for the chemical composition of *C. cyminum* and its preparations and the identity of any recognised substances of concern.[20] The presence of estragole in essential oils from fruit of *C. cyminum* is reported in the EFSA Compendium (EFSA, 2012) [21] and in several publications (e.g. Sharma et al., 2016; Merah et al., 2020). Several publications also reported the presence in cumin oil of dillapiole, an alkoxy substituted allylbenzene structurally related to estragole (e.g. Romagnoli et al., 2010; Johri, 2011).

Estragole was detected by the applicant in all seven batches of the cumin oil under assessment at an average concentration of 0.028% (range: 0.001–0.046%) and dillapiole in five batches (average: 0.031%, range: 0.027–0.040%).

3.2.2. Impurities

The applicant made reference to the 'periodic testing' of some representative flavourings premixtures for mercury, cadmium, lead, arsenic, fluoride, dioxins and polychlorinated biphenyls (PCBs), organo-chloride pesticides, organo-phosphorous pesticides, aflatoxins B1, B2, G1, G2 and ochratoxin A. However, no data have been provided. Since cumin oil is produced by steam distillation, the likelihood of any measurable carry-over of all the above-mentioned elements is low, except for mercury.

3.2.3. Shelf life

The typical shelf-life of cumin 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.

3.2.4. Conditions of use

Cumin oil is intended to be added to feed and water for drinking for all animal species without a withdrawal period. The maximum proposed use level in complete feed is 15 mg/kg for all animal species. No use level has been proposed by the applicant for the use in water for drinking.

3.3. Safety

The assessment of safety of cumin oil is based on the maximum use levels proposed by the applicant.

Many of the components of cumin oil, accounting for about 90% of the GC peak areas, have been previously assessed and considered safe for use as flavourings, and are currently authorised for use in food[7] without limitations and for use in feed[8] at individual use levels higher than those resulting from the intended use of the essential oil in feed. The list of the compounds already evaluated by the EFSA Panels and JECFA is given in Table 1 (see Section 1.2).

Three compounds, δ-cadinene [01.021], 3,7,10-humulatriene [01.043] and β-phellandrene [01.055] have been evaluated in Flavouring Group Evaluation 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 food (EFSA CEF Panel, 2010). For these compounds, for which there is no concern for

[20] Technical dossier/Supplementary information July 2021/Literature search_cumin_oil.
[21] Online version: https://www.efsa.europa.eu/en/data-report/compendium-botanicals
[22] Technical dossier/Section II.

genotoxicity, EFSA requested additional subchronic toxicity data (EFSA CEF Panel, 2011b). In the absence of such data, the EFSA CEF Panel was unable to complete its assessment. As a result, these compounds are not authorised for use as flavours in food. For these compounds, the FEEDAP Panel applies the approach recommended in the Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA SC, 2019a).

Twenty-seven volatile components of cumin oil have not been previously assessed for use as flavourings. The FEEDAP Panel notes that most of them (17) are aliphatic mono- or sesquiterpenes structurally related to flavourings already assessed in CG 8, 16 and 31 and for which a similar metabolic and toxicological profile is expected.[23] These 17 lipophilic compounds, accounting together for about 5% of the GC area, are expected to be rapidly absorbed from the gastrointestinal tract, oxidised to polar oxygenated metabolites, conjugated and excreted (EFSA FEEDAP Panel, 2012b, 2015, 2016a,b).

The following sections focus on the *p*-allylalkoxybenzenes estragole and dillapiole, which are substances of concern, and on the other 10 compounds[24] (accounting together for about 6% of the GC area) not previously assessed or not structurally related to flavourings previously assessed, based on the evidence provided by the applicant in the form of literature searches and Quantitative Structure–Activity Relationship (QSAR) analysis.

3.3.1. Absorption, distribution, metabolism and excretion

3.3.1.1. Estragole and dillapiole

Estragole is a lipophilic compound and, as such, readily and completely absorbed from the gastrointestinal tract. Phase I metabolism is catalysed by cytochrome P450 (CYP450) enzymes mainly in the liver. Demethylation of the 4-methoxygroup with formation of 4-allylphenol is followed by conjugation with glucuronic acid or sulfate and renal excretion. Oxidation of the allyl-side chain leads to estragole-2′,3′-epoxide, which is hydrolysed to the corresponding diol with subsequent glucuronidation and excretion. Both metabolic pathways result in the detoxification of estragole. The formation of genotoxic metabolites is initiated by oxidation of the side chain with formation of 1′-hydroxyestragole. Sulfate conjugation of the hydroxyl group leads to 1′-sulfooxyestragole, which is unstable and breaks down to form a highly reactive carbonium ion, which can react covalently with DNA (as reviewed in EMA, 2021).

The metabolism of estragole was evaluated in experimental animals with special focus on the formation of its proximate metabolite, 1′-hydroxyestragole, and the influence of the dose administered on the quantity excreted in urine (Zangouras et al., 1981; Anthony et al., 1987). When ^{14}C-estragole (4-[^{14}C-methoxyl]-allylbenzene) was given in low doses to rodents, the radioactivity was mainly excreted as $^{14}CO_2$ in exhaled air as a result of demethylation and only a minor portion in urine in the form of several metabolites resulting from hydroxylation at 1′-C and epoxidation at 2′,3′-C followed by ring hydrolysis. In a single study conducted in two volunteers orally given 100 μg of methoxy-^{14}C-estragole, 1′-hydroxyestragole was quantified in urine of both individuals at 0.2% and 0.4% of the given dose; the majority of the dose was excreted in expired air as $^{14}CO_2$ in the first 8 h (Sangster et al., 1987). The metabolites identified in urine indicate that estragole follows a similar biotransformation profile in rats, mice, and humans. There are no studies in human volunteers with high doses of estragole. However, studies performed in rats and in mice (Zangouras et al., 1981; Anthony et al., 1987) consistently demonstrated that increasing the oral dose of estragole showed significantly higher urinary levels of 1′-hydroxyestragole as glucuronide.

No data on the ADME of dillapiole are available. However, the same metabolic pathways described for estragole have been reported for compounds structurally related to dillapiole, such as methoxy-substituted allylbenzenes (methyleugenol and elemicin) and methylenedioxy-substituted allylbenzenes

[23] Six components (fenchone, trans-sabinene hydrate, 2,3-dihydro-1,8-cineole, α-thujene, α-copaene and α-fenchene) representing about 0.26% of the GC area are structurally related to compounds already authorised for use in food and feed as flavourings. Eleven additional constituents (*p*-1-menthene, p-mentha-3,8-diene, *o*-cymene, *m*-cymene, cumene, α-curcumene, daucene, α-neocallitropsene, (*E*)-α-bergamotene, β-acoradiene and α-alaskene) representing on average 4.6% of % GC area, are allocated to CG 31.

[24] Ten compounds not evaluated for use in food accounting for 6% of the GC area: carotol, 1,8-*p*-menthadien-4-ol, 3-*p*-menthen-7-al, *p*-menth-4(8)-en-7-ol, phellandral, γ-terpinen-7-al, *p*-1,4-menthadien-7-ol, *p*-mentha-1(7),5-dien-2-ol, carvotan acetone and carvenone.

(safrole, myristicin and apiole) (WHO, 2009). Therefore, a similar ADME is expected for dillapiole, including the formation of the 1′-sulfoxymetabolite.

Apiole, elemicin and dillapiole have more *methoxy and methylendioxy substituents* at the aromatic ring as compared to estragole, methyleugenol and safrole. The higher substitution increases the sterically hindrance and the likelihood that demethylation of the methoxygroup(s) followed by conjugation would occur, affecting the extent of formation of the 1′-sulfoxymetabolite. The application of physiologically based kinetic (PBK) models predicted that the formation of the 1′-sulfoxymetabolite in rat liver would be about 3 times lower for highly ring-substituted substances such as apiole than for safrole (Alajlouni et al., 2016). Similarly, for elemicin the formation of the DNA reactive 1′-sulfoxymetabolite was predicted to be 11- and 2-fold lower compared to the formation of the 1′-sulfoxymetabolites of estragole and methyleugenol, respectively (van den Berg et al., 2012). Based on considerations on the structure of dillapiole, a similar reduced formation of 1′-hydroxydillapiole is expected.

3.3.2. Genotoxicity and carcinogenicity

For fully defined mixtures, the EFSA Scientific Committee (EFSA SC) recommends applying a component-based approach, i.e. assessing all components individually for their genotoxic potential using all available information, including read-across and QSAR considerations about their genotoxic potential (EFSA SC, 2019b). Therefore, the potential genotoxicity of identified constituents is first considered. Then, *in vitro* genotoxicity studies performed with cumin oils similar to the additive under assessment are described.

The genotoxic potential for 10 substances (carotol, 1,8-*p*-menthadien-4-ol, 3-*p*-menthen-7-al, *p*-menth-4(8)-en-7-ol, phellandral, γ-terpinen-7-al, *p*-1,4-menthadien-7-ol, *p*-mentha-1(7),5-dien-2-ol, carvotan acetone and carvenone) was predicted by the applicant using the QSAR Toolbox.[25] No structural alerts were found for carotol and *p*-menth-4(8)-en-7-ol. Structural alerts for 1,8-*p*-menthadien-4-ol, *p*-menth-4(8)-en-7-ol and *p*-mentha-1(7),5-dien-2-ol were due to the presence of the vinyl/allyl alcohol group; for 3-*p*-menthen-7-al and phellandral, to the presence of aldehydes; for γ-terpinen-7-al, to the presence of aldehydes and α,β-unsaturated carbonyls; and for carvotan acetone and carvenone, to the presence of α,β-unsaturated vinyl/allyl ketones. For these compounds, the mutagenicity (Ames test) prediction was made by read-across analyses of data available for similar substances (i.e., analogues obtained by categorisation). Categories were defined using general mechanistic and endpoint profilers as well as empirical profilers. Mutagenicity read-across-based predictions were found consistently negative for all categories of analogues. On this basis, the alerts raised were discounted.

Estragole and dillapiole

Cumin oil contains estragole (up to 0.046%), a compound with experimentally proven genotoxicity and carcinogenicity in rodents (as reviewed in SCF, 2001; EMA, 2021), and dillapiole (up to 0.040%), another compound belonging to the class of p-allylalkoxybenzenes, structurally related to safrole.

Estragole was included in the diet of female CD-1 mice at 0, 2.3 or 4.6 g/kg diet for 12 months. At least 50% of the animals in the exposed groups developed hepatic tumours by 18 months,[26] which were diagnosed as hepatomas type A (hepatocellular adenomas) or B (hepatocellular adenocarcinomas) or mixed types A and B. The animals fed the control diet did not show any hepatic tumour (Miller et al., 1983). However, the FEEDAP Panel notes that there is high uncertainty in derivation of a benchmark dose (BMD) lower confidence limit for a benchmark response of 10% ($BMDL_{10}$) for estragole from a carcinogenicity study in CD-1 mice.[27]

Since estragole shares the same mode of action as methyleugenol, both being representatives of the group of *p*-allylalkoxybenzenes, the FEEDAP Panel applies to estragole a $BMDL_{10}$ of 22.2 mg/kg body eight (bw) per day, derived from a carcinogenicity study in rat with methyleugenol (NTP, 2000) by applying model averaging (Suparmi et al., 2019) (for details, see EFSA FEEDAP Panel, 2022).

The possible carcinogenic activity of a variety of alkenylbenzenes, including **dillapiole,** was investigated in newborn male mice, injected intraperitoneally (i.p.) with nine different compounds at

[25] Technical dossier/Supplementary information July 2021/Annex_V_Sin reply_cumin_oil_QSAR.
[26] Incidence of hepatomas in female mice (0/50, 25/50, 35/50).
[27] This strain of mice spontaneously develops a high incidence of hepatocellular adenomas and carcinomas, and the relevance of these tumours for human risk assessment is questionable. In addition, BMD modelling with only two dose levels is adding extra uncertainty in the derivation of the $BMDL_{10}$ value.

day 1, 8, 15 and 22 after birth. Among these, estragole, safrole and methyleugenol induced a significant number of hepatomas at 13 months, whereas anethol, elemicin, myristicin, dillapiole, parsley apiole and eugenol did not under the limited conditions of the study (Miller et al., 1983). Although there is a clearly demonstrated difference between the two groups of substances, the design of the study showed significant limitations due to the dosing regime, route of administration and duration,[28] which prevented a conclusion to be reached.

In another experiment using the same treatment protocol, DNA was isolated from the liver of the treated mice and the occurrence and quantity of DNA adducts was investigated (Phillips et al., 1984). The highest amount of DNA-adducts was observed with methyleugenol, estragole and safrole (73, 30 and 15 pmol/mg DNA, respectively). The yield of DNA adducts with myristicin, elemicin and dillapiole were 7.8, 2.7 and 1.2 pmol/mg DNA and the correspondent values for parsley apiole and anethole were below the LOQ of 1 pmol/mg DNA. No adducts at all were detected with eugenol. The incidence of DNA adducts correlated to the tumour incidence obtained in the experiment by Miller et al. *(*1983*)*. Two other studies on the induction of DNA adducts in liver of adult mice after i.p. injection of alkenylbenzenes (Randerath et al., 1984) and in human hepatoma cells in culture (Zhou et al., 2007) were also available. Methyleugenol was the most potent in all three studies. The two *in vivo* studies resulted in the same order of potency (i.e., methyleugenol > safrole > estragole > myristicin > elemicin > dillapiole). In the *in vitro* study, estragole was more potent than methyleugenol and safrole.

The evidence available indicates that dillapiole forms DNA adducts (measured by ^{32}P-postlabelling), although to a limited extent. This suggests that the substance may be genotoxic, similarly to structurally related compounds (methyleugenol, safrole and estragole), which are well known genotoxic carcinogens. The FEEDAP Panel notes that the use of ^{32}P-post-labelling techniques does not allow the structural identification of DNA adducts.

Although dillapiole was not carcinogenic in one study in mice (Miller et al., 1983), based on this study it is not possible to exclude that dillapiole is carcinogenic, when administered via diet under conditions mirroring lifetime oral exposure.

Overall, considering the evidence available for dillapiole and for structurally similar compounds sharing the same metabolic pathway and the same mode of action, it cannot be excluded that dillapiole is a genotoxic carcinogen, although less potent than safrole, estragole and methyleugenol. The limitations in the available dataset do not allow to derive a relative potency factor from the relative ratio of DNA adducts for dillapiole compared to methyeugenol, estragole and safrole.

Genotoxicity studies with the cumin oils

Nirogi et al. (2014) performed an Ames test for the assessment of the mutagenic potential of Indian *C. cyminum* fruit oil (cuminaldehyde (15–40%), terpinenes (18–29%), α-pinene (1.3%), β-pinene (2.0%), menthadienal (30%) and variable amounts of cineole, p-cymene and limonene). Cytotoxicity was observed in the range of 0.08–2.5 μL/plate in the absence and presence of metabolic activation with no concurrent increase in the number of revertant colonies.

Goyal et al. (2019) evaluated the clastogenic activity of Indian *C. cyminum* fruit oil (cuminaldehyde (15–40%), terpinenes (18–29%), α-pinene (1.3%), β-pinene (2.0%), menthadienal (30%), and variable amounts of cineole, *p*-cymene and limonene) by means of an *in vitro* micronucleus test using CHO-K1 cells. The test was performed according to the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 487. Based on cytotoxicity, precipitation and pH analysis, the product was tested at 0.005, 0.016 and 0.05 μL/mL in the presence and absence of metabolic activation. No increase in the frequency of micronuclei in binucleated cells was observed in any experimental condition.

The test items in both genotoxicity tests meet the specifications of the additive under evaluation for the main components, cuminaldehyde and γ-terpinene, but they differ in the concentrations reported for other components such as β-pinene and menthadienal and are not characterised for their concentrations of estragole and dillapiole. Therefore, the Panel considers the results of these tests of limited relevance.

[28] Although more susceptible new-born mice were used, the limited administration on a few days via intraperitoneal injection is not comparable with lifetime exposure; only the cumulative dose was available in the report.

3.3.3. Other toxicological studies

The applicant submitted a repeated-dose oral toxicity study in rats (45 days) performed with an essential oil obtained from the fruit of *C. cyminum* (Taghizadeh et al., 2017). The GC analysis showed that the essential oil tested is similar in composition and content of the main components to the essential oil under assessment (Table 4). Among the major components, the main differences are due to the relative proportions of three aldehydes, cuminaldehyde, 1,3-*p*-menthadien-7-al and γ-terpinen-7-al. However, these three compounds, accounting together for about 45–47% of the composition of the oils, are structurally related and have a similar toxicological profile.

Table 4: Comparison of the test item used in the subchronic oral toxicity study (A) and the cumin oil under assessment (B)

Constituent	Essential oil A (%)	Essential oil B (%)
Cuminaldehyde	38.9	32.3 (29.8–34.3)
γ-Terpinene	18.3	20.0 (19.9–22.7)
p-Cymene (1-isopropyl-4-methylbenzene)	15.4	14.0 (11.8–18.8)
β-Pinene (pin-2(10)-ene)	11.7	11.2 (10.2–12.7)
1,3-p-Menthadien-7-al	5.3	8.3 (7.18–10.9)
γ-Terpinen-7-al	2.8	4.07 (2.77–6.66)
α-Pinene (pin-2(3)-ene)	0.7	0.88 (0.67–1.07)
	93.1	77.5

A total of 80 female Wistar rats (20 animals per group) were given 0 (control), 250, 500 or 1,000 mg essential oil A/kg body weight (bw) per day by oral gavage for 23 or 45 days. The control group received water by gavage, the test item was administered in solution in olive oil. Ten rats per group were treated for each defined period and subject to examination and necropsied at the end of that period. There were no deaths and no significant differences in feed and water intake between groups. A significant dose-related decrease in body weight gain was observed in the treated groups compared to the control group between days 23 and 45. The results of haematology, blood chemistry, gross pathology and histopathology showed no evidence of any treatment-related adverse effects. At day 23, serum chemistry showed higher level of alanine aminotransferase (ALT) in the highest dose group (1,000 mg/kg bw) and lactic dehydrogenase (LDH) in all treated groups compared to control; similar differences were not seen in the groups treated for 45 days. Minor histopathological changes were seen in livers of all the essential oil-treated rats that included mild infiltration of mononuclear cells and mild dilation of sinusoids. Due to the reference to histopathological changes at all doses, the short duration of this study and lack of compliance with OECD TG,[29] the FEEDAP Panel concluded that is not possible to derive a no observed adverse effect level (NOAEL).

3.3.4. Safety for the target species

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

In the absence of toxicological data with the additive under assessment, 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. 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.

As the additive under assessment is a fully defined mixture (> 99.5% of the components were identified, see Section 3.2.1), the FEEDAP Panel applied a component-based approach to assess the safety for target species of the essential oil, except for estragole and dillapiole, which are assessed separately.

[29] Areas of non-compliance: the control does not use the vehicle; there is no functional observation battery (FOB) test; the limited tissues taken at necropsy (liver, spleen, kidneys and lungs) for histopathology; no organ weights.

Components other than estragole and dillapiole

Based on considerations related to structural and metabolic similarities, the components were allocated to nine assessment groups, corresponding to the chemical groups (CGs) 3, 6, 7, 8, 16, 23, 25, 31 and 32, as defined in Annex I of Regulation (EC) No 1565/2000. For chemical group 31 ('aliphatic and aromatic hydrocarbons'), sub-assessment groups as defined in FGE.25 and FGE.78 were applied (EFSA CEF Panel, 2015a,b). 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 of 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 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 5.

For hazard characterisation, each component of an assessment group was first assigned to the structural class according to Cramer classification. For some components in the assessment group, toxicological data were available to derive NOAEL values. Structural and metabolic similarity among the components in the assessment groups were assessed to explore the application of read-across. If justified, extrapolation from a known NOAEL of a component of an assessment group to the other components of the group with no available NOAEL was made. If sufficient evidence was available for the members of a (sub-)assessment group, a (sub-)assessment group NOAEL was derived.

Toxicological data for sub-chronic studies, from which NOAEL values could be derived, were available for *trans*-2-nonenal [05.072] and deca-2(*trans*),4(*trans*)-dienal [05.140] in CG 3 (EFSA FEEDAP Panel, 2019a), terpineol[30] [02.230] and linalool [02.013] in CG 6 (EFSA FEEDAP Panel, 2012a), 1,8-cineole in CG 16 (EFSA FEEDAP Panel, 2012b, 2021a), and for the representative compounds for sub-assessment groups of CG 31, myrcene [01.008], d-limonene [01.045], p-cymene [01.002] and β-caryophyllene [01.007] (EFSA FEEDAP Panel, 2015, 2016a) and β-caryophyllene epoxide [16.043] in CG 32 (EFSA CEF Panel, 2014). For cuminaldehyde [05.022] and 4-isopropylbenzyl alcohol [02.039] in CG 23 the FEEDAP Panel concluded that the maximum proposed concentration of 5 mg/kg complete feed is safe, based on their structural and metabolic relationship with benzoic acid, which was considered safe up to 125 mg/kg complete feed (EFSA FEEDAP Panel, 2012c). In addition, for benzyl alcohol the FAF Panel established an acceptable daily intake (ADI) of 4 mg/kg bw based on a NOAEL of 400 mg/kg bw per day from a carcinogenicity study in rats (EFSA FAF Panel, 2019). A group NOAEL of 25 mg/kg bw per day was applied for the compounds belonging to CG 25, carvacrol [04.031], thymol [04.006] and 3-methylphenol [04.026] (EFSA FEEDAP Panel, 2012d).

In its assessment of CG 3, the FEEDAP Panel applied the NOAEL of 34 mg/kg bw per day for deca-2(*trans*),4(*trans*)-dienal [05.140] to all linear compounds sharing the same 2-*trans*, 4-*trans*-dienal structure (EFSA FEEDAP Panel, 2019a). In line with the assessment done by JECFA (WHO, 2010a,b), the FEEDAP Panel considers that the same NOAEL could be applied to 1,3-*p*-menthadien-7-al [05.133], a cyclic compound sharing the same 2-*trans*, 4-*trans*-dienal structure. This NOAEL was selected as a group NOAEL for CG 7 compounds.

For 4-terpinenol [02.072] in CG 6, the reference point was selected based on the NOAEL of 250 mg/kg bw per day available for terpineol [02.230] and d-limonene [01.045].

Considering the structural and metabolic similarities, the NOAEL of 400 mg/kg bw per day for benzyl alcohol [02.010] was applied to cuminaldehyde [05.022] and 4-isopropylbenzyl alcohol [02.039]. The group NOAEL for CG 25 is also applied to 4-isopropylphenol [04.073]. The NOAELs 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 sub-assessment group II, III and V (EFSA CEF Panel, 2015a,b).

For the remaining compounds, 2-(4-methylphenyl)propan-2-ol [02.042], carotol, 1,8-*p*-menthadien-4-ol, carvotan acetone, *p*-mentha-1(7),5-dien-2-ol, fenchone [02.016], carvenone, pinocarveol [02.010] and 3,7,10-humulatriene [02.043], toxicity studies and NOAEL values performed with the compounds under assessment were not available and read-across was not possible. Therefore, the

[30] Terpineol is a mixture of four isomers: α-terpineol [02.014], a mixture of (*R*)-(+)-α-terpineol and (*S*)-(−)-α-terpineol, β-terpineol, γ-terpineol and 4-terpinenol [02.072] (or δ-terpineol). The specification for terpineol [02.230] covers α-, β-, γ and δ-terpineol. Composition of mixture: 55–75% α-terpineol, 16–23% γ-terpineol, 1–10% cis-β-terpineol, 1–13% *trans*-β-terpineol and 0–1% δ-terpineol (EFSA CEF Panel, 2015c).

threshold of toxicological concern (TTC) approach was applied (EFSA FEEDAP Panel, 2012a, 2017b). All these compounds belong to Cramer class I except fenchone and carvenone (Cramer class II).

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). 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 SC, 2019a). A MOET > 100 allowed for interspecies- and intra-individual variability (as in the default 10 × 10 uncertainty factor).

The approach to the safety assessment of cumin 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 15 mg/kg complete feed. The compounds resulting individually in a 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.[31]

Table 5: Compositional data, intake values (calculated for chickens for fattening at 15 mg/kg complete feed), reference points and margin of exposure (MOE) for the individual components of cumin oil classified according to assessment groups

Essential oil composition			**Exposure**		**Hazard characterisation**		**Risk characterisation**	
Assessment group	**FLAVIS-No**	**Highest conc. in the oil**	**Highest feed conc.**	**Intake[(a)]**	**Cramer Class[(b)]**	**NOAEL[(c)]**	**MOE**	**MOET**
Constituent	–	**%**	**mg/kg**	**mg/kg bw per day**	–	**mg/kg bw per day**	–	–
CG 6								
2-(4-Methylphenyl) propan-2-ol	02.042	0.31	0.047	0.0042	I	*3*	714	
Carotol	–	0.20	0.029	0.0026	I	*3*	1,142	
1,8-*p*-Menthadien-4-ol	–	0.07	0.011	0.0010	I	*3*	3,052	
								381
CG 7								
1,3-*p*-Menthadien-7-al	05.133	10.93	1.640	0.1472	(I)	34	231	
1,4-*p*-Menthadien-7-al	–	6.66	0.999	0.0897	(I)	34	379	
3-*p*-Menthen-7-al	–	0.93	0.140	0.0125	(I)	34	2,715	
1,4-*p*-Menthanedien-7-ol	–	0.37	0.056	0.0050	(I)	34	6,806	
Phellandral	–	0.28	0.042	0.0038	(I)	34	9,017	
p-Menth-4(8)-en-7-ol	–	0.08	0.012	0.0011	(I)	34	30,791	
								131

[31] Compounds included in the assessment groups but not reported in the table: *trans*-2-nonenal (CG 3); 4-terpinenol and linalool (CG 6); *trans*-sabinene hydrate (CG 8); 2,3-dihydro-1,8-cineole (CG 16); 3-methylphenol (CG 25); β-phellandrene, α-terpinene, *p*-mentha-3,8-diene, terpinolene, β-bisabolene and *p*-1-menthene (CG 31, III); ar-curcumene, *o*-cymene, *m*-cymene and *p*-cymene (CG 31, IVe); β-caryophyllene, daucene, (*E*)-α-bergamotene, α-alaskene, δ-3-carene, δ-cadinene, α-copaene, camphene and α–fenchene (CG 31, V); β-caryophyllene epoxide (CG 32).

Essential oil composition			Exposure		Hazard characterisation		Risk characterisation	
Assessment group	**FLAVIS-No**	**Highest conc. in the oil**	**Highest feed conc.**	**Intake[a]**	**Cramer Class[b]**	**NOAEL[c]**	**MOE**	**MOET**
Constituent	–	**%**	**mg/kg**	**mg/kg bw per day**	–	**mg/kg bw per day**	–	–
CG 8								
Carvotan acetone	–	0.40	0.060	0.0054	II	*0.91*	169	
p-Mentha-1(7),5-dien-2-ol	–	0.16	0.024	0.0022	I	*3*	1,375	
Fenchone	02.016	0.05	0.008	0.0007	II	*0.91*	1,300	
Carvenone	–	0.05	0.008	0.0007	II	*0.91*	1,275	
Pinocarveol	02.100	0.04	0.006	0.0006	I	*3*	5,181	
								191
CG 16								
1,8-Cineole	03.001	0.16	0.024	0.0022	(II)	**100**	46,414	
CG 23								
Cuminaldehyde	05.022	34.3	5.145	0.4619	(I)	200[d]	433	
4-Isopropylbenzyl alcohol	02.039	0.82	0.123	0.0110	(I)	**400**	36,269	
								428
CG 25								
Carvacrol	04.031	0.33	0.050	0.0045	(I)	25	5,592	
4-Isopropylphenol	04.073	0.10	0.015	0.0013	(I)	25	18,944	
Thymol	04.006	0.06	0.009	0.0008	(I)	25	30,942	
								3,550
CG 31, II (Acyclic alkanes)								
Myrcene	01.008	0.74	0.111	0.0099	(I)	**44**	4,434	
β-Farnesene	01.041	0.28	0.042	0.0037	(I)	44	11,796	
MOET CG 31, II								3,222
CG 31, III (Cyclohexene hydrocarbons)								
γ-Terpinene	01.020	22.70	3.405	0.3057	(I)	250	818	
α-Phellandrene	01.006	1.14	0.171	0.0154	(I)	250	16,285	
Limonene	01.001	0.52	0.079	0.0071	(I)	**250**	35,430	
MOET CG 31, III								762
CG 31, IVe (Benzene hydrocarbons, alkyl)								
p-Cymene	01.002	18.8	2.820	0.2532	(I)	**154**	608	
4-Isopropenyl-4-methylbenzene	01.010	0.41	0.061	0.0055	I	*3*	545	
								288
CG 31, V (Bi-, tricyclic, non aromatic hydrocarbons)								
α-Pinene	01.004	12.70	1.905	0.1710	(I)	222	1,298	
β-Acoradiene	–	3.34	0.501	0.0450	(I)	222	4,936	
β-Pinene	01.003	1.07	0.161	0.0144	(I)	222	15,408	
α-Neocallitropsene	–	0.44	0.066	0.0059	(I)	222	37,468	
Sabinene	01.059	0.39	0.059	0.0053	(I)	222	42,056	
α-Thujene	–	0.34	0.051	0.0046	(I)	222	48,631	
MOET CG 31, V								887
CG 31, VI (macrocyclic non aromatic hydrocarbons)								
3,7,10-Humulatriene	01.043	0.06	0.008	0.0008	I	*3*	3,978	

(a): Intake calculations for the individual components are based on the use level of 15 mg/kg in feed for chickens for fattening, the species with the highest ratio of feed intake/body weight. The MOE for each component is calculated as the ratio of the reference point (NOAEL) to the intake. 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.
(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 NOAEL of 400 mg/kg bw per day for cumin alcohol was halved to take into account the higher reactivity of the aldehyde and the uncertainty in the read-across.

As shown in Table 5, for all the assessment groups, the MOET was ≥ 131. Therefore, no safety concern was identified for the cumin oil (without considering the presence of estragole and dillapiole) when used as a feed additive for chickens for fattening at the proposed use levels (15 mg/kg feed). From the lowest MOE of 131 for chickens for fattening, the MOE for CG 7 compounds was calculated for the other target species considering the respective daily feed intake and conditions of use. The results are summarised in Table 6.

Table 6: Combined margin of exposure (MOET) for CG 7 calculated for the different target animal categories at the proposed use level in feed

Animal category	Body weight (kg)	Feed intake (g DM/day)	Use level (mg/kg feed)(1)	Lowest MOET CG 7
Chicken for fattening	2	158	15	131
Laying hen	2	106	15	195
Turkey for fattening	3	176	15	175
Piglet	20	880	15	235
Pig for fattening	60	2,200	15	280
Sow lactating	175	5,280	15	345
Veal calf (milk replacer)	100	1,890	15	545
Cattle for fattening	400	8,000	15	517
Dairy cows	650	20,000	15	334
Sheep/goat	60	1,200	15	517
Horse	400	8,000	15	517
Rabbit	2	100	15	207
Salmon	0.12	2.1	15	575
Dog	15	250	15	609
Cat(2)	3	60	15	517
Ornamental fish	0.012	0.054	15	2,070

DM: dry matter.
(1): Complete feed containing 88% DM, milk replacer 94.5% DM.
(2): The MOET for cats is increased to 500 because of the reduced capacity of glucuronidation.

Table 6 shows that for all species the MOET exceeds the value of 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 (Court and Greenblatt, 1997; Lautz et al., 2021), the use of cumin oil as additive in cat feed needs a wider margin of exposure. A MOET of 500 is considered adequate. Therefore, for all species, no safety concern (without considering the presence of estragole and dillapiole) was identified for cumin oil, when used as a feed additive at the proposed use level of 15 mg/kg complete feed.

No specific proposals have been made by the applicant for the use level in water for drinking. The 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 (EFSA FEEDAP Panel, 2010).

Estragole and dillapiole

Low concentrations of estragole (0.001–0.046%) and dillapiole (0.027–0.040%) were detected in all batches of the additive under assessment. The use of cumin oil at the proposed use level of 15 mg/kg

complete feed would result in concentrations ranging from 0.15 to 6.9 μg estragole/kg complete feed and 4.05 to 6 μg dillapiole/kg complete feed.

The maximum daily intake of estragole and dillapiole in μg/kg bw was calculated at the maximum proposed use level of the additive in feed and considering the maximum analysed value in the additive (0.46% and 0.40%, respectively). The calculated combined intake values range between 0.066 μg/kg bw per day (in ornamental fish) and 1.158 μg/kg bw per day (in chickens for fattening).

Estragole and dillapiole belong to the same structural group (*p*-allylalkoxybenzenes) and share the same metabolic pathways, particularly the formation of the reactive 1′-sulfoxymetabolite (see Section 3.3.1), and the same mode of action. Although the available data do not allow to conclude on the genotoxic potential of dillapiole, they indicate that it is certainly less potent than estragole with respect to its genotoxicity/carcinogenicity effects (see Section 3.3.2). However, in the current assessment, in the absence of data that would allow to estimate a relative potency factor for dillapiole, estragole and dillapiole are grouped together and considered equally potent as a worst-case scenario.

The FEEDAP Panel identified the $BMDL_{10}$ of 22.2 mg/kg bw per day derived from rodent carcinogenicity studies with methyleugenol (NTP, 2000; Suparmi et al., 2019) as the reference point for the entire group of *p*-allylalkoxybenzenes (EFSA FEEDAP Panel, 2022). In the current assessment, this reference point is also applied to dillapiole. When the estimated combined exposures to estragole and dillapiole for the different animal categories are compared to the $BMDL_{10}$ of 22.2 mg/kg bw per day, a combined margin of exposure (MOET) is calculated for the different target species.

The highest daily intake of estragole and dillapiole for the different target animal categories and the corresponding MOET are reported in Table 7.

Table 7: Combined intake of estragole and dillapiole and combined margin of exposure (MOET) calculated at the maximum proposed use level of the additive in feed (15 mg/kg complete feed)

Animal category	Daily feed intake	Body weight	Use level in feed	Estragole+ diallapiole[(a)] intake	MOET[(b)]
	kg DM/day	kg	mg/kg feed	μg/kg bw per day	
Chicken for fattening	0.158	2	15	1.158	19,170
Laying hen	0.106	2	15	0.777	28,574
Turkey for fattening	0.176	3	15	0.860	25,814
Piglet	0.88	20	15	0.645	34,419
Pig for fattening	2.2	60	15	0.538	41,302
Sow lactating	5.28	175	15	0.442	50,194
Veal calf (milk replacer)	1.89	100	15	0.258	86,047
Cattle for fattening	8	400	15	0.293	75,721
Dairy cow	20	650	15	0.451	49,219
Sheep/goat	1.2	60	15	0.293	75,721
Horse	8	400	15	0.293	75,721
Rabbit	0.1	2	15	0.733	30,288
Salmon	0.0021	0.12	15	0.257	86,538
Dog	0.25	15	15	0.244	90,865
Cat	0.06	3	15	0.293	75,721
Ornamental fish	0.00054	0.012	15	0.066	336,537

DM: dry matter; bw: body weight.
(a): The intake values of estragole and dillapiole are calculated considering the highest analysed value in the additive for both compounds.
(b): The MOE for estragole is calculated as the ratio of the reference point ($BMDL_{10}$) to the intake.

When the estimated exposures for the different animal categories are compared to the $BMDL_{10}$ of 22.2 mg/kg bw per day derived for methyleugenol by Suparmi et al. (2019) from a rodent carcinogenicity study (NTP, 2000, see Section 3.2.2), an MOET of at least 19,000 is calculated (see Table 7). The magnitude of this MOET is indicative of low concern for the target species.

3.3.4.1. Conclusions on safety for the target species

Cumin oil is considered as safe up to the maximum proposed use level of 15 mg/kg complete feed for all animal species. The use in water for drinking is considered as safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed.

3.3.5. Safety for the consumer

Cumin fruit and cumin oil are 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 1.95 mg/kg bw per day for cumin fruit (FEMA 2340) and 0.0013 mg/kg bw per day for cumin oil (FEMA 2343). Fenaroli also reports use levels of cumin oil in food and beverages in the range of 0.03 mg/kg up to 100 mg/kg.

The majority 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 1, Section 1.2).

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 cumin oil are expected to be extensively metabolised and excreted in the target species. Also for estragole and dillapiole, which are present in cumin oil at very low concentrations in the ranges of 0.001–0.046% and 0.027–0.040%, respectively, the available data indicate that they are absorbed, metabolised and rapidly excreted, and are not expected to accumulate in animal tissues and products (see Section 3.3.1).

Considering the above and the reported human exposure due to direct use of cumin fruit and cumin oil in food (Burdock, 2009), it is unlikely that consumption of products from animals given cumin oil at the proposed maximum use level would increase human background exposure.

Consequently, no safety concern would be expected for the consumer from the use of cumin oil up to the maximum proposed use level in feed for the target animals.

3.3.6. Safety for the user

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

The applicant produced a safety data sheet[32] for cumin oil, where hazards for users have been identified.

There is some evidence for dermal phototoxicity of cumin oil. A positive effect is reported by Opdyke (1974), Kaidbey and Kligman (1978) and by Forbes et al. (1977). Phototoxicity is also mentioned in the International Fragrance Association (IFRA) standard for cumin oil (IFRA, 2020).

The FEEDAP Panel notes that the additive contains a variety of compounds, such as aldehydes (about 45%), known to cause allergic reactions in sensitive persons. Therefore, sensitisation may occur in users handling the additive.

The essential oil under assessment should be considered as irritant to skin and eyes, and as a dermal and respiratory sensitiser.

When handling the essential oil, exposure of unprotected users to estragole (and dillapiole) cannot be excluded. Therefore, to reduce the risk, the exposure of the users should be minimised.

3.3.7. Safety for the environment

C. cyminum is not a native species to Europe. Therefore, the safety for the environment is assessed based on the individual components of the essential oil.

The major components (cuminaldehyde, γ-terpinene, α-pinene and β-pinene) and additional 20 components (1-isopropyl-4-methylbenzene, α-phellandrene, 4-isopropylbenzyl alcohol, myrcene, limonene, carvacrol, 1-isopropenyl-4-methylbenzene, β-caryophyllene, 2-(4-methylphenyl)propan-2-ol, 4-terpinenol, α-terpinene, 1,8-cineole, 4-isopropylphenol, terpinolene, thymol, *trans* 2-nonenal, δ-3-carene, linalool, camphene and 3-methylphenol) accounting together for about 83% of the composition of the oil, have been evaluated by EFSA as sensory additives for animal feed. They were considered to be safe for the environment at individual use levels higher than those resulting from the use of the essential oil in feed (see Table 1, Section 1.2).

[32] Technical dossier/Supplementary Information July 2021/Annex_VII_SIn reply_cumin oil_MSDS_4. Aspiration hazard (H304, category 1), Hazards for skin corrosion/irritation (H315, category 2), skin sensitisation (H317, category 1).

The remaining identified constituents of the essential oil are mainly aliphatic mono- or sesquiterpenes partially substituted with functional groups. They are structurally related to the substances evaluated by EFSA in CG 6 and CG 31 for use in animal feed (EFSA FEEDAP Panel, 2012b, 2015, 2016a) for which EFSA concluded that they were 'extensively metabolised by the target species (see Section 3.3) and excreted as innocuous metabolites or carbon dioxide'. Therefore, no risk for the safety for the environment is foreseen. Average feed levels of constituents of the essential oil are much lower than the use levels for substances belonging to CG 6 and CG 31.

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

3.4. Efficacy

The fruit of *C. cyminum* and its oil are listed in Fenaroli's Handbook of Flavour Ingredients (Burdock, 2009) and by FEMA with the reference number 2340 (cumin fruit) and 2,343 (cumin oil).

Since the fruit of *C. cyminum* and its oil are recognised to flavour food and their function in feed would be essentially the same as that in food, no further demonstration of efficacy is considered necessary.

4. Conclusions

Cumin oil from *C. cyminum* L. 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 cumin oil which contains ≤ 0.046% estragole and ≤ 0.040% dillapiole and is produced by steam distillation of the fruit of *C. cyminum*.

The use of cumin oil from *C. cyminum* is considered as safe up to the maximum proposed use level of 15 mg/kg complete feed for all animal species. The FEEDAP Panel considers the use of cumin oil in water for drinking as safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed.

No concerns for consumers were identified following the use of the additive at the maximum proposed use level in feed.

The essential oil under assessment should be considered as irritant to skin and eyes, and as a dermal and respiratory sensitiser. When handling the essential oil, exposure of unprotected users to estragole (and dillapiole) cannot be excluded. Therefore, to reduce the risk, the exposure of the users should be minimised.

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

Since the fruit of *C. cyminum* and its oil are recognised to flavour food and their function in feed would be essentially the same as that in food, no further demonstration of efficacy is considered necessary.

5. Recommendation

The specification should ensure that the concentration of estragole and dillapiole in the additive should be as low as possible and should not exceed 0.05% each.

6. Documentation provided to EFSA/Chronology

Date	Event
28/10/2010	Dossier received by EFSA. Botanically defined flavourings from Botanical Group 02 - Apiales and Austrobaileyales for all animal species and categories. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)
09/11/2010	Reception mandate from the European Commission
26/02/2013	EFSA informed the applicant (EFSA ref. 7150,727) 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

Date	Event
27/02/2019	Partial withdrawal by applicant (EC was informed) for the following additives: dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract and opoponax oil
24/06/2019	Application validated by EFSA – Start of the scientific assessment
03/07/2019	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 the target species, safety for the consumer, safety for the user, safety for the environment*
30/09/2019	Comments received from Member States
09/07/2021	Reception of supplementary information from the applicant (partial dataset on cumin oil) - Scientific assessment remains suspended
16/09/2022	The application was split and a new EFSA-Q-2022-00566 was assigned to the preparation included in the present assessment
31/10/2022	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives - Scientific assessment re-started
22/11/2022	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment for the preparation included in the present assessment. The assessment of other preparations is still ongoing

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Abbreviations

AFC	EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
BDG	Botanically defined group
BMD	Benchmark dose
$BMDL_{10}$	benchmark dose (BMD) lower confidence limit for a benchmark response of 10%
bw	body weight
CAS	Chemical Abstracts Service
CD	Commission Decision
CDG	chemically defined group
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CG	chemical group
DM	dry matter
EEIG	European economic interest grouping
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
FEMA	Flavor Extract Manufacturers Association
FFAC	Feed Flavourings authorisation Consortium of (FEFANA) the EU Association of Specialty Feed Ingredients and their Mixtures
FGE	Flavouring Group Evaluation
FLAVIS	the EU Flavour Information System
FL-No	FLAVIS number
GC	gas chromatography
GC-FID	gas chromatography with flame ionisation detector
GC–MS	gas chromatography–mass spectrometry
IFRA	International Fragrance Association

ISO	International Organization for Standardization
LOD	limit of detection
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MOE	margin of exposure
MOET	combined margin of exposure (total)
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
PCBs	polychlorinated biphenyls
QSAR	Quantitative Structure–Activity Relationship
sb	solvent-based
SC	EFSA Scientific Committee
TTC	threshold of toxicological concern
UF	uncertainty factor
WHO	World Health Organization