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Safety and efficacy of feed additives consisting of essential oils from the bark and the leaves of *Cinnamomum verum* J. Presl (cinnamon bark oil and cinnamon leaf 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 essential oils from the bark and the leaves of *Cinnamomum verum* J. Presl (cinnamon bark oil and cinnamon leaf oil), when used as sensory additives (flavourings) in feed and water for drinking for all animal species. Owing to the presence of styrene in the essential oils under assessment, the FEEDAP Panel is not in the position to conclude on the safety for long-living animals and animals for reproduction. For 'short-living' animals, the FEEDAP Panel concluded that cinnamon bark oil and cinnamon leaf oil are considered as safe up to the maximum proposed use levels in complete feed. For 'short-living' animals, the Panel considered the use of cinnamon bark 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. For cinnamon leaf oil, the proposed use level in water for drinking of 3 mg/L is considered as safe for 'short-living' animals. No concerns for consumers were identified following the use of the additives at the use level considered safe in feed for the target species. Based on the presence of safrole ≥0.1%, cinnamon leaf oil and bark oil are classified as carcinogen (category 1B) and handled accordingly. The use of the additives under the proposed conditions in animal feed was not expected to pose a risk for the environment. Since *C. verum* and its preparations are recognised to flavour food and its function in feed would be essentially the same, no further demonstration of efficacy is considered necessary for cinnamon essential oils.

Keywords: sensory additives, flavouring compounds, *Cinnamomum verum* J. Presl, cinnamon bark oil, cinnamon leaf oil, cinnamaldehyde, safrole

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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 feed additive shall submit an application in accordance with Article 7. In particular, Article 10(2) of that Regulation specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, within a maximum of 7 years after the entry into force of this Regulation.

The European Commission received a request from the 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 a feed additive for all animal species (category: sensory additives; functional group: flavouring compounds). During the assessment, the applicant withdrew the applications for eight preparations.[3] These preparations were deleted from the register of feed additives.[4] In addition, during the course of the assessment, the application was split and the present opinion covers only one out of the 10 remaining preparations under application: cinnamon oil from *Cinnamomum verum* J. Presl[5] for all animal species. During the assessment, the applicant clarified that the two types of additives fall into the definition "cinnamon oil", i.e. an essential oil from the bark and an essential oil from the leaves of *C. verum* (cinnamon bark oil and cinnamon leaf oil). The two preparations from C. *verum* will be assessed individually.

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 of an essential oil from *C. verum* J. (cinnamon bark oil and cinnamon leaf oil), when used under the proposed conditions of use (see Sections 3.2.1.3 and 3.3.1.3).

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

Cinnamon bark oil and cinnamon leaf oil from *Cinnamomum zeylanicum* Bl., *C. verum* J.S. Presl are currently authorised as feed additives according to the entry in the European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003 (2b natural products – botanically defined).[6] They have not been assessed as feed additives in the EU.

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

[2] On 13/03/2013, EFSA was informed by the applicant that the applicant company changed to FEFANA asbl, Avenue Louise 130 A, Box 1, 1,050 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] Register of feed additives, Annex II, withdrawn by OJ L162, 10.05.2021, p. 5.

[5] Accepted name: *Cinnamomum verum* J. Presl; synonym: *Cinnamomun zeylanicum* Blume.

[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

There is no specific EU authorisation for any *C. zeylanicum* preparation when used to provide flavour in food. However, according to Regulation (EC) No 1334/2008[7] flavouring preparations produced from food, may be used without an evaluation and approval as long as 'they do not, on the basis of the scientific evidence available, pose a safety risk to the health of the consumer, and their use does not mislead the consumer'.

The European Medicines Agency (EMA) issued two summary reports for veterinary use on '*Cinnamomi ceylanici aetheroleum*' and '*Cinnamomi ceylanici cortex*', the stembark of *Cinnamonum verum* J. Presl (synonym: *C. zeylanicum* Blume) (EMA, 1998, 2000).

For *C. verum* J. Presl, cortex and cortices aetheroleum the European Medicines Agency (EMA) issued a monograph for human medicinal use and an assessment report (EMA, 2011a,b) and an addendum to the assessment report (EMA, 2021).

'Cinnamon' (Cinnamomi cortex) is described in a monograph of the European Pharmacopoeia 10.0 (PhEur, 2020a). It is defined as the dried bark, freed from the outer cork and the underlying parenchyma, and shoots grown on cut stock of *C. verum* J. Presl.

'Cinnamon bark oil, Ceylon (Cinnamomi zeylanicii corticis aetheroleum)' is described in a monograph of the European Pharmacopoeia 10.0 (PhEur, 2020b). It is defined as the essential oil obtained by steam distillation of the bark of young shoots of *C. verum* J. Presl.

'Cinnamon leaf oil, Ceylon (Cinnamomi zeylanici folii aetheroleum)' is described in a monograph of the European Pharmacopoeia 10.0 (PhEur, 2020c). It is defined as the essential oil obtained by steam distillation of the leaves of *C. verum* J. Presl.

Many of the individual components of cinnamon bark and leaf oils have been already assessed as chemically defined flavourings for use in feed and food by the FEEDAP Panel, the EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC), the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) and the EFSA Panel on Food Additives and Flavourings (FAF). The list of flavouring compounds currently authorised for food[8] and feed[6] 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 is given in Table 1.

[7] 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.

[8] 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.

[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.

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
01	Straight-chain primary aliphatic alcohols/ aldehydes/acids, acetals and esters with esters containing saturated alcohols and acetals containing saturated aldehydes	Butyl 2-methylbutyrate	09.519	2013
02	Branched-chain primary aliphatic alcohols/ aldehydes/acids, acetals and esters with esters containing branched-chain alcohols and acetals containing branched-chain aldehydes	2-Methylbutyl 2-methylbutyrate[(a)]	09.516	(#)
06	Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters with esters containing tertiary alcohols ethers	Linalool	02.013	2012a
		α-Terpineol	02.014	
		4-Terpinenol	02.072	
		2-(4-Methylphenyl)propan-2-ol	02.042	
		(*E*)-3,7-Dimethylocta-1,5,7-trien-3-ol[(a)]	02.146	2015a, CEF
08	Secondary alicyclic saturated and unsaturated alcohols, ketones, ketals and esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols	d,l-Borneol	02.016	2016a
		d-Camphor[(b)]	07.215	
13	Furanones and tetrahydrofurfuryl derivatives	Linalool oxide	13.140	2012b
15	Phenyl ethyl alcohols, phenylacetic acids, related esters, phenoxyacetic acids and related esters	2-Phenylethan-1-ol	02.019	2012c
		Phenethyl acetate	09.031	
		Phenethyl isovalerate	09.466	
16	Aliphatic and alicyclic ethers	1,8-Cineole	03.001	2012d, 2021a
18	Allylhydroxybenzenes	Eugenol	04.003	2011
		4-Allyl-2,6-dimethoxyphenol	04.051	
		Eugenyl acetate	09.020	
		Allylphenol[(a)]	04.058	2009a, AFC
21	Aromatic ketones, secondary alcohols and related esters	Acetophenone	07.004	2016b
22	Aryl-substituted primary alcohol, aldehyde, acid, ester and acetal derivatives	Cinnamyl alcohol	02.017	2017a
		3-Phenylpropan-1-ol	02.031	
		Cinnamaldehyde[(c)]	05.014	
		3-Phenylpropanal	05.080	
		Cinnamyl acetate	09.018	
		3-Phenylpropyl acetate[(a)]	09.032	2009b, AFC
23	Benzyl alcohols/aldehydes/ acids/esters/ acetals	Benzyl alcohol	02.010	2012e
		Benzaldehyde	05.013	
		4-Methoxybenzaldehyde	05.015	
		Benzyl acetate	09.014	
		Benzyl isovalerate	09.458	
		Methyl benzoate	09.725	
		Ethyl benzoate	09.726	
		Benzyl benzoate	09.727	
		Methyl salicylate	09.749	

CG	Chemical Group	Product – EU register name (common name)	FLAVIS No	EFSA opinion, * Year
25	Phenol derivatives containing ring-alkyl, ring-alkoxy and side-chains with an oxygenated functional group	Thymol	04.006	2012f
		Carvacrol	04.031	
31	Aliphatic and aromatic hydrocarbons and acetals containing saturated aldehydes	Limonene[(a,d)]	01.001	2008, AFC
		1-Isopropyl-4-methylbenzene (*p*-cymene)	01.002	2015
		Terpinolene	01.005	
		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	2016c
		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,e)]	01.021	2011, CEF
		Germacra-1(10),4(14),5-triene (δ-Germacrene)[(a,e)]	01.042	
		3,7,10-Humulatriene[(a,e)]	01.043	
		α-Muurolene[(a,e)]	01.052	
		β-Phellandrene[(a,e)]	01.055	
		4(10)-Thujene (sabinene)[(a)]	01.059	2015b, CEF
		cis-3,7-Dimethyl-1,3,6-octatriene (*cis*-β-Ocimene)[(a)]	01.064	
32	Epoxides	β-Caryophyllene epoxide[(a)]	16.043	2014, CEF

*: FEEDAP opinion unless otherwise indicated. (#) evaluated by JECFA before 2000.
(a): Evaluated for use in food. According to Regulation (EC) 1,565/2000, flavourings evaluated by JECFA before 2000 are not required to be re-evaluated by EFSA.
(b): JECFA and EFSA evaluated the enantiomer d-camphor [07.159] (name in the register (1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1] heptan-2-one) for use in food (EFSA, 2008) and in feed (EFSA FEEDAP Panel, 2016a).
(c): EFSA evaluated cinnamaldehyde [05.014] (EFSA FEEDAP Panel, 2017a). The configuration of the double bond in cinnamaldehyde [05.014] has not been specified. However, the substance is anticipated to contain more than 97% *trans*-cinnamaldehyde (EFSA, 2009b).
(d): 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).
(e): Evaluated applying the 'Procedure' described in the Guidance on the data required for the risk assessment of flavourings to be used in or on food (EFSA CEF Panel, 2010).

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 cinnamon bark oil and cinnamon leaf oil from *C. verum* as feed additives.

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. The applicant submitted a written agreement to use the data submitted for the assessment of chemically defined flavourings (dossiers, publications and

[10] FEED dossier reference: FAD-2010-0218.

unpublished reports) for the risk assessment of preparations belonging to BDG 6, including the current ones under assessment.[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 botanically defined flavourings from Group 06 – Laurales, Magnoliales, Piperales. During the assessment, upon request from EC and EFSA, the EURL issued two amendments of the original report.[12] For the additive under assessment, cinnamon oil, the evaluation of the method of analysis is included in the second amendment. The Executive Summary of the EURL report can be found in Annex A.[13]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of cinnamon bark oil and cinnamon leaf oil from *C. verum* is in line with the principles laid down in Regulation (EC) No 429/2008[14] and the relevant guidance documents: 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, 2012g), Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012h), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017b), Guidance on the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017c), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017d), 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 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) and 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).[15]

3. Assessment

The additives under assessment, cinnamon bark oil and cinnamon leaf oil, are essential oils obtained by steam distillation of the bark or the leaves from *C. verum* J. Presl. They are intended for use as sensory additives (functional group: flavouring compounds) in feed and water for drinking for all animal species.

3.1. Origin and extraction

C. verum J. Presl (synonym: *C. zeylanicum*) is an evergreen tree belonging to the Lauraceae and is commonly referred as to Ceylon cinnamon tree or true cinnamon tree. It is native to Sri Lanka and is cultivated in Madagascar, India, Vietnam and Indonesia.

The essential oils are extracted from either the bark or the leaves by steam distillation and then separated from the aqueous phase by decantation.

[11] Technical dossier/Supplementary information/Letter dated 29/04/2021.
[12] Preparations included in the first amendment: ylang ylang oil, camphor white oil and cinnamon tincture; preparations included in the second amendment: nutmeg oil, laurel leaves oil, pepper oil black, cinnamon oil, cassia oil and pepper oleoresin black.
[13] The full report is available on the EURL website: https://joint-research-centre.ec.europa.eu/publications/fad-2010-0218_en
[14] 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.
[15] https://www.efsa.europa.eu/sites/default/files/2021-05/general-approach-assessment-botanical-preparations-containing-genotoxic-carcinogenic-compounds.pdf

3.2. Cinnamon bark oil

3.2.1. Characterisation of cinnamon bark oil

The essential oil obtained from bark is a pale yellow to yellow, clear slightly viscous liquid with a characteristic aroma. In five batches of the additive (from two different producers, all originating from Sri Lanka), the density (20°C) ranged between 1,022 and 1,029 kg/m^3 (specification: 1,015–1,035 kg/m^3), the refractive index (20°C) between 1.584 and 1.588 (specification: 1.581–1.591) and the specific optical rotation (at 20 °C, three batches) between −2° and −1°.[16] Cinnamon bark oil is identified with the single Chemical Abstracts Service (CAS) number 8015-91-6,[17] the European Inventory of Existing Commercial Chemical Substances (EINECS) number 283–479-0, the Flavor Extract Manufacturers Association (FEMA) number 2291 and Council of Europe (CoE) number 133.

For cinnamon bark oil, the specifications used by the applicant are based on the four main constituents listed in the European Pharmacopoeia for cinnamon bark oil (04/2011:1501),[18] adapted to reflect the concentrations of the main components of the essential oil. Four components contribute to the specification as shown in Table 2, with (*E*)-cinnamaldehyde selected as the phytochemical marker. Analysis of three batches of the additive showed compliance with these specifications when analysed by gas-chromatography with flame ionisation detection (GC-FID) and expressed as % of gas chromatographic peak area (% GC area).[19] The applicant provided the full characterisation of the five batches obtained by gas chromatography–mass spectrometry (GC–MS).[16] The four compounds account for 86.8% on average (range 81.8–90.0%) of % GC area (Table 2).

Table 2: Major constituents of the essential oil from the bark of *Cinnamomum verum* J. Presl as defined by specifications and batch to batch variation based on the analysis of five 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			% GC area		
EU register name	**CAS No**	**FLAVIS No**	**Specification**	**Mean[(a)]**	**Range**
(*E*)-Cinnamaldehyde	14,371–10-9	05.014[(b)]	55–75[(c)]	69.0	64.7–70.8
Eugenol	97–53-0	04.003	≤ 7.5	6.43	5.72–7.22
β-Caryophyllene	87–44-5	01.007	1.0–7.5	6.33	5.54–7.01
Linalool	78–70-6	02.013	1.0–7.5	5.02	3.94–6.08
Total				86.8	81.8–90.0

CAS no: Chemical Abstracts Service number; FLAVIS number: EU Flavour Information System numbers.
(a): Mean calculated on five batches.
(b): EFSA evaluated cinnamaldehyde [05.014] (EFSA FEEDAP Panel, 2016c). The configuration of the double bond in cinnamaldehyde [05.014] has not been specified. However, the substance is anticipated to contain more than 97% *(E)*-cinnamaldehyde (EFSA, 2009b).
(c): Specification given for cinnamaldehyde.

In total, up to 61 peaks were detected in the chromatogram, 60 of which were identified and accounted on average for 99.7% (99.3–99.9%) of the product (as the % GC area). Besides the four compounds indicated in the product specifications, 24 other compounds were detected at individual levels ≥ 0.05% and are listed in Table 3. These 28 compounds together account on average for 99.4% (98.8–99.8%) of the product. The remaining 32 compounds (ranging between 0.04% and 0.003%)

[16] Technical dossier/Supplementary information October 2020/Annex_II_ SIn_Reply_cinnamon_oil_COA_chromatograms.
[17] The CAS number 8007-80-5 is associated to cinnamon bark oil in Fenaroli's Handbook (Burdock, 2009).
[18] Technical dossier/Supplementary information October 2020/Annex_III_ SIn_Reply_cinnamon_oil_ISO_Eur_Pharm.
[19] Technical dossier/Supplementary information October 2020/ SIn reply_BDG06_cinnamon oil/GC-FID analysis: (E)-cinnamaldehyde (71.3–72.2%), eugenol (4.83–5.45%), linalool (5.88–6.24%) and β-caryophyllene (5.97–6.14%).

and accounting for 0.32% (0.1–0.61%) are listed in the footnote.[20] Based on the available data on the characterisation, cinnamon bark oil is considered a fully defined mixture.

Table 3: Other constituents of the essential oil from the bark of *Cinnamomum verum* J. Presl, accounting for ≥ 0.05% of the composition (based on the analysis of five batches) not included in the specification. 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[(a)]	Range
Cinnamyl acetate	103–54-8	09.018	5.47	3.24–6.64
α-Phellandrene	99–83-2	01.006	0.81	0.21–1.53
1-Isopropyl-4-methylbenzene (*p*-cymene)	99–87-6	01.002	0.79	0.45–1.58
Benzyl benzoate	120–51-4	09.727	0.77	0.36–1.39
1,8-Cineole	470–82-6	03.001	0.73	0.11–1.17
Pin-2(3)-ene (α-pinene)	80–56-8	01.004	0.73	0.24–1.52
β-Phellandrene	555–10-2	01.055	0.58	0.37–1.04
α-Copaene	3,856-25-5	–	0.34	0.19–0.58
3,7,10-Humulatriene	6,753-98-6	01.043	0.32	0.23–0.45
Safrole	94–59-7	–	0.27	0.12–0.34
Camphene	79–92-5	01.009	0.23	0.07–0.49
(*Z*)-Cinnamaldehyde	57,194–69-1	05.014[(b)]	0.20	0.14–0.29
Pin-2(10)-ene (β-pinene)	127–91-3	01.003	0.20	0.06–0.44
Limonene	138–86-3	01.001	0.19	0.15–0.26
β-Caryophyllene epoxide	1,139-30-6	16.043	0.17	0.08–0.25
Eugenyl acetate	93–28-7	09.020	0.16	0.11–0.21
alpha-Terpinene	99–86-5	01.019	0.13	0.07–0.21
4-Methoxybenzaldehyde	123–11-5	05.015	0.12	0.09–0.15
α-Thujene	2,867-05-2	–	0.11	0.04–0.23
α-Terpineol	98–55-5	02.014	0.09	0.04–0.16
Benzaldehyde	100–52-7	05.013	0.07	0.03–0.17
Terpinolene	586–62-9	01.005	0.07	0.02–0.12
Myrcene	123–35-3	01.008	0.06	0.03–0.11
δ-3-Carene	13,466–78-9	01.029	0.05	0.01–0.12
Total			12.6	9.67–17.07

CAS no: Chemical Abstracts Service number; FLAVIS number: EU Flavour Information System numbers.
(a): Mean calculated on five batches.
(b): EFSA evaluated cinnamaldehyde [05.014] (EFSA FEEDAP Panel, 2016c). The configuration of the double bond in cinnamaldehyde [05.014] has not been specified. However, the substance is anticipated to contain more than 97% (*E*)-cinnamaldehyde (EFSA, 2009b).

The applicant made a literature search for the chemical composition of *C. verum* and its preparations and the identity of any recognised substances of concern,[21] which identified methyleugenol, safrole, 1,8-cineole, camphor and coumarin. These compounds are reported in the EFSA Compendium of botanicals as substances of concern for the essential oil obtained from the bark of *C. verum* (EFSA, 2012).[22] The applicant undertook analyses to establish whether the substances of concern were present. Besides safrole (0.12–0.34%, see Table 3), cinnamon bark oil was also shown

[20] Additional constituents: constituents (n = 26) between <0.05 and ≥ 0.01%: 2-methylbutyl 2-methylbutyrate, isocaryophyllene, δ-cadinene, 4-terpinenol, 3-phenylpropyl acetate, thymol, 1-isopropenyl-4-methylbenzene, 3-phenylpropan-1-ol, borneol, 3-phenylpropanal, α-cubebene, 2-phenylethan-1-ol, styrene, *trans*-3,7-dimethyl-1,3,6-octatriene, γ-terpinene, β-elemene, *cis*-3,7-dimethyl-1,3,6-octatriene, 4(10)-thujene, β-calacorene, α-calacorene, 4-allyl-2,6-dimethoxyphenol, (*E*)-2-methoxycinnamaldehyde, linalool oxide, camphor, cinnamyl alcohol, 2-(4-methylphenyl)propan-2-ol; constituents (n = 6) <0.01 and >0.003%: α-muurolene, γ-cadinene, γ-muurolene, phenethyl acetate, methyleugenol and acetophenone.
[21] Technical dossier/Supplementary information October 2020/Literature search_cinnamon_oil.
[22] Online version: https://www.efsa.europa.eu/en/data-report/compendium-botanicals.

to contain methyleugenol in one batch (0.004%). Camphor was detected in two batches (on average: 0.013%, range: 0.007–0.018%) whereas coumarin was not detected by GC–MS (limit of detection, LOD 0.01%). In addition, cinnamon bark oil contains low concentrations of styrene (on average: 0.020%, range: 0.016–0.024%). The occurrence of styrene in cinnamon bark oil is most probably due to oxidation of cinnamaldehyde to cinnamic acid with subsequent decarboxylation to yield styrene. Styrene concentrations in essential oils from various sources (*C. zeylanicum* Nees and *C. cassia*) have been evaluated to be 120–450 mg/kg (Fragniére et al., 2003).

3.2.1.1. Impurities

The applicant makes reference to the 'periodic testing' of some representative flavourings premixtures for mercury, cadmium, lead, arsenic, fluoride, dioxins and polychlorinated biphenyls (PCBs), organochloride pesticides, organophosphorous pesticides, aflatoxins B1, B2, G1, G2 and ochratoxin A. However, no data were provided on the presence of these impurities. Since cinnamon bark oil is produced by steam distillation, the likelihood of any measurable carry-over of all the above-mentioned elements is low except for mercury.

3.2.1.2. 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).[23] However, no data supporting this statement were provided.

3.2.1.3. Conditions of use

Cinnamon bark oil is intended to be added to feed for all animal species without a withdrawal time. The maximum proposed use level in complete feed for the different target species is 5 mg/kg complete feed for poultry, rabbits, salmonids and ornamental fish, cats and dogs, 10 mg/kg for ruminants and horses, 25 mg/kg for pigs for fattening, and 50 mg/kg for piglets and sows.

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

3.2.2. Safety

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

Many of the components of cinnamon bark oil, accounting for about 97% of the GC peak areas, have been previously assessed and considered safe for use as flavourings, and are currently authorised for use in food[8] without limitations and for use in feed[6] 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 is given in Table 1 (see Section 1.2). The FEEDAP Panel considers that the conclusions of the assessment of cinnamaldehyde [05.014] (a mixture of (*E*)- and (*Z*)-isomers) apply to the geometric isomers (*E*)- and (*Z*)-cinnamaldehyde present in the additive (EFSA FEEDAP Panel, 2017a), and that the assessment of d-camphor [07.215] is relevant for camphor (EFSA FEEDAP Panel, 2016a).

(*E*)-2-Methoxycinnamaldehyde has not been evaluated for use as a flavouring but is closely related to the flavouring compounds already assessed in CG 22 (EFSA FEEDAP Panel, 2017a).

Three compounds, δ-cadinene [01.021], α-muurolene [01.052] and β-phellandrene [01.055], have 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 these compounds, 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 are currently 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).

Few volatile components accounting for <0.5% of the GC area (*trans*-3,7-dimethyl-1,3,6-octatriene, β-elemene, β-chalacorene, α-chalacorene, α-copaene, α-thujene, isocaryophyllene, α-cubebene, γ-cadinene and γ-muurolene) have not been previously assessed for use as flavourings. The FEEDAP Panel notes that they are mono- or sesqui-terpene derivatives structurally related to flavourings

[23] Technical dossier/Section II.

already assessed in CG 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, 2015, 2016c).

The following sections focus on those compounds not previously assessed for use as flavourings or considered substances of concern, i.e. safrole, methyleugenol and styrene, based on the evidence provided by the applicant in the form of literature searches.

3.2.2.1. Absorption, distribution, metabolism and excretion

Safrole and methyleugenol

Safrole is a lipophilic compound and, as such, readily and completely absorbed from the gastrointestinal tract. Phase I metabolism is catalysed by cytochromes P450 (CYP450) enzymes mainly in the liver. Metabolism involves two major routes: (i) the oxidation of the allyl-side chain leading to 1′-hydroxy-safrole with subsequent isomerisation to 3′-hydroxysafrole, which is excreted in conjugated form mainly as glucuronides (Miller et al., 1983) and (ii) the oxidation of the methylenedioxy group with subsequent cleavage to form 4-allyl catechol. Besides these two major pathways, the epoxidation of the allyl-side chain leads to safrole-2′,3′-epoxide, which is hydrolysed to the corresponding diol with subsequent glucuronidation and excretion. These three oxidation pathways give rise to reactive metabolites. However, the formation of genotoxic metabolites is mainly due to the formation of 1′-hydroxy-safrole and its conjugation with sulfate, leading to 1′-sulfooxy-safrole, which is unstable and breaks down to form a highly reactive carbonium ion, which can react covalently with DNA (as reviewed in EC, 2002; Miller et al., 1983). Minor pathways involve the epoxidation of the aromatic ring and the gamma oxidation of the allylic side chain leading to a carboxylic acid (piperonylic acid) which is further conjugated with glycine (piperonylglycine) and excreted.

Similar metabolic pathways have been described for methyleugenol (as reviewed in EMA, 2005, IARC, 2018) and other structurally related *p*-allylalkoxybenzenes.

Styrene

The metabolism of styrene has been widely investigated in humans and experimental animals and has been summarised in the IARC assessment (IARC, 2019).

Due to the impact of styrene in occupational exposure, most published ADME studies were performed by administering styrene by inhalation and dermal routes and only few after oral administration. In a study carried out by Sbrana et al. (1983), aimed at evaluating the genotoxicity of styrene, a kinetic study was performed in parallel after administration of the compound to mice by gavage at daily doses of 200 mg/kg body weight (bw) for 70 days. Blood was collected on days 1 and 70 at selected time intervals. Urine was collected at the same days over a period of 24 h after styrene administration for quantification of metabolites by GC–MS. Styrene was rapidly absorbed with a plasma Cmax of 10 μg/mL 1 h after administration by gavage. Excretion was rapid, with a half-life ($t_{1/2}$) of 36 min. No differences were observed between styrene kinetics in blood on days 1 and 70 of administration. In urine, styrene metabolites derived from styrene-7,8-oxide (i.e. phenylethylene glycol, mandelic acid, benzoic acid, phenylglyoxylic acid and hippuric acid) and from styrene-7,8-oxide conjugation with glutathione (i.e. mercapturic acid) accounted for 79% and 71% of the administered dose, respectively after day 1 and day 70 of administration.

Mendrala et al. (1993) made an *ex vivo* comparative evaluation of the relevant enzymes responsible for the metabolism of styrene, measuring the activities of monooxygenase and epoxide hydrolase in the microsomal fraction and of glutathione-*S*-transferase in the cytosolic fraction of the liver from rats and mice not exposed or previously exposed to styrene via inhalation. The same enzymes were measured in human liver fractions prepared from accident victims submitted to liver transplantation. Mice showed the greatest and humans the lowest capacity to form styrene epoxide and the activity of epoxide hydrolase relative to monooxygenase activity was higher in the human than in the rodent liver. The data indicate that, in rodents, the formation of styrene epoxide is greater and its inactivation by hydrolysis is slower compared to humans. However, it is questionable whether this difference impacts the metabolic activation at human dietary exposure levels.

The blood levels of styrene and styrene epoxide were measured *in vivo* after oral administration of 500 mg styrene/kg bw to non-exposed rats or to rats previously exposed to 1,000 mg/kg bw styrene (Mendrala et al., 1993). Styrene blood levels in both groups of rats were similar during the first 6 h after administration, the mean value ranging from 22 to 53 μg/g, decreasing to 0.4 μg/g at 24 h. Mean blood levels of styrene oxide ranged from 0.07 to 0.53 μg/g during the first 10 h after dosing,

being not detected after this time. The area under the curve (AUC) of styrene and styrene oxide was similar in both groups indicating that no enzymatic induction occurred from the previous exposure to styrene.

Plotnick and Weigel (1979; only the abstract is available) studied the distribution and excretion of ^{14}C-styrene orally administered to rats at a dose of 20 mg/kg bw. Radioactivity in tissues peaked at 4 h after administration. Kidney was the organ with the highest concentration, followed by liver and pancreas. Excretion was almost complete in urine after 24 h, only 2% of the dose was excreted in faeces.

In humans, following inhalation or dermal exposure, styrene is readily absorbed and distributed throughout the body tissues. Repeated exposure to styrene leads to a gradual accumulation in the adipose tissue but not in other tissues. In humans, styrene is initially oxidised by cytochrome P450s (CYPs) through three distinct pathways: (i) epoxidation of the vinyl double bond, the major metabolic pathway; (ii) oxidation on the vinyl group; and (iii) oxidation on the phenyl ring (reviewed in IARC, 2019). Metabolites from all three pathways have been detected in humans exposed to styrene and in experimental studies in laboratory animals. The majority of the absorbed styrene (about 90%) is metabolised in the liver by oxidation of the vinyl double bond to styrene-7,8-oxide, the main reactive metabolite, which, if not hydrolysed, can form adducts with DNA leading to mutations and cancer (Vodicka et al., 2016). In the main metabolic pathway, styrene-7,8-oxide is further metabolised by epoxide hydrolase to styrene glycol and excreted in the urine mainly as mandelic acid (60–80%) and phenylglyoxylic acid (about 30%). Minor amounts of hippuric acid are also excreted. Styrene-7,8-oxide can also be conjugated with glutathione to yield glutathione conjugates, which are further catabolised to isomeric phenylhydroxyethylmercapturic acids. Minor pathways involve the oxidation of the vinyl group resulting in the formation of 1- and 2-phenylethanol or the oxidation of the aromatic ring with the formation of vinylphenols, mainly 4-vinylphenol, which are excreted as glucuronide and sulfate-conjugates. The intermediate styrene-3,4-epoxide may also be formed (Watabe et al., 1982). About 1 to 2% of the dose is excreted unchanged in urine.

In summary, studies made in experimental animals and data from humans exposed to styrene show that styrene is rapidly absorbed, widely distributed in the organism, extensively biotransformed through similar metabolic pathways and almost completely excreted in urine.

3.2.2.2. Genotoxicity and carcinogenicity

For fully defined mixtures, the EFSA Scientific Committee recommends applying a component-based approach, i.e. assessing all components individually for their genotoxic potential using all available information, including read-across and quantitative structure–activity relationship (QSAR) considerations about their genotoxic potential (EFSA SC, 2019b).

Safrole and methyleugenol are compounds with experimentally proven genotoxicity and carcinogenicity in rodents (as reviewed in EC, 2002, WHO, 2009; EMA, 2005; IARC, 2018).

In 2019, the International Agency for Research on Cancer (IARC, 2019) classified styrene and its metabolite styrene-7,8-oxide as 'probably carcinogenic to humans' (Group 2A).

Safrole and methyleugenol

Safrole was negative or weakly positive in bacterial mutagenicity tests with *Salmonella* Typhimurium (Green and Savage, 1978; Swanson et al., 1979; Baker and Bonin, 1985, as referenced in EC, 2002). The addition of 3′-phosphoadenosine-5-phosphosulfate (PAPS) causes a further increase of the mutagenic effect, showing that the formation of sulfo-conjugates may be essential for the activation to an ultimate mutagen (Honda et al., 2016). Safrole induced intra-chromosomal recombination in *Saccharomyces cerevisiae* with and without metabolic activation. Safrole was also positive in various mammalian cell genotoxicity assays such as chromosomal aberration assays and sister chromatid exchange assays (Ishidate and Sofuni, 1985; Bradley, 1985 as referenced in EC, 2002). The *in vivo* genotoxicity of safrole was proven by a sister chromatid exchange assay in F344 rats (Daimon et al., 1998, as referenced in EC, 2002). Safrole showed a dose related induction of unscheduled DNA synthesis in primary rat hepatocytes in culture (Howes et al., 1990; Chan and Caldwell, 1992; as referenced in EC, 2002). DNA adducts could be isolated from mouse liver after exposure to safrole and identified as guanine adducts. The same adducts were obtained after exposure of primary rat hepatocytes in culture (Phillips et al., 1984).

Safrole was included in the diet of female CD-1 mice at 0, 2.5 or 5.0 g/kg diet for 12 months. At least 70% of the animals in the exposed groups developed hepatic tumours by 18 months,[24] which were diagnosed as hepatomas types A (hepatocellular adenomas) or B (hepatocellular adenocarcinomas) or mixed types A and B. The animals fed with the control diet did not show any hepatic tumour (Miller et al., 1983).

Van den Berg et al. (2011) performed an evaluation of the available evidence using the benchmark dose (BMD) approach and found that the application of the appropriate dose–response modelling on toxicity study (Miller et al., 1983) using hepatocellular carcinomas as response, yielded a BMD lower confidence limit for a benchmark response of 10% ($BMDL_{10}$) of 1.9 mg safrole/kg bw per day. However, the FEEDAP Panel notes that there is high uncertainty in derivation of a $BMDL_{10}$ for safrole from a carcinogenicity study in CD-1 mice, particularly with a strain known to spontaneously develop a high incidence of hepatocellular adenomas and carcinomas. In addition, BMD modelling with only two dose-levels is adding extra uncertainty in the derivation of the $BMDL_{10}$ value.

Miller et al. (1983) also investigated the possible carcinogenic activity of a variety of *p*-allylalkoxybenzenes and related compounds in newborn male mice, injected intraperitoneally (i.p.) with nine different compounds at days 1, 8, 15 and 22 after birth. Among these, estragole, safrole and methyleugenol induced a significant number of hepatomas (hepatocellular adenomas and carcinomas) at 13 months, whereas anethol, elemicin, myristicin, dillapiole, parsley apiole and eugenol did not, under the limited conditions of the study.

In another experiment using the same treatment protocol, DNA was isolated from the liver of the exposed 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 apiol and anethol where below the LOQ of 1 pmol/mg DNA. No adducts at all were observed for 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) confirmed methyleugenol as the most potent derivative. 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.

Methyleugenol was not mutagenic in the bacterial mutagenicity assay with *Salmonella* Typhimurium and *Escherichia coli* WP-*uvrA* in the presence and absence of S9-mix. However, positive results were obtained in a modified strain of *Salmonella* Typhimurium (TA100-hSULT1C2) expressing sulfotransferase (Honda et al., 2016), indicating that the formation of sulfate esters plays a key role in the genotoxicity of alkenylbenzenes. In Chinese hamster ovary (CHO) cells, sister chromatid exchange (SCE) was induced by methyleugenol exposure in the presence and absence of microsomal activation and chromosomal aberrations only in the presence of microsomal activation (NTP, 2000). The induction of malignant transformation by methyleugenol was demonstrated in Syrian hamster ovary cells (Kerkaert et al., 1996). DNA repair was induced by methyleugenol in primary hepatocytes from rats and mice (Howes et al., 1990; Chan and Caldwell, 1992; Burkey et al., 2000). The DNA damaging effects could be inhibited by addition of sulfotransferase inhibitors (Herrmann et al., 2014). *In vitro*, DNA adducts were detected in the livers of female CD-1 mice after i.p. injection of methyleugenol and in human HepG2 cells exposed to methyleugenol (Zhou et al., 2007).

The carcinogenicity of methyleugenol was investigated in a 2-year National Toxicology Program (NTP) carcinogenicity study in rats and mice (NTP, 2000) using oral doses of 0, 37, 75, or 150 mg/kg bw per day in both species and a higher dose of 300 mg/kg bw per day in rats. Rats of both sexes receiving methyleugenol showed dose-related increased incidences of hepatocellular carcinomas and neuroendocrine tumours of the glandular stomach.[25] Higher incidences of kidney neoplasms, malignant

[24] Incidence of hepatomas in female mice (0/50, 34/50, 39/50).

[25] Male rats: hepatocellular adenoma (5/50, 12/50, 23/50, 38/50, 32/50), hepatocellular carcinoma (2/50, 3/50, 14/50, 25/50, 36/50), hepatocellular adenoma or carcinoma combined (7/50, 14/50, 28/50, 43/50, 45/50), hepatocholangioma or hepatocolangiocarcinoma (0/50, 0/50, 1/50, 2/50, 13/50); glandular stomach (0/50, 0/50, 0/50, 7/50, 4/50)Female rats: hepatocellular adenoma (1/50, 8/50, 11/49, 33/49, 43/50), hepatocellular carcinoma (0/50, 0/50, 4/49, 8/49, 22/50), hepatocellular adenoma or carcinoma combined (1/50, 8/50, 14/49, 34/49, 43/50), hepatocholangioma or hepatocolangiocarcinoma (0/50, 0/50, 0/50, 3/50, 13/17); glandular stomach (0/50, 1/50, 25/50, 34/50, 41/50).

mesothelioma, mammary gland fibroadenoma and subcutaneous fibroma and fibrosarcoma were observed in male rats only.[26] Increased incidence of hepatocellular carcinomas was seen in both sexes of mice although the incidence was not related to the dose. Neuroendocrine tumours of the glandular stomach were also observed in male mice but only at the highest dose. The NTP concluded that there was clear evidence for the carcinogenicity of methyleugenol in rats and mice.

Suparmi et al. (2019) performed an evaluation of the available evidence using BMD approach and found that dose–response modelling, applying model averaging as recommended by the EFSA Scientific Committee (EFSA SC, 2017) on the long-term chronic toxicity study (NTP, 2000) using hepatocellular carcinomas in male rats as a response, yielded a BMD lower confidence limit for a benchmark response of 10% ($BMDL_{10}$) of 22.2 mg/kg bw per day. Based on the above considerations on the relative potency of *p*-allylalkoxybenzenes, the FEEDAP Panel selects the $BMDL_{10}$ derived from the rat study with methyleugenol, with three test doses and derived applying model averaging, as reference point for the assessment group of *p*-allylalkoxybenzenes.

Styrene: carcinogenicity and genotoxicity

In 2019, IARC updated the evaluation of styrene (IARC, 2002) in which the substance had been classified as 'possibly carcinogenic to humans' (Group 2B). In this last monograph (IARC, 2019), IARC categorised styrene and its metabolite styrene-7,8-oxide as 'probably carcinogenic to humans' (Group 2A). Furthermore, IARC considered that 'there is strong evidence that both styrene and styrene-7,8-oxide are genotoxic, and that this mechanism can also operate in humans'.

The EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) evaluated the impact of the conclusions of IARC on the safety assessment of the substance styrene (FCM No 193) for its use in plastic food contact materials (EFSA CEP Panel, 2020).

As summarised by EFSA (EFSA CEP Panel, 2020), 'The recent IARC monograph classified styrene as 'probably carcinogenic to humans' (Group 2A), on the basis of 'limited evidence' in humans and 'sufficient evidence' in experimental animals. Increased incidence of, or mortality, from leukaemia and lymphomas were reported in several epidemiological studies in cohorts of workers exposed to styrene by inhalation, mainly in the reinforced plastics industries; there was also a strong signal for sinonasal adenocarcinoma, a rare cancer in humans, based on a few cases observed in a single large study. Overall, IARC concluded that *the epidemiological studies provide some credible evidence that exposure to styrene causes lymphohaematopoietic malignancies in humans, but confounding, bias or chance cannot be ruled out*'. (...)

'Nine studies of carcinogenicity of styrene in mice were reported (three by gavage, five via inhalation, one intraperitoneal). Increased incidence of bronchioloalveolar adenoma or carcinoma of the lung was described in two studies by inhalation in CD1 mice and in one study of transplacental exposure followed by gavage in O20 mice. In a study in B6C3F1 mice, styrene administered by gavage significantly increased the incidence of bronchioloalveolar adenoma or carcinoma in males, and a significant positive trend in the incidence of hepatocellular adenoma in females. Nine studies of carcinogenicity of styrene in rats were reported (four by gavage, one in drinking water, two via inhalation, one via intraperitoneal administration and one via subcutaneous injection). One study out of two carcinogenicity studies in rats exposed to styrene by inhalation described a significant increase in the incidences of malignant tumours of the mammary gland. No significant increase in the incidence of any tumour type was observed in the other rat studies'.

'The IARC Monograph concluded that there is "strong evidence" for a genotoxic mechanism of styrene, mediated by its metabolic activation to the electrophilic styrene-7,8-oxide, an epoxide that is genotoxic and directly reactive to DNA. (...).

The large majority of *in vitro* studies on styrene genotoxicity, described in the IARC monograph, showed positive results only in the presence of metabolic activation. Gene mutations in bacterial cells (Ames test) were found in *Salmonella* Typhimurium strains that detect base-pair substitutions (TA100, TA1530 and TA1535) but not in strains that detect frameshift mutations (TA98, TA1537 and TA1538) and in *Escherichia coli* strains. Positive results were reported for gene mutation in mammalian cells. Cytogenetic studies (chromosomal aberration test, micronucleus assay and sister chromatid exchange (SCE)) in mammalian cell lines (V79, CHO) also showed positive results. Positive results without metabolic activation were reported in cytogenetic studies in human whole blood lymphocytes. The

[26] Males rats: kidney neoplasms (4/50, 6/50, 17/50,13/50, 20/50), malignant mesothelioma (1/50, 3/50, 5/50, 12/50, 5/50), mammary gland fibroadenoma (5/50, 5/50, 15/50, 13/50, 6/50), subcutaneous fibroma or fibrosarcoma (1/50, 12/50, 8/50, 8/50, 4/50).

IARC monograph also reports a large number of *in vivo* genotoxicity studies carried out by inhalation or intraperitoneal injection. These studies showed positive results for markers of DNA damage (DNA-adducts, single-strand breaks detected by Comet assay and SCE), while negative or weakly positive results were reported for chromosomal damage (structural chromosomal aberrations and micronuclei). Two *in vivo* oral studies described in the IARC Monograph reported negative results for chromosomal aberrations in bone marrow of male and female mice exposed up to the maximum tolerated doses, after single or repeated administrations (Loprieno et al., 1978; Sbrana et al., 1983). In one of these oral studies, separate experiments carried out in parallel with styrene oxide at the same range of doses showed a statistically significant dose-related increase in chromosomal aberrations (Loprieno et al., 1978). The IARC Monograph supports that the mechanism of genotoxicity of styrene observed in experimental systems is likely to operate also in humans.

(…) The large majority of the human biomonitoring studies were carried out in the reinforced plastics industry, using DNA damage biomarkers, i.e. DNA adducts, oxidative DNA damage, single-strand breaks by Comet assay, chromosomal aberrations, micronucleus test and SCE. Mixed results were described in studies applying different genotoxicity biomarkers, and a lack of consistency was also shown among the studies using the same genotoxicity biomarker. DNA adducts in peripheral blood cells have been reported to be significantly higher in exposed workers than in unexposed controls in a number of studies. The majority, but not all, of the several available studies showed increased levels of DNA damage as measured by the Comet assay. Studies using the Comet assay to assess oxidative damage to DNA were negative, studies measuring 8-hydroxy-2′-deoxyguanosine in DNA were inconsistent. In the few studies on gene mutation, no clear relationship was found with occupational exposure to styrene. Mixed results were reported in the studies on chromosomal endpoints (chromosomal aberration, micronuclei frequency) in blood cells of exposed workers'.

In its assessment of the impact of the IARC Monograph Vol. 121 on the safety of the substance styrene (FCM No 193) for its use in plastic food contact materials, *the EFSA CEP Panel* concluded that based on the data provided in the IARC Monograph and by the industry, a concern for genotoxicity associated with oral exposure to styrene remains. EFSA also recommended that 'a systematic review of genotoxicity and mechanistic data, comparative toxicokinetics and analysis of species differences is required for assessing the safety of styrene' (EFSA CEP Panel, 2020).

3.2.2.3. Subchronic toxicity studies

Methyleugenol

Methyleugenol was tested in a repeated dose toxicity assay over a period of 14 weeks in rats and mice dosed with 10, 30, 100, 300 or 1,000 mg/kg bw by gavage for 5 days per week (NTP, 2000). In the rat, changes of organ weight and function, including effects on liver and the glandular stomach, were observed at doses of 100 mg/kg bw and higher. A no observed adverse effect level (NOAEL) of 30 mg/kg bw could be identified from the rat study. In the mice study, increased liver weights and lesions of the glandular stomach occurred at a dose of 30 mg/kg bw and above. Thus, the NOAEL for non-neoplastic lesions identified in the mouse study was 10 mg/kg bw per day.

Safrole

Groups of young adult Osborne-Mendel rats of both sexes received safrole by gavage at doses of 250, 500 or 750 mg/kg bw per day up to 105 days. At the dose of 750 mg/kg bw per day for 19 days 9/10 animals died; with 500 mg/kg bw per day only 1/10 animals died after 46 days; with 250 mg/kg bw per day no animal died within 34 days. The following effects were observed: liver hypertrophy and focal necrosis plus slight fibrosis fatty infiltration (steatosis), bile duct proliferation, adrenal enlargement with fatty infiltration (Hagan et al., 1965, as referenced in EC, 2002). From this study, a NOAEL could not be derived.

Considering the structural similarity and the similar mode of action of *p*-allylalkoxybenzenes, the FEEDAP Panel retains the NOAEL of 10 mg/kg bw per day derived from the mice study with methyleugenol, as reference point for the assessment group of *p*-allylalkoxybenzenes for non-neoplastic endpoints.

Styrene

In a 2-year oral toxicity study, Charles River COBS CD (SD) rats received 0, 125 or 250 mg of styrene/L drinking water. At 250 mg/L, females showed significantly lower terminal body weight than control females. No other treatment-related effects were seen. The parameters studied were clinical

signs, mortality, growth, food and water intake, haematology, clinical chemistry, urinalysis, gross necropsy and histopathology. The NOAEL in this study was 125 mg/L (corresponding to 7.7 mg/kg bw for males and 12 mg/kg of bw for females) (Litton Bionetics, 1980,[27] as referenced in WHO, 2003).

3.2.3. 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 (EFSA SC, 2019a).

As the additive under assessment is a fully defined mixture (> 99% 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. Substances for which a concern for genotoxicity has been identified (safrole, methyleugenol and styrene) are assessed separately.

Components other than safrole, methyleugenol and styrene

Based on considerations related to structural and metabolic similarities, the components were allocated to 12 assessment groups, corresponding to the chemical groups (CGs) 2, 6, 8, 13, 15, 16, 18, 21, 22, 23, 31 and 32, as defined in Annex I of Regulation (EC) No 1565/2000. For chemical group 31 ('aliphatic and aromatic hydrocarbons'), the application of sub-assessment groups as defined in Flavouring Group Evaluation 25 (FGE.25) and FGE.78 is applied (EFSA CEF Panel, 2015a,b). The allocation of the components to the (sub-)assessment groups is shown in Table 4 and in the corresponding footnote.

For each component in the assessment group, exposure in target animals was estimated considering the use levels in feed, the percentage of the component in the oil and the default values for feed intake according to the guidance on the safety of feed additives for target species (EFSA FEEDAP Panel, 2017c). 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 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 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 members of a (sub-)assessment group, a (sub-)assessment group NOAEL was derived.

Toxicological data for subchronic studies, from which NOAEL values could be derived, were available for linalool [02.013] and terpineol [02.230][28] and in CG 6 (EFSA FEEDAP Panel, 2012a), 1,8-cineole in CG 16 (EFSA FEEDAP Panel, 2012d, 2021a), eugenol [04.003] in CG 18 (EFSA FEEDAP Panel, 2011), cinnamaldehyde [05.014] in CG 22 (EFSA FEEDAP Panel, 2017a), 4-methoxybenzaldehyde [05.015] in CG 23 (EFSA FEEDAP Panel, 2012e), thymol [04.006] in CG 25 (EFSA FEEDAP Panel, 2012f), myrcene [01.008], d-limonene [01.045], 1-isopropyl-4-benzene [01.002] and β-caryophyllene [01.007] in CG 31 (EFSA FEEDAP Panel, 2015, 2016c), and β-caryophyllene oxide in CG 32 (EFSA CEF Panel, 2014). For benzaldehyde [05.013] in CG 23, the FEEDAP Panel concluded that the maximum proposed concentration of 25 mg/kg complete feed is safe, based on its structural and metabolic relationship with benzoic acid, which was considered safe up to 125 mg/kg complete

[27] WHO (World Health Organization), 2003, ref 19: Litton Bionetics. Toxicological study on styrene incorporated in drinking water of rats for 2 years in conjunction with a three-generation reproduction study. Styrene. Revised final report, weeks 1–105. Vol. I. Washington, DC, Chemical Manufacturers Association, 1980.

[28] 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).

feed (EFSA FEEDAP Panel, 2012e). In addition, for benzyl alcohol the FAF Panel established an acceptable daily intake (ADI) of 4 mg/kg bw per day based on a NOAEL of 400 mg/kg bw per day from a carcinogenicity study in rats (EFSA FAF Panel, 2019). For benzyl benzoate [09.727], the applicant provided a recent review which indicated a NOAEL of 194 mg/kg bw per day for developmental and reproductive toxicity (Api et al., 2020).

For the subgroup of terpinyl derivatives in CG 6, i.e. α-terpineol [02.072] and 4-terpinenol [02.072], 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, read-across was applied using the NOAEL of 300 mg/kg bw per day for eugenol [04.003] to extrapolate to eugenyl acetate [09.020] and other components[29] in CG 18 (EFSA FEEDAP Panel, 2011) and the NOAEL of 275 mg/kg bw per day for cinnamaldehyde [05.014] to extrapolate to cinnamyl acetate [09.018] and other cinnamyl and phenylpropyl derivatives in CG 22 (EFSA FEEDAP Panel, 2017). The NOAEL of 400 mg/kg bw per day for benzyl alcohol [02.010] was applied to all benzoates and benzyl esters[30] in CG 23 (EFSA FEEDAP Panel, 2012e).

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 groups II, III and V, respectively (EFSA CEF Panel, 2015a, 2015b).

For the remaining compounds,[31] toxicity studies performed with the compounds under assessment and NOAEL values derived from toxicity studies were not available and read-across was not possible. Therefore, the threshold of toxicological concern (TTC) approach was applied (EFSA FEEDAP Panel, 2012g; 2017c). All these compounds belong to Cramer class I except camphor and linalool oxide (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).

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 compounds resulting individually in an MOE > 50,000 were not further considered in the assessment group as their contribution to the MOE(T) is negligible.[32]

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

[29] 4-Allyl-2,6-dimethoxyphenol [04.051] and allylphenol [04.058] present in cinnamon leaf oil.

[30] Benzoates (methyl benzoate [09.725] and ethyl benzoate [09.726]) and benzyl esters (benzyl acetate [09.014] and benzyl isovalerate [09.458]) present in cinnamon leaf oil.

[31] 2-Methylbutyl 2-methylbutyrate [09.516], 2-(4-methylphenyl)propan-2-ol, [02.042], borneol [02.016], camphor, linalool oxide [13.140] 2-phenylethan-1-ol [02.019], phenethyl acetate [09.031], β-elemene, 1-isopropenyl-4-methylbenzene [01.010], β-calacorene, α-calacorene and 3,7,10-humulatriene [01.043].

[32] Compounds included in the assessment groups but not reported in the table: 4-terpinenol, α-terpineol and 2-(4-methylphenyl) propan-2-ol (CG 6); phenethyl acetate (CG 15); eugenyl acetate and trans-anethole (CG 18); acetophenone (CG 21); (Z)-cinnamaldehyde, 3-phenylpropyl acetate, 3-phenylporpyl-1-ol, 3-phenylpropanal, (E)-2-methoxycinnamaldehyde and cinnamyl alcohol (CG 22); benzaldehyde (CG 23); thymol (CG 25); myrcene, trans-3,7-dimethyl-1,3,6-octatriene and cis-3,7-dimethyl-1,3,6-octatriene (CG 31, II); β-phellandrene, limonene, α-terpinene, terpinolene and γ-terpinene (CG 31, III); α-copaene, camphene, β-pinene, α-thujene, δ-3-carene, isocaryophyllene, δ-cadinene, α-cubebene, sabinene, α-muurolene, γ-cadinene and γ-muurolene (CG 31, V); bicyclogermacrene (CG 31, VI); α-thujone and β-thujone.

Table 4: Compositional data, intake values (calculated for chickens for fattening at 5 mg/kg complete feed), reference points and margin of exposure (MOE) for the individual components of cinnamon bark 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 2								
2-Methylbutyl 2-methylbutyrate	09.516	0.05	0.002	0.0002	I	*3*	14,529	
CG 6								
Linalool	02.013	6.08	0.304	0.0273	(I)	**117**	4,287	
CG 8								
Borneol	02.016	0.03	0.001	0.0001	I	*3*	24,754	
Camphor	–	0.02	0.001	0.0001	II	*0.91*	11,263	
MOET CG 8								7,741
CG 13								
Linalool oxide	13.140	0.01	0.001	0.0001	II	*0.91*	14,481	
CG 15								
2-Phenylethan-1-ol	02.019	0.03	0.002	0.0001	I	*3*	22,278	
CG 16								
1,8-Cineole	03.001	1.17	0.059	0.0053	(II)	**100**	19,096	
CG 18								
Eugenol	04.003	7.22	0.361	0.0324	(I)	**300**	9,257	
CG 22								
(*E*)-Cinnamaldehyde	(05.014)	70.7	3.535	0.3173	(I)	**275**	867	
Cinnamyl acetate	09.018	6.64	0.332	0.0298	(I)	275	9,227	
MOET CG 22								792
CG 23								
Benzyl benzoate	09.727	1.39	0.070	0.0062	(I)	**194**	31,094	
4-Methoxybenzaldehyde	05.015	0.15	0.008	0.0007	(I)	**10**[d]	14,852	
								10,051
CG 31, III (Cyclohexene hydrocarbons)								
α-Phellandrene	01.006	1.53	0.077	0.0077	(I)	250	36,403	
β-Elemene	–	0.02	0.001	0.0001	I	*3*	37,131	
MOET CG 31, III								18,382
CG 31, IVe (Benzene hydrocarbons, alkyl)								
p-Cymene	01.002	1.58	0.079	0.0071	(I)	**154**	21,714	
1-Isopropenyl-4-methylbenzene	01.010	0.03	0.001	0.0001	I	*3*	23,870	
β-Calacorene	–	0.02	0.001	0.0001	I	*3*	33,418	
α-Calacorene	–	0.02	0.001	0.001	I	*3*	39,315	
MOET CG 31, IVe								6,978
CG 31, V (Bi-, tricyclic, non-aromatic hydrocarbons)								
β-Caryophyllene	01.007	7.01	0.351	0.0315	(I)	**222**	7,055	
α-Pinene	01.004	1.52	0.076	0.0068	(I)	222	32,538	
CG 31, V								5,798
CG 31, VI (macrocyclic non aromatic hydrocarbons)								
3,7,10-Humulatriene	01.043	0.45	0.023	0.0020	I	*3*	1,485	

(a): Intake calculations for the individual components are based on the use level of 5 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 20 mg/kg bw per day was halved to take into account of the short duration of the study (EFSA FEEDAP Panel, 2012e).

As shown in Table 4, for all the assessment groups, the MOET was ≥ 792 (CG 22, cinnamyl derivatives). Therefore, no safety concern was identified for the cinnamon bark oil (without considering the presence of safrole, methyleugenol and styrene) when used as a feed additive for chickens for fattening at the proposed use level (5 mg/kg). From the lowest MOET of 792 (for CG 22, cinnamyl derivatives) in chickens for fattening, the MOET was calculated for the other target species considering the respective daily feed intake/kg bw and conditions of use. The results are summarised in Table 5.

Table 5: Combined margin of exposure (MOET) for the assessment group CG 22 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)	Lowest MOET
Chicken for fattening	2	158	5	792
Laying hen	2	106	5	1,181
Turkey for fattening	3	176	5	1,060
Piglet	20	880	50	1,422
Pig for fattening	60	2,200	25	1,691
Sow lactating	175	5,280	50	2,086
Veal calf (milk replacer)	100	1,890	10	3,293
Cattle for fattening	400	8,000	10	3,128
Dairy cows	650	20,000	10	2,018
Sheep/goat	60	1,200	10	3,128
Horse	400	8,000	10	3,128
Rabbit	2	100	5	1,251
Salmon	0.12	2.1	5	3,476
Dog	15	250	5	3,680
Cat	3	60	5	3,128
Ornamental fish	0.012	0.054	5	12,514

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 5 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 cinnamon bark 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 safrole, methyleugenol and styrene) was identified for cinnamon bark 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 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 (EFSA FEEDAP Panel, 2010).

Safrole and methyleugenol

Low concentrations of safrole (0.12–0.34%) were detected in all batches of the additive under assessment. The use of cinnamon bark oil at the proposed use levels (5–50 mg/kg complete feed), would result in concentrations ranging from 17 to 170 μg safrole/kg complete feed. The concentration

of methyleugenol detected in one batch of the additive under assessment was 100-fold lower (0.004%), resulting in concentrations in feed ranging from 0.2 to 2 μg methyleugenol/kg complete feed.

Methyleugenol and safrole share the same structural features, the same metabolic pathways, particularly the formation of the reactive 1′-sulfoxymetabolite (see Section 3.3.1) and the same mode of action. They are allocated to the same assessment group (*p*-allylalkoxybenzenes) and an assessment of the combined exposure is performed as described 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). 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 (EFSA FEEDAP Panel, 2021b), different reference points and a different magnitude of the MOET for long-living animals and for 'short-living' animals are used. 'Short-living' animals are defined as those animals raised for fattening whose lifespan under farming conditions makes it very unlikely that they develop cancer as a result of the exposure to genotoxic and/or carcinogenic substances in the diet.

For long-living animals and reproductive animals, including those animals reared for laying/breeding/reproduction, a MOE(T) > 10,000 when comparing estimated exposure to genotoxic and/or carcinogenic substances with a $BMDL_{10}$ from a rodent carcinogenicity study is considered indicative of low concern. 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 applied to the sum of safrole and methyleugenol. The assessment of the combined exposure to safrole and methyleugenol for long-living animals is reported in Table 6.

Table 6: Combined exposure and combined margin of exposure (MOET) for the assessment group *p*-allylalkoxybenzenes calculated at the maximum proposed use level of the additive in feed for long-living animals based on $BMDL_{10}$ of 22.2 mg/kg bw per day derived from rodent carcinogenicity studies with methyleugenol

Animal category	Daily feed intake	Body weight	Use level in feed	Methyeugenol+ safrole intake	MOET
	kg DM/day	kg	mg/kg feed	μg/kg bw per day	
Laying hen	0.106	2	5	1.036	21,430
Sow lactating	5.28	175	50	5.897	3,786
Dairy cow	20	650	10	1.203	18,319
Pet horse	8	400	10	0.782	28,395
Dog	0.25	15	5	0.326	66,811
Cat	0.06	3	5	0.391	56,789
Ornamental fish	0.00054	0.012	5	0.088	227,157

bw: body weight; DM: dry matter.

When the estimated exposures for long-living animals to methyleugenol and safrole are compared to the $BMDL_{10}$ of 22.2 mg methyleugenol/kg bw per day (Suparmi et al., 2019), a MOET > 10,000 is calculated for all species except sows (Table 6).

For 'short-living' animals genotoxicity and carcinogenicity endpoints are not considered relevant, therefore a lower magnitude of the MOE(T) (> 100) when comparing estimated exposure with a reference point based on non-neoplastic endpoints is considered adequate (EFSA FEEDAP Panel, 2021).

The FEEDAP Panel identified a NOAEL of 10 mg/kg bw per day for non-neoplastic lesions (effect on liver and the glandular stomach) from a 90-day study in mice with methyleugenol which is applied to the sum of safrole and methyleugenol (NTP, 2000). In the current assessment, this reference point is applied to the sum of safrole and methyleugenol.

The assessment of the combined exposure to safrole and methyleugenol for 'short-living' animals is reported in Table 7.

Table 7: Combined exposure and combined margin of exposure (MOET) for the assessment group *p*-allylalkoxybenzenes calculated at the maximum proposed use level of the additive in feed for 'short-living' animals based on a NOAEL of 10 mg/kg bw per day derived from a 90-day study in mice with methyleugenol

Animal category	Daily feed intake	Body weight	Use level in feed	Methyeugenol+safrole intake	MOET
	kg DM/day	kg	mg/kg feed	µg/kg bw per day	
Chicken for fattening	0.158	2	5	1.544	6,476
Turkey for fattening	0.176	3	5	1.147	8,671
Piglet	0.88	20	50	8.600	1,163
Pig for fattening	2.2	60	25	3.583	2,765
Veal calf (milk replacer)	1.89	100	10	0.688	13,463
Cattle for fattening	8	400	10	0.782	12,790
Sheep/goat	1.2	60	10	0.782	12,790
Rabbit	0.1	2	5	0.977	10,232
Salmon	0.0021	0.12	5	0.342	28,422

bw: body weight; DM: dry matter.

For 'short-living' animals (Table 7), the magnitude of the MOET is >100 when comparing the exposures to methyleugenol and safrole to the reference point for methyleugenol based on non-neoplastic endpoints. This is considered adequate.

Styrene

Low concentrations of styrene (0.016–0.024%) were detected in all batches of the additive under assessment. The use of cinnamon bark oil at the proposed use levels (5–50 mg/kg complete feed), would result in concentrations ranging from 1.2 to 12 µg styrene/kg complete feed.

The average and the highest intake of styrene for the different target species is reported in Table 8, considering the analysed values of styrene reported in Section 3.2.1.

Table 8: Target animal intake of styrene (as µg/kg bw per day) at the maximum proposed use level of the additive in feed for each species. The values of styrene in feed are calculated considering the average and the highest analysed values in the additive

Animal category	Daily feed intake	Body weight	Use level in feed	Average styrene intake	Highest Styrene intake
	kg DM/day	kg	mg/kg feed	µg/kg bw per day	
Chicken for fattening	0.158	2	5	0.090	0.108
Laying hen	0.106	2	5	0.060	0.072
Turkey for fattening	0.176	3	5	0.067	0.080
Piglet	0.88	20	50	0.500	0.600
Pig for fattening	2.2	60	25	0.208	0.250
Sow lactating	5.28	175	50	0.343	0.411
Veal calf (milk replacer)	1.89	100	10	0.043	0.048
Cattle for fattening	8	400	10	0.045	0.055
Dairy cow	20	650	10	0.070	0.084
Sheep/goat	1.2	60	10	0.045	0.055
Horse	8	400	10	0.045	0.055
Rabbit	0.1	2	5	0.057	0.068
Salmon	0.0021	0.12	5	0.020	0.024
Dog	0.25	15	5	0.019	0.023
Cat	0.06	3	5	0.023	0.027

Animal category	Daily feed intake	Body weight	Use level in feed	Average styrene intake	Highest Styrene intake
	kg DM/day	kg	mg/kg feed	µg/kg bw per day	
Ornamental fish	0.00054	0.012	5	0.005	0.006

bw: body weight; DM: dry matter.

The use of cinnamon bark oil at the proposed use level in feed would result in an average intake of styrene ranging from 0.005 µg/kg bw per day in ornamental fish and 0.5 µg/kg bw per day in piglets (highest intake 0.6 µg/kg bw per day in piglets).

Styrene is a ubiquitous air pollutant and is present in many foods as such or as a biodegradation/fermentation product. EFSA estimated dietary exposure of the consumers to styrene migrating from styrene-based plastics in the order of 0.1 µg/kg bw per day, in the same range as exposure from styrene present in foods as such, with an exposure from food of 0.12–0.38 µg/kg bw per day. The EFSA CEP Panel estimated that the daily exposure to styrene by inhalation is in the range of 0.1–0.6 µg/kg bw for adults (EFSA CEP Panel, 2020).

The FEEDAP Panel notes that cinnamic acid is widely present in feed of plant origin. It is likely that the processing of feed containing cinnamic acid or flavoured with cinnamaldehyde or cinnamic acid would produce styrene, particularly when feed is pelleted at high temperatures. Although it would be reasonable to assume that animal feed or the air inhaled by animals are also contaminated by styrene from other sources, comparable styrene intake figures are not available for target animals, which would allow a quantitative risk assessment to be performed. Therefore, the FEEDAP Panel could not evaluate whether the exposure of target animals to styrene is likely to be increased by the use of cinnamon leaf oil as feed additive compared to the intake from other dietary sources (as described in EFSA FEEDAP Panel, 2021).

Considering that a concern for genotoxicity associated with oral exposure to styrene remains and pending the outcome of the overall safety assessment of styrene by oral route, the FEEDAP Panel is not in the position to conclude on the safety of cinnamon bark oil as feed additive for long-living animals and for animals for reproduction.

The FEEDAP Panel noted that genotoxicity and carcinogenicity are relevant endpoints for long-living animals, whereas in the case of 'short-living' animals other non-neoplastic endpoints are considered more appropriate for the risk assessment (EFSA FEEDAP Panel, 2021). When the estimated exposure of 'short-living' animals is compared to the NOAEL of 7.7 mg styrene/kg bw per day (see Section 3.2.2.3), a MOE ranging from 71,477 in chickens for fattening and 322,667 in salmonids is calculated. Therefore, the FEEDAP Panel concludes that the use of the cinnamon bark oil at the proposed use levels in feed is not expected to be of concern for 'short-living' animals.

3.2.3.1. Conclusions on safety for the target species

Owing to the presence of styrene in cinnamon bark oil, the FEEDAP Panel is not in the position to conclude on the safety of the additive for long-living animals and reproductive animals including those animals reared for laying/breeding/reproduction. Concerning the exposure of these species to safrole and methyleugenol, a margin of exposure >10,000, which is indicative of low concern, is calculated for all animals except sows.

For 'short-living' animals, the FEEDAP Panel considers cinnamon bark oil as safe up to the maximum proposed use levels in complete feed of 5 mg/kg for poultry species for fattening, 25 mg/kg for pigs for fattening, 50 mg/kg for piglets and other minor *Suidae*, 10 mg/kg for ruminants for fattening and horses for meat production, 5 mg/kg for rabbits, salmonids and other fin fish, and other minor species.

For 'short-living' animals, the Panel considers 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.

3.2.4. Safety for the consumer

Cinnamon bark oil is added to a wide range of food categories for flavouring purposes. Although individual consumption figures are not available, the Fenaroli's handbook of flavour ingredients (Burdock, 2009) cites values of 3.0 mg/kg bw per day for cinnamon and of 0.014 mg/kg bw per day for cinnamon bark oil (FEMA 2291). Fenaroli also reports use levels in food and beverages in the range of 7.7 mg/kg up to 490 mg/kg for cinnamon bark oil.

Many 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 cinnamon bark oil are expected to be extensively metabolised and excreted in the target species. Also for safrole, methyleugenol and styrene, the available data indicate that they are absorbed, metabolised and rapidly excreted and are not expected to accumulate in animal tissues and products. Consequently, residues in food products are unlikely (see Section 3.2.2.1).

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

3.2.5. 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 cinnamon bark oil,[33] where hazards for users have been identified.

The applicant made a literature search aimed at retrieving studies related to the safety of preparations obtained from *C. verum* for the users.[34] None of the studies identified during the literature search provided data on endpoints relevant to user safety. Studies where animals were exposed dermally to cinnamon leaf oil for various reasons (e.g. Fichi et al., 2007; Ghosh et al., 2013) were conducted at concentrations well below those needed to assess any irritant potential. Therefore, no conclusion can be reached on the irritant potential of cinnamon bark oil for the skin or the eye.

Data are present in the literature which support the allergenic potential of cinnamon and its products. Isaac-Renton et al. (2015) described several cases of patients with intraoral allergic contact dermatitis caused by cinnamaldehyde contained in breath fresheners or in toothpaste, or by cinnamon powder in apple snacks. Leifer (1951) reviewed literature on contact dermatitis caused by 'cinnamon oil'. A positive reaction to patch tests with cinnamon and cinnamon sugar in a baker with dermatitis of the hands is reported. Cases of stomatitis, dermatitis and cheilitis due to 'cinnamon oil' are also described.

The FEEDAP Panel concludes that cinnamon bark oil is irritant to skin and eyes and a skin sensitiser. The possibility that cinnamon bark oil may also be a respiratory sensitiser cannot be excluded.

Based on the presence of safrole[35] in cinnamon bark oil in a typical concentration $\geq$ 0.1%, cinnamon bark oil is classified as carcinogenic (category 1B) in accordance with the classification criteria in Annex I of the CLP Regulation (1,272/2008/EC),[36] and handled accordingly.[37]

3.2.6. Safety for the environment

C. verum J. Presl is not native to Europe. Therefore, the safety for the environment is assessed based on the individual components of the essential oil.

The major components (cinnamaldehyde, cinnamyl acetate, eugenol and linalool) and additional 27 components accounting for > 0.1% of the composition of the additive (α-terpineol, benzyl benzoate,

[33] Technical dossier/ Supplementary Information October 2020/Annex_IX_cinnamon_bark_oil_MSDS. Aspiration hazard (H304, category 1), Hazards for skin corrosion/irritation (H315), skin sensitisation (H317, category 1A), serious eye irritation (H319), may cause cancer (H350).

[34] Technical dossier/Supplementary information October 2020/Literature_search_cinnamon_oil.

[35] Safrole is considered to be a carcinogen category 2B (the agent is possibly carcinogenic to humans; the exposure circumstance entails exposures that are possibly carcinogenic to humans) by the International Agency for the Research on Cancer (IARC) from the World Health Organization (WHO) (IARC Monograph Volume 10). Under the European Dangerous Substance Directive, safrole is considered to be a carcinogen category 2 (substance which should be regarded as if they are carcinogenic to humans). According to Regulation 1272/2008/EC (CLP), safrole is considered to be a carcinogen category 1B (may cause cancer).

[36] Regulation (EC) No 1271/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1,355.

[37] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC). OJ L 158, 30.4.2004, p. 50.

4-methoxybenzaldehyde, benzaldehyde, 1,8-cineole, myrcene, α-phellandrene, β-phellandrene, limonene, α-terpinene, terpinolene, *p*-cymene, β-caryophyllene, α-pinene, camphene, β-pinene) accounting together for 95% of the composition of the oil have been evaluated by EFSA as sensory additives for animal feed (see Table 1, Section 1.2), 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 identified constituents of the essential oil are mainly aliphatic mono or sesquiterpenes partially with functional groups; they are chemically related to the substances evaluated by EFSA as CG 31 for use in animal feed (EFSA FEEDAP Panel, 2015, 2016) for which EFSA concluded that they were extensively metabolised by the target species (see Section 3.2.2.1) 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 CG 31 substances.

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

3.3. Cinnamon leaf oil

3.3.1. Characterisation of cinnamon leaf oil

The essential oil obtained from leaves is a brownish grey, clear mobile liquid with a characteristic aroma. In five batches of the additive (from two different producers, all originating from Sri Lanka), the density (20°C) ranged between 1,044 and 1,048 kg/m^3 (specification: 1,030–1,060 kg/m^3), the refractive index (20°C) between 1.533 and 1.534 (specification: 1.5240–1.5360) and the specific optical rotation (at 20°C, three batches) between 0° and 1°.[16] *C. zeylanicum* leaf oil is identified with the single CAS number 8015-91-6, the EINECS number 283–479-0, the FEMA number 2292, and Council of Europe (CoE) number 133.

For cinnamon leaf oil, the product specifications used by the applicant are based on those developed by the International Organization for Standardization (ISO) 3,524:2003 and on the European Pharmacopoeia for cinnamon leaf oil (01/2008:1608),[18] adapted to reflect the concentrations of the main components of the essential oil. Four components contribute to the specification as shown in Table 9, with (*E*)-cinnamaldehyde selected as the phytochemical marker. Analysis of three batches of the additive showed compliance with these specifications when analysed by GC-FID and expressed as % GC area.[38] When five batches of the additive were analysed by GC–MS, the four compounds accounted for 86.1% on average (range 83.8–88.5%) of the product, expressed as area % of the GC profile (Table 9).

Table 9: Constituents of the essential oil from the leaves of *Cinnamomum verum* J. Presl as defined based on ISO standard (3,214:2000): specifications and batch to batch variation based on the analysis of five 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[(a)]	Range
Eugenol	97–53-0	04.003	70–85	79.0	76.1–82.6
Eugenyl acetate	93–28-7	09.020	1.3–5.0	2.71	1.55–4.68
Benzyl benzoate	120–51-4	09.727	2.0–4.5	3.54	3.15–4.08
(*E*)-Cinnamaldehyde	14,371–10-9	05.014[(b)]	≤ 3[(c)]	0.86	0.59–1.13
Total				86.1	83.8–88.5

CAS no: Chemical Abstracts Service number; FLAVIS number: EU Flavour Information System numbers.
(a): Mean calculated on five batches.
(b): EFSA evaluated cinnamaldehyde [05.014] (EFSA FEEDAP Panel, 2016c). The configuration of the double bond in cinnamaldehyde [05.014] has not been specified. However, the substance is anticipated to contain more than 97% (*E*)-cinnamaldehyde (EFSA, 2009b).
(c): Specification given for cinnamaldehyde.

[38] Technical dossier/Supplementary information October 2020/ SIn reply_BDG06_cinnamon oil/GC-FID analysis: eugenol (76–77%), eugenyl acetate (3.75%), benzyl benzoate (3.0–3.4%) and (*E*)-cinnamaldehyde (1.0–1.2%).

The applicant provided the full characterisation of the five batches obtained by GC–MS.[16] In total, up to 79 peaks were detected in the chromatogram, 77 of which were identified and accounted on average for 99.8% (99.5–100%) of the product (as % GC area). Besides the four compounds indicated in the product specifications, 27 other compounds were detected at individual levels > 0.05% and are listed in Table 10. These 31 compounds together account on average for 99.3% (98.6–99.8%) of the product. The remaining 52 compounds (ranging between 0.05% and 0.003%) and accounting for 0.57% (0.17–0.95%) are listed in the footnote.[39] Based on the available data on the characterisation, cinnamon leaf oil is considered a fully defined mixture.

Table 10: Other constituents of the essential oil from the leaves of *Cinnamomum verum* J. Presl accounting for > 0.05% of the composition (based on the analysis of five batches) not included in the specification. 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	% GC area	
			Mean[(a)]	Range
β-Caryophyllene	87–44-5	01.007	3.28	3.08–3.54
Linalool	78–70-6	02.013	1.66	1.33–2.33
Cinnamyl acetate	103–54-8	09.018	1.41	1.05–1.65
Safrole	94–59-7	–	0.92	0.81–1.09
α-Phellandrene	99–83-2	01.006	0.87	0.64–1.07
α-Pinene (pin-2(3)-ene)	80–56-8	01.004	0.75	0.61–0.87
p-Cymene (1-isopropyl-4-methylbenzene)	99–87-6	01.002	0.68	0.57–0.82
α-Copaene	3,856-25-5	–	0.64	0.47–0.62
3,7,10-Humulatriene	6,753-98-6	01.043	0.55	0.23–0.50
β-Caryophyllene epoxide	1,139-30-6	16.043	0.40	0.18–0.35
Limonene	138–86-3	01.001	0.26	0.21–0.31
β-Phellandrene	555–10-2	01.055	0.26	0.18–0.28
Camphene	79–92-5	01.009	0.23	0.16–0.25
β-Pinene (pin-2(10)-ene)	127–91-3	01.003	0.20	0.13–0.28
α-Terpineol	98–55-5	02.014	0.20	0.05–0.22
3-Phenylpropyl acetate	122–72-5	09.032	0.13	0.07–0.22
Benzaldehyde	100–52-7	05.013	0.10	0.07–0.13
α-Thujene	2,867-05-2	–	0.09	0.07–0.12
1,8-Cineole	470–82-6	03.001	0.09	0.07–0.13
Cinnamyl alcohol	104–54-1	02.017	0.08	0.07–0.09
α-Terpinene	99–86-5	01.019	0.08	0.06–0.10
Terpinolene	586–62-9	01.005	0.08	0.07–0.13
Bicyclogermacrene	67,650–90-2	–	0.07	0.04–0.13
delta-Cadinene	29,350–73-0	01.021	0.07	0.03–0.17
Myrcene	123–35-3	01.008	0.06	0.05–0.09
1-Isopropenyl-4-methylbenzene	1,195-32-0	01.010	0.05	0.04–0.09
δ-3-Carene	13,466–78-9	01.029	0.05	0.07–0.13
Total			13.14	11.10–14.84

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

[39] Additional constituents: constituents (n = 24) between <0.05 and ≥ 0.01%: aromadendrene, viridiflorene, 4-terpinenol, 4-allylphenol, 3-phenylpropan-1-ol, spathulenol, 3-phenylpropanal, 2-methylbutyl 2-methylbutyrate, humulene oxide II, methyleugenol, (*Z*)-cinnamaldehyde, benzyl alcohol, benzyl acetate, benzyl isovalerate, borneol, thymol, γ-cadinene, β-elemene, *trans*-3,7-dimethyl-1,3,6-octatriene, 2-(4-methylphenyl)propan-2-ol, phenethyl acetate; constituents (n = 28) <0.01 and >0.002%: α-muurolene, 4-allyl-2,6-dimethoxyphenol, γ-muurolene, *cis*-3,7-dimethyl-1,3,6-octatriene, γ-terpinene, linalool oxide, α-cubebene, germacra-1(10),4(14),5-triene, (*E*)-3,7-dimethylocta-1,5,7-trien-3-ol, phenethyl isovalerate, carvacrol, m-cymene, 1-isopropenyl-4-methylbenzene, alloaromadendrene, styrene, δ-cadinol, T-cadinol, camphor, β-cadinene, acetophenone, methyl benzoate, carvotan acetone, ethyl benzoate, α-cadinene, 4(10)-thujene, butyl 2-methylbutyrate, α-gurjunene and methyl salicylate.

The applicant undertook analyses to establish whether the substances of concern identified by the literature search[21] (see Section 3.2.1) were present. Besides safrole (0.81–1.09%, see Table 10), cinnamon leaf oil also contains methyleugenol (on average: 0.028%, range: 0.025–0.030%). Camphor was detected in two batches (on average: 0.006%, range: 0.005–0.007%), whereas coumarin was not detected (LOD, 0.01%). Styrene was detected in four batches (on average: 0.009%, range: 0–0.013%) of cinnamon leaf oil.

3.3.1.1. Impurities

The applicant makes reference to the 'periodic testing' of some representative flavourings premixtures for mercury, cadmium and lead, arsenic, fluoride, dioxins and polychlorinated biphenyls (PCBs), organochloride pesticides, organophosphorous pesticides, aflatoxins B1, B2, G1, G2 and ochratoxin A. However, no data were provided on the presence of these impurities. Since cinnamon leaf oil is produced by steam distillation, the likelihood of any measurable carry-over of all the above-mentioned elements is low except for mercury.

3.3.1.2. 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).[23] However, no data supporting this statement were provided.

3.3.1.3. Conditions of use

Cinnamon leaf oil is intended to be added to feed for all animal species without withdrawal. The maximum proposed use level in complete feed for the different target species is 25 mg/kg complete feed for salmonids and ornamental fish, cats and dogs, 40 mg/kg for chickens for fattening and 50 mg/kg for the other species/categories. The proposed use level in water for drinking is 3 mg/L using propylene glycol as emulsifier.

3.3.2. Safety

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

Many of the major volatile components, accounting for about 97% of the GC area, have been previously assessed and considered safe for use as flavourings, and are currently authorised for food[8] and feed[6] uses. The list of the compounds already evaluated by the EFSA Panels is given in Table 1 (see Section 1.2).

Additional considerations on the volatile components not assessed by EFSA have been addressed in Section 3.2.2.

In addition to the compounds already considered in cinnamon bark oil, 11 components not previously assessed for use as flavourings were identified in cinnamon leaf oil. Seven compounds, accounting for < 0.1% of the GC area (bicyclogermcrene, aromadendrene, viridofleorene, alloroaromadendrene β-cadinene, α-cadinene and α-gurjunene) are mono- or sesqui-terpene derivatives structurally related to flavourings already assessed in CG 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, 2015, 2016c). Four additional compounds belonging to CG 6 (spathulenol, δ-cadinol and T-cadinol) and to CG 08 (carvotan acetone) were screened with the Organisation for Economic Co-operation and Development (OECD) QSAR Toolbox. For spathulenol, δ-cadinol and T-cadinol, no alert was identified for *in vitro* mutagenicity, for genotoxic and non-genotoxic carcinogenicity and for any other toxicity endpoint.[40] Structural alerts for carvotan acetone were due to the presence of α,β-unsaturated vinyl/allyl ketones. For this compound, 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 alert raised for carvotan acetone were discounted.

The ADME and the considerations relevant to safrole, methyeugenol and styrene have been already addressed in Sections 3.2.2.1 and 3.2.2.2.

[40] Technical dossier/Supplementary information October 2020/Annex VI_SIn_reply_cinnamon_oil_QSAR. Structural alerts for α-curcumene were due to the presence of arenes. α-Curcumene.

3.3.3. Safety for the target species

Tolerance studies and/or toxicological studies made with the essential oil under application were not submitted.

As the additive under assessment is a fully defined mixture (> 99% of the components were identified, see Section 3.3.1), the FEEDAP Panel applied a component-based approach to assess the safety for target species of the essential oil. Substances for which a concern for genotoxicity has been identified (safrole, methyleugenol and styrene) are assessed separately.

Components other than safrole, methyleugenol and styrene

The approach followed, i.e. the allocation of the components to the (sub-)assessment groups, the estimate of exposure for the target species, the identification of a reference point for each constituent (hazard characterisation) and the calculation of the MOET for each assessment group (risk characterisation), is described in Section 3.2.3.

For those compounds[41] for which NOAEL values derived from toxicity studies were not available and read-across was not possible, the TTC approach was applied (EFSA FEEDAP Panel, 2012g; EFSA FEEDAP Panel, 2017c).

The compounds resulting individually in an MOE > 50,000 were not further considered in the assessment group as their contribution to the MOE(T) is negligible.[42]

The approach to the safety assessment of cinnamon leaf oil expressed for the target species is summarised in Table 11. The calculations were done for chickens for fattening, the species with the highest ratio of feed intake/body weight at the use level of 40 mg/kg complete feed.

Table 11: Compositional data, intake values (calculated for chickens for fattening at 40 mg/kg complete feed), reference points and margin of exposure (MOE) for the individual components of cinnamon leaf 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 1								
Butyl 2-methylbutyrate	09.519	0.003	0.001	0.0001	I	*3*	27,848	
CG 2								
2-Methybutyl 2-methylbutyrate	09.516	0.05	0.020	0.0018	I	*3*	1,705	
CG 6								
Linalool	02.013	2.33	0.932	0.0837	(I)	**117**	1,398	
α-Terpineol	02.014	0.28	0.113	0.01010	(I)	250	24,688	
2-(4-Methylphenyl) propan-2-ol	02.042	0.02	0.008	0.0007	I	*3*	4,177	
Spathulenol	–	0.05	0.021	0.0019	I	*3*	16,07	
δ-Cadinol	–	0.01	0.003	0.0003	III	*0.15*	597	

[41] Butyl 2-methylbutyrate [09.519], 2-methylbutyl 2-methylbutyrate [09.516], 2-(4-methylphenyl)propan-2-ol [02.042], spathulenol, δ-cadinol, T-cadinol, borneol [02.016], camphor, carvotan acetone, linalool oxide [13.140], 2-phenylethan-1-ol [02.019], phenethyl acetate [09.031], 4-allylphenol [04.058], β-elemene, 1-isopropenyl-4-methylbenzene [01.010], 3,7,10-humulatriene [01.043] and germacra-1(10),4(14),5-triene [01.042].

[42] Compounds included in the assessment groups but not reported in the table: 4-terpineol and (*E*)-3,7-dimethylocta-1,5,7-trien-3-ol (CG 6); allylphenol and 4-allyl-2,6-dimethoxyphenol (CG 18); acetophenone (CG 21); (*Z*)-cinnamaldehyde, 3-phenylpropyl-1-ol, 3-phenylpropanal and cinnamyl alcohol (CG 22); benzaldehyde, benzyl acetate, benzyl alcohol, benzyl isovalerate, methyl benzoate, ethyl benzoate and methyl salicylate (CG 23); carvacrol (CG 25); *cis*-3,7-dimethyl-1,3,6-octatriene (CG 31, II); α-terpinene, terpinolene and γ-terpinene (CG 31, III); *m*-cymene (CG IVe); α-thujene, δ-3-carene, δ-cadinene, α-cubebene, sabinene, α-muurolene, γ-cadinene, γ-muurolene, bicyclogermacrene, aromadendrene, viridoflorene, alloroaromadendrene, β-cadinene, α-cadinene and α-gurjunene (CG 31, V); germacra-1(10),4(14),5-triene (CG 31, VI), humulene oxide (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**
T-cadinol	–	0.01	0.002	0.0002	III	*0.15*	696	
MOET CG 6								211
CG 8								
Borneol	02.016	0.04	0.018	0.0016	I	*3*	1,899	
Camphor	–	0.01	0.003	0.0003	II	*0.91*	3,620	
Carvotan acetone	–	0.01	0.002	0.0002	II	*0.91*	5,068	
MOET CG 8								1,000
CG 13								
Linalool oxide	13.140	0.02	0.006	0.0006	II	*0.91*	1,584	
CG15								
Phenethyl acetate	09.031	0.03	0.012	0.0011	I	*3*	2,785	
Phenethyl isovalerate	09.466	0.01	0.004	0.0004	I	*3*	8,354	
MOET CG 15								2,089
CG 16								
1,8-Cineole	03.001	1.13	0.051	0.0046	(II)	**100**	21,928	
CG 18								
Eugenol	04.003	82.6	33.04	2.6102	(I)	**300**	101	
Eugenyl acetate	09.020	4.68	1.872	0.1479	(I)	300	1,785	
MOET CG 18								96
CG 22								
Cinnamyl acetate	09.018	1.65	0.660	0.0593	(I)	275	4,641	
(*E*)-Cinnamaldehyde	05.014	1.13	0.452	0.0406	(I)	275	6,777	
3-Phenylproyl acetate	09.032	0.22	0.086	0.0077	(I)	*275*	35,620	
MOET CG 22								2,557
CG 23								
Benzyl benzoate	09.727	4.08	1.632	0.1289	(I)	**194**	1,326	
CG 25								
Thymol	04.006	0.02	0.010	0.0009	(I)	36	41,772	
CG 31, II								
Myrcene	01.008	0.09	0.034	0.0031	(I)	**44**	14,415	
Trans-3,7-dimethyl-1,3,6-ocatriene	–	0.04	0.015	0.0014	(I)	44	32,245	
								9,962
CG 31, III (Cyclohexene hydrocarbons)								
α-Phellandrene	01.006	1.07	0.428	0.0428	(I)	250	6,507	
Limonene	01.045	0.35	0.141	0.0126	(I)	**250**	19,778	
β-Phellandrene	01.055	0.31	0.124	0.0111	(I)	250	22,458	
β-Elemene	–	0.02	0.009	0.0008	I	*3*	3,632	
								1,908
CG 31, IVe (Benzene hydrocarbons, alkyl)								
p-Cymene	01.002	0.82	0.328	0.0259	(I)	**154**	5,224	
Isopropenyl-4-methylbenzene	01.010	0.09	0.037	0.0033	I	*3*	908	
								774
CG 31, V (Bi-, tricyclic, non-aromatic hydrocarbons)								
β-Caryophyllene	01.007	3.54	1.416	0.1271	(I)	**222**	1,746	

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**
α-Pinene	01.004	0.87	0.348	0.0312	(I)	222	7,114	
α-Copaene	-	0.70	0.281	0.0252	(I)	222	8,807	
Camphene	01.009	0.28	0.113	0.0102	(I)	222	21,846	
β-Pinene	01.003	0.25	0.100	0.0090	(I)	222	24,729	
CG 31, V								1,095
CG 31, VI								
3,7,10-Humulatriene	01.043	0.62	0.248	0.0222	I	*3*	135	
CG 32								
β-Caryophyllene oxide	16.043	0.50	0.200	0.0179	(III)	**109**	6,083	

(a): Intake calculations for the individual components are based on the use level of 10.5 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.

As shown in Table 11, for all the assessment groups, the MOET was ≥96. From the lowest MOET of 96 for chickens for fattening, the MOET was calculated for the other target species considering the respective daily feed intake/kg bw and conditions of use. The results are summarised in Table 12.

Table 12: Combined margin of exposure (MOET) for CG 18 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)	Lowest MOET
Chicken for fattening	2	158	40	96
Laying hen	2	106	50	114
Turkey for fattening	3	176	50	103
Piglet	20	880	50	138
Pig for fattening	60	2,200	50	164
Sow lactating	175	5,280	50	202
Veal calf (milk replacer)	100	1,890	50	319
Cattle for fattening	400	8,000	50	303
Dairy cows	650	20,000	50	196
Sheep/goat	60	1,200	50	303
Horse	400	8,000	50	303
Rabbit	2	100	50	121
Salmon	0.12	2.1	25	674
Dog	15	250	25	714
Cat	3	60	25	607
Ornamental fish	0.012	0.054	25	2,427

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 12 shows that for all species the MOET is close to or 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 cinnamon leaf oil as additive in cat feed needs a wider

margin of exposure. A MOET of 500 is considered adequate. Therefore, no safety concern (without considering the presence of safrole, methyleugenol and styrene) was identified for cinnamon leaf oil, when used as a feed additive at the proposed use levels.

The FEEDAP Panel concludes that the proposed use level in water for drinking of 3 mg/L is safe for all animal species (without considering the presence of safrole, methyleugenol and styrene).

Methyleugenol and safrole

Safrole was detected in all batches of the additive under assessment (0.81–1.09%). The use of cinnamon leaf oil at the proposed use levels (10–50 mg/kg complete feed), would result in concentrations ranging from 109 to 545 μg safrole/kg complete feed.

Low concentrations of methyleugenol were detected in all batches of the additive under assessment (0.025–0.030%). The use of cinnamon leaf oil at the proposed use levels (10–50 mg/kg complete feed) would result in concentrations ranging from 3 to 15 μg methyleugenol/kg complete feed.

Since safrole and methyleugenol share the same structural features and the same mode of action, they are allocated to the same assessment group (*p*-allylalkoxybenzenes) and an assessment of the combined exposure is performed as described 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), following the approach described for cinnamon bark oil (see Section 3.2.3).

The assessment of the combined exposure to safrole and methyleugenol for the long-living species is reported in Table 13.

Table 13: Combined exposure and combined margin of exposure (MOET) for the assessment group *p*-allylalkoxybenzenes calculated at the maximum proposed use level of the additive in feed for long-living animals based on $BMDL_{10}$ of 22.2 mg/kg bw per day derived from rodent carcinogenicity studies with methyleugenol

Animal category	Daily feed intake	Body weight	Use level in feed	Methyeugenol+safrole intake	MOET
	kg DM/day	kg	mg/kg feed	μg/kg bw per day	
Long-living animals					
Laying hen	0.106	2	50	33.73	658
Sow lactating	5.28	175	50	19.20	1,163
Dairy cow	20	650	50	19.58	1,125
Pet horse	8	400	50	12.73	1,744
Dog	0.25	15	25	2.12	4,104
Cat	0.06	3	25	2.55	3,489
Ornamental fish	0.00054	0.012	25	0.57	13,955

DM: dry matter; bw: body weight.

For ornamental fish, the MOET was >10,000, which is considered indicative of low concern. For the other species, the proposed use levels resulted in a MOET <10,000.

The assessment of the combined exposure to safrole and methyleugenol for 'short-living' animals is reported in Table 14.

Table 14: Combined exposure and combined margin of exposure (MOET) for the assessment group *p*-allylalkoxybenzenes calculated at the maximum proposed use level of the additive in feed for 'short-living' animals based on a NOAEL of 10 mg/kg bw per day derived from a 90-day study in mice with methyleugenol

Animal category	Daily feed intake	Body weight	Use level in feed	Methyeugenol + safrole intake	MOET
Chicken for fattening	0.158	2	40	40.22	249
Turkey for fattening	0.176	3	50	37.33	267
Piglet	0.88	20	50	28.00	358
Pig for fattening	2.2	60	50	23.33	425

Animal category	Daily feed intake	Body weight	Use level in feed	Methyeugenol + safrole intake	MOET
Veal calf (milk replacer)	1.89	100	50	11.20	828
Cattle for fattening	8	400	50	12.73	787
Sheep/goat	1.2	60	50	12.73	787
Rabbit	0.1	2	50	31.82	315
Salmon	0.0021	0.12	25	5.57	1,749

For 'short-living' animals (Table 14), the magnitude of the MOET is >100, when comparing the exposure to the reference point for methyleugenol based on non-neoplastic endpoints, is considered adequate.

Styrene

Low concentrations of styrene (0.009–0.013%) were detected in all batches of the additive under assessment. The use of cinnamon leaf oil at the proposed use levels (10–50 mg/kg complete feed), would result in concentrations ranging from 1.3 to 6.5 μg styrene/kg complete feed.

The average and the highest intake of styrene for the different target species is reported in Table 15, considering the analysed values of styrene reported in Section 3.3.1.

Table 15: Target animal intake of styrene (as μg/kg bw per day) at the maximum proposed use level of the additive in feed for each species. The values of styrene in feed are calculated considering the average and the highest analysed values in the additive

Animal category	Daily feed intake	Body weight	Use level in feed	Average styrene intake	Highest styrene intake
	kg DM/day	kg	mg/kg feed	μg/kg bw per day	
Chicken for fattening	0.158	2	40	0.323	0.467
Laying hen	0.106	2	50	0.271	0.391
Turkey for fattening	0.176	3	50	0.300	0.433
Piglet	0.88	20	50	0.225	0.325
Pig for fattening	2.2	60	50	0.188	0.271
Sow lactating	5.28	175	50	0.154	0.223
Veal calf (milk replacer)	1.89	100	50	0.097	0.130
Cattle for fattening	8	400	50	0.102	0.148
Dairy cow	20	650	50	0.157	0.227
Sheep/goat	1.2	60	50	0.102	0.148
Horse	8	400	50	0.102	0.148
Rabbit	0.1	2	50	0.256	0.369
Salmon	0.0021	0.12	25	0.045	0.065
Dog	0.25	15	25	0.043	0.062
Cat	0.06	3	25	0.051	0.074
Ornamental fish	0.00054	0.012	25	0.012	0.017

The use of cinnamon leaf oil at the proposed use level in feed would result in an average intake of styrene ranging between 0.012 μg/kg bw per day in ornamental fish and 0.32 μg/kg bw per day in chickens for fattening (highest intake 0.47 μg/kg bw per day in chickens for fattening). These intake values are comparable or lower than the intake of styrene as an environmental pollutant (see Section 3.2.3).

However, considering that a concern for genotoxicity associated with oral exposure to styrene remains and pending the outcome of the overall safety assessment of styrene by oral route, the FEEDAP Panel is not in the position to conclude on the safety of cinnamon leaf oil as feed additive for long-living animals and for animals for reproduction.

When the estimated exposure of 'short-living' animals is compared to the NOAEL of 7.7 mg styrene/kg bw per day (see Section 3.2.2.3), a MOE ranging from 16,495 in chickens for fattening and 119,138 in salmonids is calculated. Therefore, the FEEDAP Panel concludes that the use of the cinnamon leaf oil at the proposed use levels in feed is not expected to be of concern for target species for fattening.

3.3.3.1. Conclusions on safety for the target species

Owing to the presence of styrene in cinnamon leaf oil, the FEEDAP Panel is not in the position to conclude on the safety of the additive for long-living animals and reproductive animals including those animals reared for laying/breeding/reproduction. Concerning the exposure of these species to safrole and methyleugenol, a margin of exposure > 10,000 which is indicative of low concern, is calculated for ornamental fish.

For 'short-living' animals, the FEEDAP Panel considers cinnamon leaf oil as safe up to the maximum proposed use levels in complete feed of 40 mg/kg for chickens for fattening and other minor poultry, 50 mg/kg for turkeys for fattening, pigs and ruminants for fattening, horses for meat production and rabbits, 25 mg/kg complete feed for salmonids and other fin fish, and for other minor species.

The FEEDAP Panel considers the proposed use level in water for drinking of 3 mg/L as safe for 'short-living' animals, except fish.

3.3.4. Safety for the consumer

The leaf oil of *C. verum* 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 3.02 mg/kg bw per day for cinnamon and of 0.011 mg/kg bw per day for cinnamon leaf oil originating from *C. verum*. Fenaroli also reports use levels in food and beverages in the range of 1.56 mg/kg up to 293 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 *C. verum* leaf oil are expected to be extensively metabolised and excreted in the target species (see Section 3.2.2.1). Also for safrole, methyleugenol and styrene, the available data indicate that they are absorbed, metabolised and rapidly excreted and are not expected to accumulate in animal tissues and products. Consequently, residues in food products are unlikely.

Considering the above and the reported human exposure due to the direct use of cinnamon and its preparations in food (Burdock, 2009), it is unlikely that the consumption of products from animals given cinnamon leaf 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 *C. verum* leaf oil up to the highest safe use level in feed.

3.3.5. 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 cinnamon leaf oil,[43] where hazards for users have been identified.

Based on the evidence provided in the form of a literature search (see Section 3.2.5), the FEEDAP Panel concludes that cinnamon leaf oil is irritant to skin and eyes and a skin sensitiser. The possibility that cinnamon leaf oil may also be a respiratory sensitiser cannot be excluded.

Based on the presence of safrole[35] in cinnamon leaf oil in a typical concentration of 1.2%, cinnamon leaf oil is classified as carcinogenic (category 1B) in accordance with the classification criteria in Annex I of the CLP Regulation (1,272/2008/EC)[36,44] and handled accordingly.[37]

[43] Technical dossier/ Supplementary Information October 2020/Annex_X_cinnamon_leaf_oil_MSDS: Skin sensitisation (H317, category 1A), serious eye damage/eye irritation (H319, category 2), carcinogenicity (H350, category 1B), germ cell mutagenicity (H341, category 2).

[44] https://echa.europa.eu/it/registration-dossier/-/registered-dossier/15259/7/8

3.3.6. Safety for the environment

C. verum 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 (eugenol, eugenyl acetate, benzyl benzoate and cinnamaldehyde) and additional 16 components accounting for > 0.1% of the composition of the additive (α-terpineol, benzyl benzoate, 4-methoxybenzaldehyde, benzaldehyde, 1,8-cineole, myrcene, α-phellandrene, β-phellandrene, limonene, α-terpinene, terpinolene, *p*-cymene, β-caryophyllene, α-pinene, camphene and β-pinene) accounting together for 95% 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 use individual levels higher than those resulting from the use of the essential oil in feed.

The remaining identified constituents of the essential oil are mainly aliphatic mono or sesquiterpenes partially with functional groups, they are chemically related to the substances evaluated by EFSA as CG 31 for use in animal feed (EFSA FEEDAP Panel, 2015, 2016) for which EFSA concluded that they were extensively metabolised by the target species (see Section 3.2.2.1) 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 CG 31 substances.

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

3.4. Efficacy

Cinnamon bark oil and cinnamon leaf oil are listed in Fenaroli's Handbook of Flavour Ingredients (Burdock, 2009) and by FEMA with the reference numbers 2,291 and 2,292, respectively.

Since *C. verum* and its extracts 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

Cinnamon bark oil and cinnamon leaf oil from *C, verum* J. Presl may be produced from plants of different geographical origins and by various processes resulting in preparations with different composition and toxicological profiles. Therefore, the following conclusions apply only to cinnamon bark oil which contains ≤ 0.34% safrole, ≤ 0.04% methyleugenol and ≤ 0.024% styrene and to cinnamon leaf oil which contains ≤ 1.09% safrole, ≤ 0.30% methyleugenol and ≤ 0.013% styrene, which are obtained by steam distillation of the bark and the leaves of *C. verum*, respectively.

Owing to the presence of styrene in the essential oils under assessment, the FEEDAP Panel is not in the position to conclude on the safety of both products for long-living animals and reproductive animals including those animals reared for laying/breeding/reproduction.

For 'short-living' animals, the FEEDAP Panel concluded that

- the use of cinnamon bark oil is considered as safe up to the maximum proposed use levels in complete feed of 5 mg/kg for poultry species for fattening, 25 mg/kg for pigs for fattening, 50 mg/kg for piglets and other minor Suidae, 10 mg/kg for ruminants for fattening and horses for meat production, 5 mg/kg for rabbits, salmonids and other fin fish, and other minor species. The use of the additive in water for drinking is considered as safe for 'short-living' animals provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed.
- the use of cinnamon leaf oil is considered as safe up to the maximum proposed use levels in complete feed of 40 mg/kg for chickens for fattening and other poultry, 50 mg/kg for turkeys for fattening, pigs and ruminants for fattening, horses for meat production and rabbits, 25 mg/kg complete feed for salmonids and other fin fish, and for other minor species. The proposed use level in water for drinking of 3 mg/L is considered as safe for 'short-living' animals (except fish).

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

The essential oils under assessment should be considered as irritant to skin and eyes, and as dermal and respiratory sensitisers. Based on the presence of safrole ≥ 0.1%, cinnamon leaf oil and bark oil are classified as carcinogen (category 1B)[45] and handled accordingly.

The use of cinnamon bark oil and cinnamon leaf oil in animal feed under the proposed conditions is not expected to pose a risk for the environment.

Cinnamon bark oil and cinnamon leaf oil are recognised to flavour food. Since their function in feed would be essentially the same as that in food, no further demonstration of efficacy is considered necessary.

5. Recommendations and/or Remarks

The specification should ensure that the concentration of safrole, methyleugenol and styrene should be as low as possible and should not exceed, respectively, 0.34% 0.004% and 0.024% in cinnamon bark oil and 1.1%, 0.30% and 0.013% in cinnamon leaf oil.

Data on the generation and levels of styrene in feed and food (from, e.g. cinnamon preparations, cinnamaldehyde and cinnamic acid) are needed and should be considered in the context of genotoxicity and mechanistic data, comparative toxicokinetics and analysis of species differences to complete a full safety assessment of styrene.

6. Documentation provided to EFSA/Chronology

Date	Event
28/10/2010	Dossier received by EFSA. Botanically 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: analytical methods*
05/04/2011	Comments received from Member States
20/04/2012	Reception of supplementary information from the applicant
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
02/08/2013	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives
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
18/12/2018	EFSA informed the applicant that the evaluation process 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: characterisation, safety for target species, safety for the consumer, safety for the user and environment*
01/10/2020	Reception of supplementary information from the applicant (partial submission: cinnamon oil)
16/02/2022	The application was split and a new EFSA-Q-2022-00105 was assigned to the preparations included in the present assessment. Scientific assessment re-started
24/06/2022	Reception of an amendment of the Evaluation report of the European Union Reference Laboratory for Feed Additives related to ylang ylang oil, camphor white oil and cinnamon tincture
31/08/2022	Reception of a second amendment of the Evaluation report of the European Union Reference Laboratory for Feed Additives related to nutmeg oil, laurel leaves oil, pepper oil black, cinnamon oil, cassia oil and pepper oleoresin black
27/09/2022	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

[45] in accordance with the classification criteria in Annex I of the CLP Regulation (1,272/2008/EC).

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Abbreviations

ADI	acceptable daily intake
AFC	EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
bw	body weight
CAS	Chemical Abstracts Service
CD	Commission Decision
CDG	chemically defined group
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CG	chemical group
CoE	Council of Europe
ECHA	European Chemicals Agency
EINECS	European Inventory of Existing Chemical Substances
EMA	European Medicines Agency
EURL	European Union Reference Laboratory
FAO	Food Agricultural Organization
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
FFAC	Feed Flavourings authorisation Consortium of FEFANA (EU Association of Specialty Feed Ingredients and their Mixtures)
FGE	food group evaluation
FLAVIS	The EU Flavour Information System
FL-no	FLAVIS number
GC-FID	gas chromatography-flame ionisation detection
GC–MS	gas chromatography–mass spectrometry
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LOD	limit of detection
LOQ	limit of quantification
MOE	margin of exposure
MOET	combined margin of exposure
NOAEL	no observed adverse effect level

NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PCBs	polychlorinated biphenyls
QSAR	Quantitative Structure–Activity Relationship
SC	EFSA Scientific Committee
SCF	Scientific Committee on Food
TTC	threshold of toxicological concern
UF	uncertainty factor
WHO	World Health Organization

Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis for eighteen compounds from botanically defined Group 06 (Laurales, Magnoniales, Piperales) – second amendment of the EURL report

In the period between the publication of the original EURL evaluation report [1] and the current date, eight flavouring compounds *(cassia bark extract, cinnamon bark oleoresin, laurel leaves extract/ oleoresin, boldo extract, boldo tincture, mace oil, nutmeg oleoresin* and *kawakawa tincture)* were withdrawn from the grouped application FAD-2010-0218 *Botanically defined flavourings from Group 06 - Laurales, Magnoliales, Piperales* [2].

Upon request of DG SANTE, the EURL evaluated the new methods of analysis provided by the Applicant for three *feed additives* from the group, namely: *ylang ylang oil, camphor white oil* and *cinnamon tincture* and recently issued a partial amendment of the original EURL report [3].

Following an additional request from EFSA [4], the EURL evaluated in the frame of this second amendment the new supplementary information provided by the Applicant related to the methods of analysis proposed for other six *feed additives* so-called: *nutmeg oil, laurel leaves oil, pepper oil black, cinnamon oil, cassia oil* and *pepper oleoresin black* which belong to the same grouped application.

Hereafter is the amended report on the evaluation of the new methods of analysis submitted by the Applicant and proposed for official control of the following *feed additives: nutmeg oil, laurel leaves oil, pepper oil black, cinnamon oil, cassia oil* and *pepper oleoresin black*. The updated recommendations of this amendment replace the ones stated for these six *feed additives* in the original report issued by the EURL [1].

For *nutmeg oil, laurel leaves oil, pepper oil black, cinnamon oil* and *cassia oil* the Applicant proposed the quantification of their respective phytochemical markers, by gas chromatography coupled with flame ionisation detection (GC-FID), based on different available ISO standard methods.

Furthermore, the Applicant provided the analytical procedure with the specific operating conditions for the GC and applied it to the mentioned *feed additives* for the quantification of their respective phytochemical markers. According to the analytical procedure, 1 µl of the oil is injected into the GC using split ratio 100:1. The eluted compounds are detected by FID and the quantification is performed using the normalisation approach for the estimation of the area percentage of individual components (including also the phytochemical marker) in the obtained chromatograms.

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Cinnamon oil

According to the Applicant, *cinnamon oil* is an essential oil obtained by distillation from bark (*cinnamon bark oil*) or from the leaves (*cinnamon leaf oil*) of the plant species *"Cinnamomum zeylanicum Bl., C. verum J.S. Presl"* being *cinnamaldehyde* the phytochemical marker in both products. The *cinnamon bark oil* has a content of cinnamaldehyde ranging from 55 to 75% while for the *cinnamon leaf oil* the content of the phytochemical marker is below 3% (expressed as the relative individual peak area in the chromatogram) [13].

For the quantification of *cinnamaldehyde* in both *cinnamon oils* the Applicant proposed a gas chromatography coupled with flame ionisation detection (GC-FID) method based on the standard ISO 3524:2003 for "Oil of cinnamon leaf, Sri Lanka type (*Cinnamomum zeylanicum Blume*)" [14]. Similar GC-FID methods are also described in the European Pharmacopoeia for the *cinnamon bark oil* (Eur. Pharm. 04/2011:1501) and for the *cinnamon leaf oil* (Eur. Pharm. 04/2008:1608) [14].

Furthermore, the description of the product and the range of *cinnamaldehyde* stated in the ISO standard and/or in the respective European Pharmacopoeia's monographs correspond to the range of the phytochemical marker as declared by the Applicant in the proposed specifications [13].

In addition, the Applicant presented typical chromatograms of *cinnamon bark oil* and of *cinnamon leaf oil* demonstrating a good separation of the phytochemical marker [14].

Moreover, the Applicant analysed *cinnamaldehyde* in 5 different batches of *cinnamon bark oil* and of *cinnamon leaf oil*. These analyses led to *cinnamaldehyde* contents ranging from 71.3 to 72.2% (for the *cinnamon bark oil*) and from 1.0 to 1.2% (for the *cinnamon leaf oil*) [13]. The obtained values are within the ranges as specified in the Eur. Pharm. Monograph 04/2011:1501 (for the *cinnamon leaf oil*), and within the ones specified in the ISO 3524 standard and the Eur. Pharm. monograph 01/2008:1608 (for the *cinnamon bark oil*) [14].

Given the data currently available, the EURL recommends for official control the GC-FID methods based on the ISO 3524 standard and on the Eur. Pharm. monographs 01/2008:1608 and 04/2011:1501 for the quantification of *cinnamaldehyde* (phytochemical marker) in *cinnamon oil*.

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