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Safety and efficacy of a feed additive consisting of an essential oil from *Cinnamomum camphora* (L.) J. Presl (camphor white oil) for use in all animal species (FEFANA asbl)

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Abstract

Following a request from the European Commission, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety and efficacy of an essential oil from the whole plant *Cinnamomum camphora* (L.) J. Presl (camphor white oil), when used as a sensory additive (flavouring) in feed and water for drinking for all animal species. The FEEDAP Panel concluded that the additive is safe up to the maximum proposed use levels in complete feed of 30 mg/kg for piglets, pigs for fattening, sows, horses, rabbits, fish, ornamental fish and dogs and of 50 mg/kg for calves (milk replacer), cattle for fattening, dairy cows, sheep and goats. For the other species, the calculated safe concentration in complete feed is 28 mg/kg for chickens for fattening, 42 mg/kg for laying hens, 37 mg/kg for turkeys for fattening and 22 mg/kg for cats. The FEEDAP Panel considered 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. No concerns for consumers were identified following the use of the additive at the use level considered safe in feed for the target species. The essential oil under assessment should be considered as irritant to skin and eyes, and as a skin and respiratory sensitiser. The use of the additive under the proposed conditions in animal feed was not expected to pose a risk for the environment. Camphor white oil was recognised to flavour food. Since its function in feed would be essentially the same as that in food, no further demonstration of efficacy was considered necessary.

Keywords: sensory additives, flavouring compounds, *Cinnamomum camphora* (L.) J. Presl, camphor white oil, 1,8-cineole, camphor, safrole, component-based approach

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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 18 preparations (cassia oil, cassia bark extract (sb), camphor oil, cinnamon oil, cinnamon bark oleoresin, cinnamon tincture, laurel leaves oil, laurel leaves extract/oleoresin, litsea berry oil, boldo extract (wb), boldo tincture, ylang-ylang oil, mace oil, nutmeg oil, nutmeg oleoresin, kawakawa tincture, pepper oil and pepper oleoresin) belonging to botanically defined group (BDG) 6 – Laurales, Magnoliales, Piperales, when used as feed additives for all animal species (category: sensory additives; functional group: flavouring compounds). During the assessment, the applicant withdrew the applications for eight preparations.[3] In addition, during the course of the assessment, the application was split and the present opinion covers only one out of the initial 18 preparations under application: an essential oil from the whole plant of *Cinnamomum camphora* (L.) J. Presl.[4] (camphor white oil) 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 3 January 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 an essential oil from the fruits of *C. camphora* (camphor white oil), when used under the proposed conditions of use (see Section 3.2.4).

The remaining nine preparations belonging to botanically defined group (BDG) 6 - Laurales, Magnoliales, Piperales under application are assessed in separate opinions.

1.2. Additional information

Camphor white oil from *Cinnamomum camphora* (L.) J. Presl 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.

Many of the individual components of camphor white oil have been already assessed as chemically defined flavourings for use in feed and food by the FEEDAP Panel and the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). The list of flavouring compounds currently authorised for food and feed[6] uses together with the EU Flavour Information System (FLAVIS) number,

[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, 1050 Brussels, Belgium.

[3] On 8 October 2020, EFSA was informed about the withdrawal of the applications on cassia bark extract (sb), cinnamon bark oleoresin, laurel leaves extract/oleoresin, mace oil, nutmeg oleoresin, boldo extract (wb), boldo tincture and kawakawa tincture.

[4] Accepted name: *Cinnamomum camphora* (L.) J. Presl; synonyms: *Cinnamomum camphora* L., *Cinnamomum camphora* (L.) T. Nees & C.H. Eberm., *Cinnamomum camphora* (L.) Nees & Ebermeier, *Camphora camphora* (L.) H. Karst., *Laurus camphora* L.

[5] 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.

[6] 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

the chemical group as defined in Commission Regulation (EC) No 1565/2000[7] and the corresponding EFSA opinion is 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 opinion,* Year
05	Saturated and unsaturated aliphatic secondary alcohols, ketones and esters with esters containing secondary alcohols	6-Methyhept-5-en-2-one	07.015	2015a, 2021a
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-Camphor(a)	07.215	2016a
		d-Fenchone(b)	07.159	
16	Aliphatic and alicyclic ethers	1,8-Cineole	03.001	2012a, 2021b
31	Aliphatic and aromatic hydrocarbons and acetals containing saturated aldehydes	p-Cymene	01.002	2015b
		α-Phellandrene	01.006	
		α-Terpinene	01.019	
		γ-Terpinene	01.020	
		d-Limonene	01.045	
		Pin-2(10)-ene (β-pinene)	01.003	2016b
		Pin-2(3)-ene (α-pinene)	01.004	
		Myrcene	01.008	
		Camphene	01.009	
		trans-β-Ocimene	01.018	
		δ-3-Carene	01.029	
		β-Phellandrene(c),(d)	01.055	2011, CEF
		4(10)-Thujene (sabinene)(c)	01.059	2015a, CEF

*: FEEDAP opinion unless otherwise indicated.
(a): 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 FEDAP Panel, 2016a).
(b): Present in the additive as a mixture of enantiomers (d,l-fenchone or (±)-fenchone). JECFA and EFSA evaluated the enantiomer d-fenchone [07.159] for use in food and in feed (EFSA FEDAP Panel, 2016a).
(c): 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.
(d): 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.

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[8] in support of the authorisation request for the use of camphor white oil from *C. camphora* as a feed additive.

The FEEDAP Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) 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.

[7] 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.
[8] FEED dossier reference: FAD-2010-0218.

Many of the components of the essential oil under assessment have been already evaluated by the FEEDAP Panel as chemically defined flavourings. The applicant submitted a written agreement to refer to the data submitted for the assessment of chemically defined flavourings (dossiers, publications and unpublished reports) for the risk assessment of preparations belonging to BDG 6.[9]

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for 18 compounds from botanically defined flavourings Group (BDG 06) – Laurales, Magnoliales, Piperales. The Executive Summary of the EURL report can be found in Annex A.[10]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of camphor white oil from *C. camphora* 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 for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012b); Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012c); 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 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); General approach to assess the safety for the target species of botanical preparations which contain compounds that are genotoxic and/or carcinogenic.[12]

3. Assessment

The additive under assessment, camphor white oil, is obtained from the whole plant *Cinnamomum camphora* (L.) J. Presl. It is intended for use as a sensory additive (functional group: flavouring compounds) in feed and water for drinking for all animal species.

3.1. Origin and extraction

Cinnamomum camphora (L.) J. Presl is an evergreen tree commonly known in English as the camphor tree, camphorwood or the camphor laurel. It belongs to the Lauraceae family and is native to South China, Japan and parts of SE Asia. Because of the value of its insect-resistant timber and, in particular, as a source of camphor, it is now grown commercially in many other countries. Camphor is the volatile component of the tree which, when condensed, produces a white crystalline substance. This has been used for centuries as a spice, as a component of incense and as a medicine. In more recent times, camphor has been used in the production of gunpowder and, in combination with nitrocellulose, the manufacture of celluloid.

Camphor oil is extracted by steam distillation from most parts of the camphor tree (e.g. bark, wood chips, leaves and tree stumps) followed by rectification. Several grades of camphor oil are produced but only the light fraction described as White Camphor Oil which has been fractionally distilled to reduce/remove the safrole content is used in aromatherapy or for cosmetic or medicinal use. The composition of white camphor oil varies according to the chemotype of *C. camphora* from which it was

[9] Technical dossier/Supplementary information/Letter dated 29/4/2021.

[10] The full report is available on the EURL website: https://ec.europa.eu/jrc/en/eurl/feed-additives/evaluation-reports/fad-2010-0218?search&form-return

[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.

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

obtained. The applicant sources white camphor oil from Taiwan from a chemotype which produces a 1,8-cineole-rich oil.

3.2. Characterisation

3.2.1. Characterisation of camphor white oil

The oil under assessment is a colourless clear mobile liquid, slightly viscous, with a characteristic aroma. In six batches of the additive (all originating from Taiwan), the refractive index (20°C) ranged between 1.4660 and 1.4686 (specification: 1.4640–1.4685).[13] Camphor white oil, also known as camphor Japanese white oil, is identified with the single Chemical Abstracts Service (CAS) number 8008-51-3, the EINECS number 294-760-2, the Flavor Extract Manufacturers Association (FEMA) 2231 and the Council of Europe (CoE) number 130.

The product specifications are based on the concentrations of the main volatile components, analysed by gas chromatography with flame ionisation detection (GC-FID) and expressed as % of gas chromatographic peak area (% GC area). These components are 1,8-cineole (27–43%, selected as phytochemical marker), d-limonene (18–27%), 1-isopropyl-4-methylbenzene (herein referred to as p-cymene, 6–15%) and pin-2(3)-ene (herein referred to as α-pinene, 4–10%). Analysis of six batches of the additive by gas chromatography-mass spectrometry (GC-MS) showed compliance with these specifications.[13] These four compounds account for about 75.9% on average (range 70.8–81.0%) of % GC area (Table 2).

Table 2: Major constituents of the essential oil from *Cinnamomum camphora* (L.) J. Presl as defined by specifications and batch to batch variation based on the analysis of six 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 EU register name	CAS no	FLAVIS no	% of GC area		
			Specification	Mean[(a)]	Range
1,8-Cineole	470-82-6	03.001	27–43	34.65	30.8–39.7
d-Limonene	5989-27-5	01.045	18–27	23.15	21.6–25.0
p-Cymene (1-isopropyl-4-methylbenzene)	99-87-6	01.002	6–15	10.87	7.80–13.8
α-Pinene (pin-2(3)-ene)	80-56-8	01.004	4–10	7.21	6.62–8.40
Total				75.9	70.8–81.0

EU: European Union; CAS no.: Chemical Abstracts Service number; FLAVIS number: EU Flavour Information System numbers.
(a): Mean calculated on six batches.

The applicant provided the full characterisation of the six batches obtained by GC-MS.[14] In total, up to 58 peaks were detected in the chromatogram, 19 of which were identified (see Tables 2 and 3) and accounted on average for 99.5% (99.1–100%) of the % GC area. Based on the available data on the characterisation, camphor white oil is considered a fully defined mixture.

[13] Technical dossier/Supplementary information April 2021/Annex_II_ SIn_Reply_camphor_oil_white_COA_chromatograms. The specification for the refractive index (maximum 1.4685) was slightly exceeded for one batch (1.4686).
[14] Technical dossier/Supplementary information April 2021/Annex_II_ SIn_Reply_camphor_oil_white_COA_chromatograms.

Table 3: Other constituents of the essential oil from *Cinnamomum camphora* (L.) J. Presl not included in the specification (based on the analysis of six 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 EU register name	CAS no	FLAVIS no	% of GC area	
			Mean[(a)]	Range
Sabinene (4(10)-thujene)	3387-41-5	01.059	4.50	3.65–5.45
γ-Terpinene	99-85-4	01.020	4.14	2.72–5.01
β-Phellandrene	555-10-2	01.055	3.66	3.42–4.04
Myrcene	123-35-3	01.008	3.24	2.12–4.60
α-Terpinene	99-86-5	01.019	2.70	1.64–3.72
α-Pinene (pin-2(10)-ene)	127-91-3	01.003	2.62	1.91–3.51
α-Phellandrene	99-83-2	01.006	1.50	0.92–2.10
Camphene	79-92-5	01.009	0.89	0.75–0.97
trans-para-2-menthene-1,4-diol	40735-19-1	–	0.36	0.36
δ-3-Carene	13466-78-9	01.029	0.13	0.12–0.14
δ-2-Carene	4497-92-1	–	0.10	0.08–0.12
trans-3,7-Dimethyl-1,3,6-octatriene (trans-β-ocimene)	3779-61-1	–	0.09	0.07–0.11
6-Methylhept-5-en-2-one	110-93-0	07.015	0.06	0.06–0.07
Fenchone	1195-79-5	–	0.030	0.028–0.032
2,4-Thujadiene	36262-09-6	–	0.005	0.004–0.005
Total			23.59	18.97–28.81

EU: European Union; CAS no.: Chemical Abstracts Service number; FLAVIS number: EU Flavour Information System numbers.
(a): Mean calculated on six batches.

The applicant made a literature search for the chemical composition of *C. camphora* and its preparations and the identity of any recognised substances of concern.[15] The occurrence of 1,8-cineole, camphor and safrole is reported for the wood of *C. camphora* (EFSA compendium; EFSA, 2012) and for camphor white oil (Tisserand and Young, 2014). Moayedi et al. (2018) describe the presence of traces of camphor in camphor white oil produced by steam distillation from the wood of *C. camphora*. Camphor and safrole were not detected by GC-MS in six batches of the additive under assessment (limit of detection (LOD): 0.001%). The additive is specified to contain < 0.1% camphor and < 0.0002% safrole.[16]

3.2.2. Impurities

The applicant makes reference to the 'periodic testing' of some representative flavourings premixtures for heavy metals (mercury, cadmium and 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 were provided on the presence of these impurities. Since camphor white oil is produced by steam distillation, the likelihood of any measurable carry-over of heavy metals is low except for mercury.

3.2.3. Shelf-life

The typical shelf-life of the additive 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). However, no data supporting this statement were provided.

[15] Technical dossier/Supplementary information April 2021/Literature search_camphor_oil_white
[16] Technical dossier/Supplementary information September 2021. The specification for safrole is set is based on historical data of camphor oil batches (the content of safrole was never found above 0.0002%) analysed by GC-MS using single ion monitoring as a detection method. The corresponding LOD for this analytical procedure is 0.0001%.

3.2.4. Conditions of use

Camphor white 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 50 mg/kg for chickens for fattening, laying hens, turkeys for fattening, veal calves (milk replacer), cattle for fattening, dairy cows, sheep and goats, and 30 mg/kg for piglets, pigs for fattening, sows, horses, rabbits, dogs, cats, fish and ornamental fish.

No use level has been proposed by the applicant for the use in water for drinking.

3.3. Safety

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

Many of the components of camphor white oil, accounting for about 95% of the % GC peak areas, have been previously assessed and considered safe for use as flavourings, and are currently authorised for food[5] and feed uses[6] without limitations. The list of the compounds already evaluated by the EFSA Panels is given in Table 1 (see Section 1.2).

One compound, β-phellandrene [01.055], has been evaluated in FGE25. Rev2 (EFSA CEF Panel, 2011) 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 this compound, for which there is no concern for genotoxicity, EFSA requested additional subchronic toxicity data (EFSA CEF Panel, 2011). In the absence of such toxicological data, the EFSA CEF Panel was unable to complete its assessment. As a result, these compounds currently are not authorised for use as flavours in food. In the absence of toxicity data, the FEEDAP Panel applies the threshold of toxicological concern (TTC) approach or read-across from structurally related substances.

Few volatile components accounting for < 0.5% of the % GC area (trans-para-2-menthene-1,4-diol, fenchone, δ-2-carene and 2,4-thujadiene) have not been previously assessed for use as flavourings. The FEEDAP Panel notes that trans-para-2-menthene-1,4-diol, fenchone and δ-2-carene are monoterpene derivatives structurally related to flavourings already assessed in CG 6, 8 and 31, and a similar metabolic and toxicological profile is expected. These lipophilic compounds are expected to be rapidly absorbed from the gastrointestinal tract, oxidised to polar oxygenated metabolites, conjugated and excreted (EFSA FEEDAP Panel, 2012d,2016a,b). 2,4-Thujadiene was screened for its genotoxic potential using the Quantitative Structure–Activity Relationship (QSAR) Toolbox. No structural alerts were found.[17]

3.3.1. Safety for the target species

Tolerance and/or toxicological studies 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 sufficiently characterised (> 99.1%), the FEEDAP Panel applied a component-based approach to assess the safety for target species of the essential oil.

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

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

[17] Technical dossier/Supplementary information April 2021/Annex_V_Sin reply_camphor_oil_QSAR.

FEEDAP Panel, 2017b). Default values on body weight are used to express exposure in terms of mg/kg body weight (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 4.

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 no observed adverse effect level (NOAEL) values. Structural and metabolic similarity among the components in the assessment groups were assessed to explore the application of read-across allowing extrapolation from a known NOAEL of a component of an assessment group to the other components of the group with no available NOAEL or, if sufficient evidence were available for members of a (sub-)assessment group, to derive a (sub-)assessment group NOAEL.

Toxicological data of subchronic studies, from which NOAELs could be derived, were available for 6-methylhept-5-en-2-one [07.015] in CG 5 (EFSA FEEDAP Panel, 2015a, 2021a), 1,8-cineole in CG 16 (EFSA FEEDAP Panel, 2012a, reviewed in EFSA FEEDAP Panel, 2021b), and for the representative compounds for subassessment groups of CG 31, myrcene [01.008], limonene [01.045], 1-isopropyl-4-benzene [01.002] and β-caryophyllene [01.007] (EFSA FEEDAP Panel, 2015b, 2016b).

Considering the structural and metabolic similarities, 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 subassessment group II (trans-β-ocimene [01.018]), group III (γ-terpinene [01.020], β-phellandrene [01.055], α-terpinene [01.019] and α-phellandrene [01.006]) and group V (α-pinene [01.004], sabinene [01.059], β-pinene [01.003], camphene [01.009], δ-2-carene and δ-3-carene [01.029]) (EFSA CEF Panel, 2015a,2015b).

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

The approach to the safety assessment of camphor white oil for chickens for fattening is summarised in Table 4.

Table 4: Compositional data, intake values (calculated for chickens for fattening at 50 mg/kg complete feed), reference points and margin of exposure (MOE) for the individual components of camphor white oil classified according to assessment groups

Essential oil composition			**Exposure**		**Hazard characterisation**		**Risk characterisation**	
Assessment group	**FLAVIS-no**	**Max conc. in the oil**	**Max 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 5								
6-Methylhept-5-en-2-one	07.015	0.07	0.034	0.0031	(II)	**50**	16,381	
CG 6								
trans-para-2-menthene-1,4-diol	–	0.36	0.179	0.0160	II	*0.91*	57	
CG 8								
Fenchone	02.016	0.03	0.016	0.0014	II	*0.91*	634	
CG 16								
1,8-Cineole	03.001	39.7	19.85	1.7820	(II)	**100**	56	

Essential oil composition			Exposure		Hazard characterisation		Risk characterisation	
Assessment group	**FLAVIS-no**	**Max conc. in the oil**	**Max 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 31, II (Acyclic alkanes)								
Myrcene	01.008	4.60	2.300	0.2065	(I)	**44**	213	
β-trans-Ocimene	01.018	0.11	0.057	0.0051	(I)	44	8,675	
MOET CG 31, II								208
CG 31, III (Cyclohexene hydrocarbons)								
d-Limonene	01.045	25.00	12.500	1.1222	(I)	**250**	223	
γ-Terpinene	01.020	5.01	2.505	0.2249	(I)	250	1,112	
β-Phellandrene	01.055	4.04	2.020	0.1813	(I)	250	1,379	
α-Terpinene	01.019	3.72	1.860	0.1670	(I)	250	1,497	
α-Phellandrene	01.006	2.10	1.050	0.0943	(I)	250	2,652	
MOET CG 31, III								140
CG 31, IVe (Benzene hydrocarbons, alkyl)								
p-Cymene	01.002	13.80	6.900	0.6194	(I)	**154**	249	
CG 31, V (Bi-, tricyclic, non-aromatic hydrocarbons)								
α-Pinene	01.004	8.40	4.200	0.3770	(I)	222	589	
Sabinene	01.059	5.45	2.725	0.2446	(I)	222	907	
β-Pinene	01.003	3.51	1.755	0.1576	(I)	222	1,409	
Camphene	01.009	0.97	0.487	0.0437	(I)	222	5,083	
δ-2-Carene	–	0.14	0.068	0.0061	(I)	222	495	
δ-3-Carene	01.029	0.12	0.061	0.0055	(I)	222	40,540	
2,4-Thujadiene	–	0.01	0.003	0.0002	III	0.15	668	
MOET CG 31, V								174

(a): Intake calculations for the individual components are based on the use level of 50 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 an 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.

As shown in Table 4, for all the assessment groups, the MOET was ≥ 56. From the lowest MOE of 56 for chickens for fattening, the MOE for 1,8-cineole was calculated for the other target species considering the respective daily feed intake and conditions of use. The results are summarised in Table 5.

Table 5: Margin of exposure (MOE) for 1,8-cineole (CG 16) calculated for the different target animal categories at the proposed use level in feed and maximum safe use levels in feed calculated to ensure an MOE ≥ 100 (500 for cats)

Animal category	Body weight (kg)	Feed intake (g DM/day)	Use level (mg/kg feed)	Lowest MOET	Maximum safe use level (mg/kg feed)(1)
Chicken for fattening	2	158	50	56	28
Laying hen	2	106	50	83	42
Turkey for fattening	3	176	50	75	37
Piglet	20	880	30	168	–
Pig for fattening	60	2,200	30	199	–
Sow lactating	175	5,280	30	246	–
Veal calf (milk replacer)	100	1,890	50	233	–
Cattle for fattening	400	8,000	50	221	–
Dairy cows	650	20,000	50	143	–
Sheep/goat	60	1,200	50	221	–
Horse	400	8,000	30	221	–
Rabbit	2	100	30	147	–
Salmon	0.12	2.1	30	410	–
Dog	15	250	30	434	–
Cat	3	60	30	369(2)	22
Ornamental fish	0.012	0.054	30	1,475	–

(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 5 shows an MOET above the value of 100, when the additive was used at the proposed use levels, for all species except poultry and cats. The maximum safe use levels in feed were calculated for the poultry in order to ensure an MOET ≥ 100 and for cats to ensure an MOET > 500, considering their unusually low capacity for glucuronidation (Court and Greenblatt, 1997; Lautz et al., 2021). For the other species, no safety concern was identified for camphor white oil, when used as a feed additive at the proposed use levels.

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).

Camphor

The additive is specified to contain < 0.1% camphor,[18] a compound belonging to Cramer class II (EFSA FEEDAP Panel, 2016a). At the proposed use level in feed (30–50 mg/kg), this would result in < 0.03–0.05 mg camphor/kg complete feed. These concentrations in feed would be 10-fold lower than the maximum acceptable concentrations in feed for Cramer class II compounds (0.3–0.5 mg/kg complete feed) and are considered not of concern for the target species.

Safrole

The additive is specified to contain < 0.0002% safrole.[18] This concentration of safrole at the proposed use levels of the additive in feed (ranging from 30 to 50 mg/kg complete feed, see Section 3.2.4) could lead to 0.06–0.10 μg safrole/kg complete feed.

The maximum daily intake of safrole in μg/kg bw per day was calculated at the maximum proposed use level of the additive in feed for the different target animal categories and considering that safrole is present at a concentration corresponding to the proposed specification (< 0.0002%). The calculated intake values range between 0.0003 μg/kg bw per day (in ornamental fish) and 0.009 μg/kg bw per day (in chickens for fattening, see Appendix A).

[18] Technical dossier/Supplementary information September 2021.

When the estimated exposures for the different animal categories are compared to the $BMDL_{10}$ of 1.9 mg safrole/kg bw per day, calculated by van den Berg et al. (2011) from a rodent carcinogenicity study (Miller et al., 1983) using hepatocellular carcinomas as a response, an MOE ranging between 211,000 (chickens for fattening) and 6,190,000 (ornamental fish) is calculated. The magnitude of this MOE is indicative of a low concern for the target species (see Appendix A).

Conclusions on safety for the target species

The FEEDAP Panel concludes that camphor white oil from *C. camphora* is safe up to the maximum proposed use levels in complete feed of 30 mg/kg for piglets, pigs for fattening, sows, horses, rabbits, fish, ornamental fish and dogs and of 50 mg/kg for veal calves (milk replacer), cattle for fattening, dairy cows, sheep and goats. For the other species, the calculated safe concentration in complete feed is 28 mg/kg for chickens for fattening, 42 mg/kg for laying hens, 37 mg/kg for turkeys for fattening and 22 mg/kg for cats.

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.

3.3.2 Safety for the consumer

Camphor white oil is added to a wide range of food categories for flavouring purposes. Although individual consumption figures for the EU are not available, the Fenaroli's handbook of flavour ingredients (Burdock, 2009) cites values of 0.0018 mg/kg bw per day for camphor white oil (FEMA 2231).

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).

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 camphor white oil are expected to be extensively metabolised and excreted in the target species (see Section 3.3). Therefore, a relevant increase of the uptake of the individual constituents by humans consuming products of animal origin is not expected.

Considering the reported human exposure due to direct use of camphor white oil in food (Burdock, 2009), it is unlikely that consumption of products from animals given camphor white 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 camphor white oil up to the highest safe use level in feed for the target animals.

3.3.3 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 for camphor oil,[19] where hazards for users have been identified. The essential oil under assessment should be considered as irritant to skin and eyes, and as a skin and respiratory sensitiser.

3.3.4. Safety for the environment

C. camphora 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 (1,8-cineole, d-limonene, p-cymene and α-pinene) and additional eight components accounting together for more than 91% of the composition of the oil have been evaluated by EFSA as sensory additives for animal feed and 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.

The remaining six identified constituents of the essential oil are aliphatic mono- or sesquiterpenes partially substituted with functional groups. They are structurally related to the substances evaluated by EFSA as CG 6 (trans-para-2-menthene-1,4-diol), CG 8 (fenchone) and CG 31 (sabinene, β-phellandrene, δ-2-carene and 2,4-thujadiene) for use in animal feed (EFSA FEEDAP Panel, 2012d, 2015b, 2016a,b) for which EFSA concluded that they will be 'extensively metabolised by the target species and excreted as

[19] Technical dossier/ Supplementary Information April 2021/Annex_VII_camphor_oil_white_MSDS. Aspiration hazard (H304, category 1), Hazards for skin corrosion/irritation (H315, category 2), skin sensitisation (H317, category 1).

innocuous metabolites or carbon dioxide'. Average feed levels of constituents of the essential oil are much lower than the use levels for substances belonging to CG 6, 8 and 31.

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

3.4. Efficacy

Camphor white oil is listed in Fenaroli's Handbook of Flavour Ingredients (Burdock, 2009) and by FEMA with the reference number 2231.

Since camphor white 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

Since camphor white oil from *Cinnamomum camphora* (L.) J. Presl may be produced from plants of different origins and by various processes resulting in preparations with different composition and toxicological profiles, the following conclusions apply only to camphor white oil which is specified to contain < 0.1% camphor and < 0.0002% safrole and is produced by steam distillation from the whole plant *C. camphora*.

The FEEDAP Panel concludes that camphor white oil from *C. camphora* is safe up to the maximum proposed use levels in complete feed of 30 mg/kg for piglets, pigs for fattening, sows, horses, rabbits, fish, ornamental fish and dogs and of 50 mg/kg for veal calves (milk replacer), cattle for fattening, dairy cows, sheep and goats. For the other species, the calculated safe concentration in complete feed is 28 mg/kg for chickens for fattening, 42 mg/kg for laying hens, 37 mg/kg for turkeys for fattening and 22 mg/kg for cats.

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.

No concerns for consumers are identified following the use of the additive at the use level considered safe in feed for the target animals.

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

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

Camphor white oil is recognised to flavour food. Since its 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 camphor and safrole in the additive should be as low as possible and should not exceed 0.1% camphor and 0.0002% safrole.

6. Documentation provided to EFSA/Chronology

Date	Event
05/11/2010	Dossier received by EFSA. Chemically defined flavourings from Botanical Group 06 - Laurales, Magnoliales, Piperales for all animal species and categories. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)
11/11/2010	Reception mandate from the European Commission
03/01/2011	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: EURL*
05/04/2011	Comments received from Member States
26/02/2013	EFSA informed the applicant (EFSA ref. 7150727) 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
27/06/2013	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives - Scientific assessment remains suspended

Date	Event
24/06/2015	Technical hearing during risk assessment with the applicant according to the "EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products": data requirement for the risk assessment of botanicals
17/06/2016	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". Discussion on the ongoing work regarding the pilot dossiers BDG08 and BDG 09
27/04/2017	Trilateral meeting organised by the European Commission with EFSA and the applicant FEFANA on the assessment of botanical flavourings: characterisation, substances of toxicological concern present in the botanical extracts, feedback on the pilot dossiers
18/12/2018	EFSA informed the applicant that the scientific assessment restarted
07/02/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterization, safety for the target species, safety for the consumer, safety for the user, safety for the environment*
27/02/2019	Partial withdrawal by applicant (EC was informed) for the following additives: cassia bark extract (sb), cinnamon bark oleoresin, laurel leaves extract/oleoresin, mace oil, nutmeg oleoresin, boldo extract (wb), boldo tincture and kawakawa tincture
08/04/2021	Reception of supplementary information from the applicant (partial submission)
29/04/2021	Reception of supplementary information from the applicant (partial submission)
08/09/2021	Reception of supplementary information from the applicant (partial submission)
23/09/2021	The application was split and a new EFSA-Q-2021-00514 was assigned to the preparation included in the present assessment. Scientific assessment re-started for the preparation included in the present assessment
10/11/2021	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment for the preparation included in the present assessment

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Abbreviations

BDG	Botanically defined group
BW	body weight
CAS	Chemical Abstracts Service
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CG	chemical group
CoE	Council of Europe
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

FFAC	Feed Flavourings authorisation Consortium of FEFANA (EU Association of Specialty Feed Ingredients and their Mixtures)
FGE	food 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
IUPAC	International Union of Pure and Applied Chemistry
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LOD	limit of detection
MOE	margin of exposure
MOET	combined margin of exposure (total)
MW	molecular weight
NOAEL	no observed adverse effect level
PCBs	polychlorinated biphenyls
QSAR	Quantitative Structure-Activity Relationship
SC	EFSA Scientific Committee
TTC	threshold of toxicological concern
UF	uncertainty factor
WHO	World Health Organization

Appendix A – Safrole: maximum daily intake and margin of exposure for the different target species

The maximum daily intake of safrole for the different target species and categories was calculated based on

- the default values for body weight and feed intake (EFSA FEEDAP Panel, 2017b),
- the maximum proposed use level of the additive in feed for the different target animal categories (ranging from 30 to 50 mg/kg complete feed) and,
- assuming that safrole is present at a concentration corresponding to the proposed specification (< 0.0002%).

According to the General approach to assess the safety for the target species of botanical preparations which contain compounds that are genotoxic and/or carcinogenic,[12] 'for substances for which carcinogenicity studies in rodents are available, from which a $BMDL_{10}$ can be derived, the MOE approach (EFSA, 2005; EFSA SC, 2012) can be applied. Similarly to human risk assessment, a combined (total) margin of exposure (MOET) with a magnitude of ≥ 10,000, when comparing estimated exposure to genotoxic and/or carcinogenic substances with a $BMDL_{10}$ from a rodent carcinogenicity study, would be indicative of a low concern for the target species (EFSA Scientific Committee, 2019a)'.

The margin of exposure (MOE) for each animal category is calculated as the ratio of the reference point (the $BMDL_{10}$ of 1.9 mg safrole/kg bw per day, see Section 3.3.1) to the intake.

The maximum daily intake of safrole for the different target animal categories and the corresponding MOE are reported in Table A.1.

Table A.1: Target animal intake of safrole (as μg/kg bw per day) and margin of exposure (MOE) calculated at the maximum proposed use level of the additive in feed for target animal category and considering the maximum analysed value in the additive

Animal category	Daily feed intake	Body weight	Use level		Safrole Intake[(a)]	MOE[(b)]
	kg DM/day	kg	mg/kg	μg/kg bw per day	–	
Chicken for fattening	0.158	2	50	0.0090	211,646	
Laying hen	0.106	2	50	0.0060	315,472	
Turkey for fattening	0.176	3	50	0.0067	285,000	
Piglet	0.88	20	30	0.0030	633,333	
Pig for fattening	2.2	60	30	0.0025	760,000	
Sow lactating	5.28	175	30	0.0021	923,611	
Veal calf (milk replacer)	1.89	100	50	0.0021	884,656	
Cattle for fattening	8	400	50	0.0023	836,000	
Dairy cow	20	650	50	0.0035	543,400	
Sheep/goat	1.2	60	50	0.0023	836,000	
Horse	8	400	30	0.0014	1,393,333	
Rabbit	0.1	2	30	0.0034	557,333	
Salmon	0.0021	0.12	30	0.0012	1,592,381	
Dog	0.25	15	30	0.0011	1,672,000	
Cat	0.06	3	30	0.0014	1,393,333	
Ornamental fish	0.00054	0.012	30	0.0003	6,192,593	

(a): The values of safrole in feed is calculated considering that safrole is present at a concentration corresponding to the proposed specification (< 0.0002%).
(b): The MOE for safrole is calculated as the ratio of the reference point ($BMDL_{10}$) to the intake.

Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of the Analysis for 18 compounds from botanically defined flavourings Group (BDG 06) – Laurales, Magnoliales, Piperales

The *Botanically Defined Flavourings* – Group 6 *BDG 06* (*Laurales, Magnoliales, Piperales*) is an application comprising *eighteen flavouring compounds* (*) for which authorisation as *feed additive* is sought under the category/functional group 2(b) 'sensory additives'/'flavouring compounds', according to the classification system of Annex I of Regulation (EC) No 1831/2003. In the current application submitted according to Articles 4(1) and 10(2) of Regulation (EC) No 1831/2003, the authorisation for all species and categories is requested. *Mixtures of flavouring compounds* are intended to be incorporated only into *feedingstuffs* or drinking water. The Applicant suggested no minimum or maximum levels for the different flavouring compounds, but normal contents of *flavouring compounds* in *feedingstuffs* range up to from 0.1 to 100 mg/kg.

For the identification of volatile phytochemical markers in the *feed additive*, the Applicant submitted a qualitative multi-analyte gas chromatography-mass spectrometry (GC-MS) method, using Retention Time Locking (RTL), which allows a close match of retention times on GC-MS. By making an adjustment to the inlet pressure, the retention times can be closely matched to those of a reference chromatogram. It is then possible to screen samples for the presence of target compounds using a mass spectral database of RTL spectra. The Applicant provided the typical chromatogram for the *BDG 06* of interest. In order to demonstrate the transferability of the proposed analytical method (relevant for the method verification), the Applicant tested two model premixtures of 20 chemically defined flavourings representing the whole spectrum of compounds in use as feed flavourings with respect to their volatility and polarity. All 20 substances were extracted either from a liquid premixture or a solid premixture, and subsequently analysed using the same GC/MS method. All 20 model substances were properly identified. Since the volatile phytochemical markers of *BDG 06* are within the volatility and polarity range of the model mixture tested, the Applicant concluded that the proposed analytical method is suitable to determine qualitatively the presence of the volatile phytochemical markers from *BDG 06* in the *mixture of flavouring compounds*.

For the qualitative identification of non-volatile phytochemical markers (*boldine, kavain and piperine*) in *mixture of flavouring compounds*, the Applicant submitted high-performance liquid chromatography methods with UV detection (HPLC-UV), together with the ISO 11027 standard method for the determination of piperine.

Based on the satisfactory experimental evidence provided, the EURL recommends for official control for the qualitative identification in the *feed additive* of the individual (or mixture of) *flavouring compounds* of interest (*) the GC-MS-RTL and HPLC-UV methods submitted by the Applicant.