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SCIENTIFIC OPINION

Safety and efficacy of a feed additive consisting of an essential oil derived from fresh leaves of *Melaleuca cajuputi* Maton & Sm. ex R. Powell and *Melaleuca leucadendra* (L.) L. (cajuput 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 cajuput oil obtained from fresh leaves of *Melaleuca cajuputi* Maton & Sm. ex R. Powell and *Melaleuca leucadendra* (L.) L., when used as a sensory additive for all animal species. The FEEDAP Panel concluded that cajuput oil is safe up to the maximum proposed use levels in complete feed of 30 mg/kg for sows and dogs, 50 mg/kg for horses and ornamental fish, 40 mg/kg for salmon and 5 mg/kg for cats. For the other species, the calculated safe concentrations were 18 mg/kg for chickens for fattening, 26 mg/kg for laying hens, 23 mg/kg for turkeys for fattening, 37 mg/kg for pigs for fattening, 31 mg/kg for piglets, 78 mg/kg for veal calves (milk replacer), 69 mg/kg for cattle for fattening and sheep/goats, 45 mg/kg for dairy cows and 28 mg/kg for rabbits. These conclusions were extrapolated to other physiologically related species. For any other species, the additive is safe at 5 mg/kg complete feed. The use of cajuput oil in water for drinking was considered safe provided that the total daily intake does not exceed the daily amount considered safe when consumed via feed. No concerns for consumers and the environment were identified following the use of the additive up to the highest safe use level in feed. The essential oil under assessment should be considered as an irritant to skin and eyes, and as a dermal and respiratory sensitiser. Since cajuput oil was recognised to flavour food and their function in feed would be essentially the same as that in food, no further demonstration of efficacy was considered necessary.

KEYWORDS

1,8-cineole, cajuput oil, flavouring compounds, *Melaleuca cajuputi*, *Melaleuca leucadendra*, safety, sensory additives

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1 | INTRODUCTION

1.1 | Background and Terms of Reference

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

The European Commission received a request from Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)[2] for authorisation/re-evaluation of 18 additives (namely geranium oil, geranium rose oil, eucalyptus oil, eucalyptus tincture, clove oil, clove tincture, broom teatree oil, purple loosestrife tincture, tea tree oil, melaleuca cajuputi oil, niaouli oil, allspice oil, bay oil, pomegranate bark extract, bambusa tincture, citronella oil, lemongrass oil and vetiveria oil) belonging to botanically defined group (BDG) 07 – *Geraniales, Myrtales, Poales* when used, when used as a feed additive for all animal species (category: sensory additives; functional group: flavourings). During the assessment, the applicant withdrew the application for six additives.[3] These additives were deleted from the register of feed additives.[4] During the course of the assessment, this application was split, and the present opinion covers only one out of the remaining 12 additives under application: melaleuca cajuputi oil from *Melaleuca cajuputi* Powell[5] and *Melaleuca leucadendra* (L.) L.[6] for all animal species.

The remaining 11 additives belonging to botanically defined group (BDG) 07 – Geraniales, Myrtales, Poales under application are assessed in separate opinions.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority deleted (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 21 December 2010.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the feed additive consisting of melaleuca cajuputi oil from *M. cajuputi* and *M. leucadendra* (fresh leaves), when used under the proposed conditions of use (see Section 3.2.4).

1.2 | Additional information

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

2 | DATA AND METHODOLOGIES

2.1 | Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[7] in support of the authorisation request for the use of cajuput oil from *M. cajuputi* or *M. leucadendra* as a feed additive. The dossier was received on 28 February 2024 and the general information and supporting documentation is available at https://open.efsa.europa.eu/questions/EFSA-Q-2024-00118.[8]

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.

[1]Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2]On 13/03/2013, EFSA was informed by the applicant that the applicant company changed to FEFANA asbl, Avenue Louise 130 A, Box 1, 1050 Brussels, Belgium.
[3]Broom teatree oil, geranium oil, bay oil and vetiveria oil (27 February 2019); bambusa tincture and allspice oil (18 November 2022).
[4]Register of feed additives, Annex II, withdrawn by OJ L162, 10.05.2021, p. 5.
[5]Accepted name: *Melaleuca cajuputi* Maton & Sm. ex R.Powell, according to the last update (December 2023). Former name: *Melaleuca cajuputi* Powell. Synonym: *M. Leucadendron*.
[6]Accepted name: *Melaleuca leucadendra*. Synonym: *M. Leucadendron*.
[7]Dossier reference: FAD-2010-0219.
[8]The original application EFSA-Q-2010-01282 was split on 28/02/2024 and a new EFSA-Q-2024-00118 was generated.

Many of the components of the essential oil under assessment have been already evaluated by the FEEDAP Panel as chemically defined flavourings (CDGs). The applicant submitted a written agreement to reuse the data submitted for the assessment of chemically defined flavourings (dossiers, publications and unpublished reports) for the risk assessment of preparations belonging to BDG 07, including the current one under assessment.[9]

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the phytochemical marker in the additive. The evaluation report is related to the methods of analysis for each feed additive included in the group BDG 07 (Geraniales, Myrtales, Poales). During the assessment, upon request from EFSA, the EURL issued two amendments[10] of the original report. The additive under assessment, melaleuca cajuputi oil, is included in the second amendment. In particular, the EURL recommended a method based on gas chromatography with flame ionisation detection (GC-FID) for the quantification of the phytochemical marker *1,8-cineole* in *melaleuca cajuputi oil*.[11]

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of an essential oil from *M. cajuputi* and *M. leucadendra* is in line with the principles laid down in Regulation (EC) No 429/2008[12] 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, 2012a), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a), Guidance on the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017c), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019), Guidance on the assessment of the safety of feed additives for the users (EFSA FEEDAP Panel, 2023a), Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA 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).

3 | ASSESSMENT

The additive under assessment, melaleuca cajuputi oil (herein referred to as cajuput oil[13]), is an essential oil obtained from the leaves of *Melaleuca cajuputi* Maton & Sm. ex R. Powell and *Melaleuca leucadendra* (L.) L. and is intended for use as a sensory additive (functional group: flavouring compounds) in feed and in water for drinking for all animal species.

3.1 | Origin and extraction

Melaleuca cajuputi Maton & Sm. ex R. Powell (cajuput or white samet) and *Melaleuca leucadendra* (L.) L. (weeping paperbark) are species of medium-sized evergreen trees belonging to the Myrtaceae family. Both are found growing in coastal plains and characterised by their papery bark and cream-coloured 'bottle brush' flowers. Three subspecies of *M. cajuputi* are recognised, *Melaleuca cajuputi* subsp. *cajuputi* is the most widely distributed and is native to most of south-east Asia and northern Australia and has been introduced into China, Sri Lanka and Taiwan. *Melaleuca cajuputi* subsp. *cumingiana* (Turcz.) Barlow is also native to south-east Asia and similarly has been introduced into China but is not found in Australia. The third subspecies, *Melaleuca cajuputi* subsp. *platyphylla* Barlow is found only in New Guinea and Australia. *M. leucadendra* is native to New Guinea and Australia with limited introductions elsewhere in the world. It is sometimes used as an amenity tree.

The leaves of both species are used as a herbal tea or to produce vapour which is inhaled to treat respiratory infections. However, their commercial value lies in the production of an essential oil known as cajuput oil (sometimes spelt cajaput or cajeput) from the leaves and twigs. The oil has a long tradition of use, particularly in Indonesia, for the treatment of ailments such as colds, stomach aches and insect bites and is a common household medicine in south-east Asia. With the development of plantations and less reliance on wild collections cajuput oil has become an internationally traded

[9]Technical dossier/Supplementary information February 2023/Letter dated 31/01/2023.

[10]Preparations included in the first amendment: geranium rose oil, eucalyptus oil, lemongrass oil and clove oil; preparations included in the second amendment: citronella oil, melaleuca cajuputi oil, tea tree oil, clove tincture and eucalyptus tincture.

[11]The full report is available on the EURL website: https://joint-research-centre.ec.europa.eu/publications/fad-2010-0219_en

[12]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.

[13]The oil under assessment is identified in the scientific and grey literature as 'cajuput oil' or 'cajeput oil' (FEMA 2225). Historically, tea tree oil (FEMA 3902) from *Melaleuca alternifolia* (Maiden and Betche) Cheel has been referred to as melaleuca oil (Carson & Riley, 2001). As the term 'melaleuca cajuputi oil' (used by the applicant and in the European Union Register of Feed Additives) have some ambiguity, for sake of clarity, the FEEDAP Panel will refer to the additive under assessment as to 'cajuput oil'.

commodity, finding further use as a flavour in food and food supplements and in the manufacture of soaps, other household goods and cosmetics.

The essential oil is extracted by steam distillation from the leaves of *M. cajuputi* and *M. leucadendra*. According to the applicant, fresh leaves from both species are commonly mixed prior to distillation.[14] The volatile constituents are condensed and then separated from the aqueous phase by decantation.

3.2 | Characterisation

3.2.1 | Characterisation of cajuput oil

Cajuput oil is identified with the single Chemical Abstracts Service (CAS) number 8008-98-8,[15] the European Inventory of Existing Commercial Chemical Substances (EINECS) number 931-800-6,[16] the Flavor Extract Manufacturers Association (FEMA) number 2225 and the Council of Europe (CoE) number 276.

For cajuput oil, the product specifications are based on the concentrations of the main volatile components. Three components are included in the specifications as shown in Table 1, with 1,8-cineole as the phytochemical marker. The analysis of two batches of the additive showed compliance with the specification for 1,8-cineole (51.9% and 55.5%) when analysed by GC-FID and expressed as percentage of gas chromatographic peak area (% GC area).[17] The applicant provided the full characterisation of the volatile constituents in five batches obtained by gas chromatography-mass spectrometry (GC-MS).[18] The three compounds accounted for about 75.6% on average (range 74.0%–77.0%) of % GC area (Table 1).

TABLE 1 Major constituents of the essential oil from the leaves of *Melaleuca cajuputi* Maton & Sm. ex R. Powell and *Melaleuca leucadendra* (L.) L. as defined by specifications and batch to batch variation based on the analysis of five batches by gas chromatography-mass spectrometry (GC-MS). The content of each constituent is expressed as the area percent of the corresponding chromatographic peak (% GC area), assuming the sum of chromatographic areas of all detected peaks as 100%.

Constituent			% GC area		
EU register name	**CAS No**	**FLAVIS No**	**Specification[a]**	**Mean**	**Range**
1,8-Cineole	470-82-6	03.001	50–70	61.46	58.71–63.40
α-Terpineol	98-55-5	02.014	4–12	7.87	6.53–9.28
d-Limonene	5989-27-5	01.045	3–9	6.23	5.72–6.68
Total				75.56	73.97–77.01[b]

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

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

[b]The values given for total are the lowest and the highest values of the sum of the components in the batches analysed.

In total, up to 59 peaks were detected in the chromatogram, all of which were identified and accounted on average for 100% (99.96%–100%) of the % GC area. Besides the three compounds indicated in the product specifications, 13 other compounds were detected at individual levels > 0.5% and are listed in Table 2. These 16 compounds account on average for 96.0% (95.7%–96.3%) of the % GC area. The remaining 43 compounds (ranging between 3.69% and 4.32%) and accounting on average for 3.98% of the % GC area are listed in the footnote.[19] Based on the available data on the characterisation, cajuput oil is considered a fully defined mixture (EFSA SC, 2019a).

[14]Technical dossier/Supplementary information April 2023/BDG-07_SIn_reply_melaleuca_cajuputi_oil, page 4.

[15]CAS No. 8008-98-8 is applied to the essential oil from *Melaleuca leucandendron L*.

[16]EINECS 931-800-6 refers to cajeput oil.

[17]Technical dossier/Supplementary information April 2023/EURL_appendix_melaleuca_cajuputi_oil

[18]Technical dossier/Supplementary information April 2023/Annex_II_SIn_reply_melaleuca_cajuputi_oil_CoAs_Chrom_SOC.

[19]Additional constituents:
constituents ($n = 16$) between < 0.1% and ≥ 0.05%: δ-cadinene, α-ylangene, δ-terpineol, aromadendrene, *trans*-3,7-dimethyl-1,3,6-octatriene, β-elemene, cubenol, *(Z)*-cinnamaldehyde, cubebol, sabinene, α-panasinsene, ledol, 4-epi-cubebol, δ-3-carene;
constituents ($n = 14$) between < 0.2% and ≥ 0.1%: menthol, carveol, rose furan epoxide, *(Z)*-γ-bisabolene, (–)-*trans*-isopiperitenol, germacra-1(10),4(14),5-triene, *p*-menth-1-en-3-one, *(1R,2R,5S)*-5-isopropenyl-2-methylcyclopentane carboxaldehyde, 4-epi-cubebol, *cis*-3,7-dimethyl-1,3,6-octatriene, 2,10-epoxypinane, tricyclene, α-copaene, β-elemene, d-8-*p*-menthene-1,2-epoxide, neryl formate, cubebol, 3-methyl-2(3-methylbut-2-enyl)furan, decanal and α-cadinene;
constituents ($n = 13$) between < 0.05% and ≥ 0.01%: 4-isopropylbenzyl alcohol, octane, γ-cadinene, (4ar,8as)-4a-methyl-1-methylene-7-(propan-2-ylidene) decahydronaphthalene, humulene oxide II, neointermedeol, alloaromadendrene, γ-eudesmol, α-gurjunene, 1-isopropenyl-4-methylbenzene, α-muurolene, benzaldehyde, camphene.

TABLE 2 Constituents of the essential oil from the leaves of *Melaleuca cajuputi* Maton & Sm. ex R. Powell and *Melaleuca leucadendra* (L.) L., accounting for >0.5% of the composition (based on the analysis of five batches) not included in the specifications. The content of each constituent is expressed as the area percent of the corresponding chromatographic peak (% GC area), assuming the sum of chromatographic areas of all detected peaks as 100%.

Constituent			% GC area	
EU register name	**CAS No**	**FLAVIS No**	**Mean**	**Range[a]**
β-Caryophyllene	87-44-5	01.007	3.21	2.84–3.71
γ-Terpinene	99-85-4	01.020	3.12	2.97–3.50
α-Pinene	80-56-8	01.004	3.09	2.70–3.94
β-Pinene	127-91-3	01.003	1.76	1.48–1.98
3,7,10-Humulatriene	6753-98-6	01.043	1.55	1.35–1.80
β-Selinene	17066-67-0	–	1.43	1.27–1.62
m-Cymene	535-77-3	–	1.39	1.20–1.56
Terpinolene	586-62-9	01.005	1.28	1.01–1.42
1(5),11-Guaiadiene	3691-12-1	01.023	1.16	1.03–1.31
Myrcene	123-35-3	01.008	0.70	0.64–0.76
α-Terpinyl acetate	80-26-2	09.015	0.69	0.59–0.83
Viridiflorol	552-02-3	02.215	0.54	0.43–0.67
4-Terpinenol	562-74-3	02.072	0.54	0.40–0.60
Total			20.45	19.16–21.84

Abbreviations: EU, European Union; CAS No., Chemical Abstracts Service number; FLAVIS No, EU Flavour Information System number.
[a]The values given for total are the lowest and the highest values of the sum of the components in the batches analysed.

As the leaves from the two species *M. cajuputi* and *M. leucadendra* are commonly mixed prior to oil distillation, the applicant provided data from the literature, which showed that the majority of the values reported for the three major components are within the same ranges of the specifications proposed by the applicant for the additive under assessment (Table 1).[20]

The applicant performed a literature search (see Section 3.3) for the chemical composition of *M. cajuputi* and *M. leucadendra* and its preparations to identify the presence of any recognised substances of concern.[21] The EFSA Compendium of botanicals identified methyleugenol as a potential substance of concern in *Melaleuca leucadendra* (L.) L. and its chemotypes (EFSA, 2012)[22] based on two references (Brophy, 1999; Farag et al., 2004). Different Australian chemotypes of *M. leucadendra* were described to contain methyleugenol in different percentages: 1.6% in a mono- and sequiterpene chemotype (with 10%–45% 1,8-cineole), 6%–24% in a *(E)*-methyl isoeugenol chemotype and 95%–97% in a methyleugenol chemotype (Brophy, 1999). Methyleugenol was a major constituent (96.8%) of the essential oil of *M. ericifolia* but was not detected in essential oils from other *Melaleuca* species, including *M. leucadendron* (Farag et al., 2004). Additionally, trace amounts of estragole (< 0.05%) and safrole (0.1%) were detected in an essential oil extracted by distillation from *M. leucadendra* from Cuba (Monzote et al., 2020).

Methyleugenol, estragole and safrole were not detected by GC-MS in the five batches analysed (limit of detection, LOD 0.01 mg/kg).[23]

No other substances of concern were identified in the literature provided by the applicant.

3.2.2 | Impurities

The applicant referred to the 'periodic testing' of some representative flavourings premixtures for mercury, cadmium, lead, arsenic, fluoride, polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans and polychlorinated biphenyls, organo-chloride pesticides, organo-phosphorous pesticides, aflatoxins (B1, B2, G1, G2) and ochratoxin A. However, no data were provided on the presence of these impurities. Since cajuput oil is produced by steam distillation, the likelihood of any measurable carry-over of the above-mentioned elements is considered low, except for mercury.

[20]Technical dossier/Supplementary information April 2023/Annex_IV_SIn_reply_melaleuca_oil_cajuputi_vs_leucadendra.
[21]Technical dossier/Supplementary information April 2023/Literature search_melaleuca_cajuputi_oil.
[22]Online version: https://www.efsa.europa.eu/en/data-report/compendium-botanicals
[23]Technical dossier/Supplementary information April 2023/Annex_II_SIn_reply_melaleuca_cajuputi_oil_CoAs_Chrom_SOC.

3.2.3 | Shelf-life

The typical shelf-life of cajuput oil is stated to be at least 12 months, when stored in tightly closed containers under standard conditions (in a cool, dry place protected from light).[24] However, no data supporting this statement were provided.

3.2.4 | Conditions of use

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

TABLE 3 Conditions of use for the essential oil from the leaves of *Melaleuca cajuputi* Powell and *Melaleuca leucadendra* (L.) L.: maximum proposed use levels in complete feed for the intended target species and categories.

Animal category	Maximum use level (mg/kg complete feed)
Chickens for fattening	50
Laying hens	50
Turkeys for fattening	50
Pigs for fattening	50
Piglets	50
Sows lactating	30
Veal calves (milk replacer)	235
Cattle for fattening	150
Dairy cows	50
Sheep/goats	150
Horses	50
Rabbits	50
Salmons	40
Dogs	30
Cats	5
Ornamental fish	50
Other species	5

3.3 | Safety

The assessment of safety of cajuput oil is based on the maximum use levels proposed by the applicant in complete feed for the species listed above (see Table 3).

No studies to support the safety for target animals, consumers and users were performed with the additive under assessment. The applicant carried out a structured database search to identify data related to the chemical composition and the safety of preparations obtained from *M. cajuputi* and *M. leucadendra*.[25] Four cumulative databases (LIVIVO, NCBI, OVID and ToxInfo), 13 single databases including PubMed and Web of Science and 12 publishers' search facilities including Elsevier, Ingenta, Springer and Wiley were used. The literature search (no time limits) was conducted in December 2022. The keywords used covered different aspects of safety and the inclusion and exclusion criteria were provided by the applicant.

Many of the individual components of the essential oil have already been assessed as chemically defined flavourings for use in feed and food by the FEEDAP Panel and the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). The flavouring compounds currently authorised for feed[26] and food[27] use, together with the EU

[24]Technical dossier/Section II.

[25]Technical dossier/Supplementary information March 2023/Literature_search_melaleuca_cajuputi_oil.

[26]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

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

Flavour Information System (FLAVIS) number, the chemical group as defined in Commission Regulation (EC) No 1565/2000,[28] and the corresponding EFSA opinion are listed in Table 4.

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

CG	Chemical group	Product (EU register name)	FLAVIS No	EFSA opinion,* Year
06	Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters with esters containing tertiary alcohols ethers	Linalool	02.013	2012b
		α-Terpineol	02.014	
		4-Terpinenol	02.072	
		α-Terpinyl acetate	09.015	
10	Secondary aliphatic saturated or unsaturated alcohols, ketones, ketals and esters with a second secondary or tertiary oxygenated functional group	4-Hydroxy-4-methylpentan-2-one[a]	07.165	2011a, CEF
16	Aliphatic and alicyclic ethers	1,8-Cineole	03.001	2012c, 2021
22	Aryl-substituted primary alcohol, aldehyde, acid, ester and acetal derivatives	Cinnamaldehyde	05.014	2017d
23	Benzyl alcohols/aldehydes/acids/esters/acetals	4-Isopropylbenzyl alcohol	02.039	2012d
		Benzaldehyde	05.013	
31	Aliphatic and aromatic hydrocarbons and acetals containing saturated aldehydes	Terpinolene	01.005	2015
		α-Phellandrene	01.006	
		1-Isopropenyl-4-methylbenzene	01.010	
		α-Terpinene	01.019	
		γ-Terpinene	01.020	
		d-Limonene	01.045	
		Pin-2(10)-ene (β-pinene)	01.003	2016
		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,b]	01.021	2011b, CEF
		1(5),11-Guaiadiene[a,b]	01.023	
		3,7,10-Humulatriene[a,b]	01.043	
		α-Muurulene[a,b]	01.052	
		4(10)-Thujene (sabinene)[a]	01.059	2015a, CEF
32	Epoxides	β-Caryophyllene epoxide[a]	16.043	2014, CEF

*FEEDAP opinion unless otherwise indicated.

[a]Evaluated for use in food. According to Regulation (EC) 1565/2000, flavourings evaluated by JECFA before 2000 are not required to be re-evaluated by EFSA.

[b]Evaluated applying the 'Procedure' described in the Guidance on the data required for the risk assessment of flavourings to be used in or on food (EFSA CEF Panel, 2010). No longer authorised for use as flavours in food, as the additional toxicity data requested (EFSA CEF Panel, 2011b) were not submitted and the CEF Panel was unable to complete its assessment.

As shown in Table 4, a number of components of cajuput oil, accounting for about 91% of the GC peak areas, have been previously assessed and considered safe for use as flavourings, and are currently authorised for use in food[29] without limitations and for use in feed[30] at individual use levels higher than those resulting from the intended use of the essential oil under assessment in feed.

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

[29]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.

[30]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

Three compounds listed in Table 4, 1(5),11-guaiadiene [01.023], 3,7,10-humulatriene [01.043] and α-muurulene [01.0052], have been evaluated in Flavouring Group Evaluation 25 Revision 2 (FGE.25Rev2) by applying the procedure described in the Guidance on the data required for the risk assessment of flavourings to be used in or on foods (EFSA CEF Panel, 2010). For these compounds, for which there is no concern for genotoxicity, EFSA requested additional subchronic toxicity data (EFSA CEF Panel, 2011b). In the absence of such toxicological data, the CEF Panel was unable to complete its assessment (EFSA CEF Panel, 2015a). As a result, these compounds are no longer authorised for use as flavourings in food. For these compounds, in the absence of toxicity data, the FEEDAP Panel applies the threshold of toxicological concern (TTC) approach or read-across from structurally related substances, as recommended in the Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA SC, 2019a).

Thirty-seven compounds have not been previously assessed for use as flavourings. The FEEDAP Panel notes that 30 of them[31] accounting for 8.0% of the GC-MS area are aliphatic mono- or sesquiterpenes structurally related to flavourings already assessed in chemical groups (CGs) 6, 22, 31 and 32 and for which a similar metabolic and toxicological profile is expected. Because of their lipophilic nature, they are expected to be rapidly absorbed from the gastro-intestinal tract, oxidised to polar oxygenated metabolites, conjugated and excreted (EFSA FEEDAP Panel, 2012b, 2015, 2016, 2017b).

The remaining seven compounds, cubebol, 4-epi-cubebol, (–)-globulol, viridiflorol, ledol, neointermedeol and cubenol, were screened with the Organisation for Economic Co-operation and Development (OECD) QSAR Toolbox. No alert was identified for in vitro mutagenicity, for genotoxic and non-genotoxic carcinogenicity and for other toxicity endpoints for all seven compounds.[32]

3.3.1 | Safety for the target species

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

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

As the additive under assessment is a fully defined mixture (the identified components represent > 99.9% of the % GC area, see Section 3.2.1), the FEEDAP Panel applied a component-based approach to assess the safety for target species of the essential oil.

Based on considerations related to structural and metabolic similarities, the components were allocated to eight assessment groups, corresponding to CGs 6, 8, 10, 16, 22, 23, 31 and 32, as defined in Annex I of Regulation (EC) No 1565/2000.[33] For CG 31 ('aliphatic and aromatic hydrocarbons'), subassessment groups as defined in Flavouring Group Evaluation 25 (FGE.25) and FGE.78 were established (EFSA CEF Panel, 2015a, 2015b). The allocation of the components to the (sub)assessment groups is shown in Table 5 and in the corresponding footnote.

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

For hazard characterisation, each component of an assessment group was first assigned to the structural class according to Cramer classification (Cramer et al., 1978). For some components in the assessment groups, toxicological data were available to derive no observed adverse effect level (NOAEL) values. Structural and metabolic similarity among the components in the assessment groups was assessed to explore the application of read-across, allowing extrapolation from a known NOAEL of a component of an assessment group to the other components of the group with no available NOAEL or, if sufficient evidence were available for members of a (sub)assessment group, to derive a (sub)assessment group NOAEL.

Toxicological data of subchronic studies, from which NOAEL values could be derived, were available for terpineol [02.230][34] and linalool [02.013] in CG 6 (EFSA FEEDAP Panel, 2012b), 1,8-cineole [03.001] in CG 16 (EFSA FEEDAP Panel, 2012c, 2021), cinnamaldehyde [05.014] in CG 22 (EFSA FEEDAP Panel, 2017d), myrcene [01.008], d-limonene [01.045], *p*-cymene [01.002] and β-caryophyllene in CG 31 (EFSA FEEDAP, 2015, 2016), and β-caryophyllene epoxide [16.043] in CG 32 (EFSA CEF Panel, 2014).

[31]β-Eudesmol, δ-terpineol, γ-eudesmol (CG 6); *(Z)*-cinnamaldehyde (CG 22); *trans*-3,7-dimethyl-1,3,6-octatriene, β-elemene, *m*-cymene, 4a,8-dimethyl-2-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalene, alloaromadendrene, α-amorphene, α-cadinene, α-panasinsene, α-ylangene, aromadendrene, β-selinene, δ-amorphene, epi-β-caryophyllene, γ-cadinene, α-muurolene, δ-cadinene, 1(5),11-guaiadiene, α-gurjunene, (4aR,8aS)-4a-methyl-1-methylene-7-(propan-2-ylidene) decahydronaphthalene, β-thujene, germacrene B, isoledene, *m*-xylene, octane, 3,7,10-humulatriene (CG 31); humulene oxide II (CG 32).

[32]Technical dossier/Supplementary information April 2023/Annex VI_SIn_reply_melaleuca_cajuputi_oil_QSAR.

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

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

For benzaldehyde [05.013], a NOAEL of 400 mg/kg bw for benzaldehyde was derived from a 90-day oral toxicity studies with rats (Andersen, 2006). In addition, for benzyl alcohol, the EFSA Panel on Food Additives and Flavourings (FAF) established an acceptable daily intake (ADI) of 4 mg/kg bw based on a NOAEL of 400 mg/kg bw per day from a carcinogenicity study in rats (EFSA FAF Panel, 2019).

For the subgroup of terpinyl derivatives in CG 6, i.e. α-terpineol [02.014], 4-terpinenol [02.072], α-terpinyl acetate [09.015] and δ-terpineol, 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]. The same NOAEL was applied to β-eudesmol, γ-eudesmol, neointermedeol, cubenol, cubebol and 4-epi-cubebol.

Considering the structural and metabolic similarities, the NOAEL of 275 mg/kg bw per day for cinnamaldehyde was applied to *(Z)*-cinnamaldehyde in CG 22.

In CG 23, the NOAEL of 400 mg/kg bw per day of benzyl alcohol [02.010] was applied to 4-isopropylbenzyl alcohol [02.039].

The NOAELs of 44, 250, 154 and 222 mg/kg bw per day for the representative compounds in CG 31, myrcene [01.008], d-limonene [01.045], *p*-cymene [01.002] and β-caryophyllene [01.007] were applied, respectively, using read-across to the compounds within subassessment group II (*trans*-3,7-dimethyl-1,3,6-octatriene), group III (α-phellandrene [01.008], α-terpinene [01.019], γ-terpinene [01.020], terpinolene [01.005] and β-elemene), group IV (*m*-cymene) and group V[35] (EFSA CEF Panel, 2015a,b). Read-across was also applied from β-caryophyllene [01.007] to 3,7,10-humulatriene [01.043] in CG 31, VI. The NOAEL of 222 mg/kg bw per day for β-caryophyllene [01.007] was halved to take into account the uncertainty in read-across (EFSA FEEDAP Panel, 2023b).

The NOAEL of 109 mg/kg bw per day for β-caryophyllene epoxide [16.043] was extrapolated to humulene oxide II in CG 32.

For the remaining compounds,[36] NOAEL values were not available and read-across was not possible. Therefore, the threshold of toxicological concern (TTC) approach was applied (EFSA FEEDAP Panel, 2017b). With the exception of cubenol, which belongs to Cramer Class III, all other compounds belong to Cramer Class I.

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

For risk characterisation, the margin of exposure (MOE) was calculated for each component as the ratio between the reference point and the exposure. For each assessment group, the combined (total) margin of exposure (MOET) was calculated as the reciprocal of the sum of the reciprocals of the MOE of the individual substances (EFSA SC, 2019a). An MOET > 100 allowed for interspecies- and intra-individual variability (as in the default 10 × 10 uncertainty factor). The compounds resulting individually in an MOE > 50,000 were not further considered in the assessment group as their contribution to the MOE(T) is negligible. They are listed in the footnote.[37]

The approach to the safety assessment of cajuput oil for the target species is summarised in Table 5. The calculations were done for chickens for fattening, the species with the highest ratio of feed intake/bw and represent the worst-case scenario at the use level of 50 mg/kg complete feed.

TABLE 5 Compositional data, intake values (calculated for chickens for fattening at 50 mg/kg complete feed), reference points, margin of exposure (MOE) for the individual components of cajuput oil classified according to assessment groups, and combined margin of exposure (MOET) for each assessment group.

Essential oil composition			Exposure		Hazard characterisation		Risk characterisation	
Assessment group	FLAVIS-No	Highest conc. in the oil	Highest feed conc.	Intake[a]	Cramer Class[b]	NOAEL[c]	MOE	MOET
Constituent	–	%	mg/kg	mg/kg bw per day	–	mg/kg bw per day	–	–
CG 6								
α-Terpineol	02.014	9.28	4.640	0.4165	(I)	250	600	
α-Terpinyl acetate	09.015	0.83	0.415	0.0373	(I)	250	6710	
Viridiflorol	02.215	0.67	0.335	0.0301	I	*3*	100	
4-Terpinenol	02.072	0.60	0.300	0.0269	(I)	250	9283	
(–)-Globulol	–	0.26	0.130	0.0117	I	*3*	257	

[35]Compounds in sub-assessment group V in which read-across from β-caryophyllene [01.007] was applied: α-pinene [01.004], β-pinene [01.003], 1(5),11-guaiadiene [01.023], δ-cadinene [01.021], sabinene [01.059], δ-3-carene [01.029], α-muurolene [01.052], camphene [01.009], β-selinene, β-thujene, α-amorphene, δ-amorphene, epi-β-caryophyllene, α-cadinene, isoledene, 4a,8-dimethyl-2-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalene, α-ylangene, aromadendrene, α-panasinsene, γ-cadinene, (4aR,8aS)-4a-methyl-1-methylene-7-(propan-2-ylidene)decahydronaphthalene, alloaromadendrene and α-gurjunene.

[36]Viridiflorol, (–)-globulol and ledol (CG 6); 4-hydroxy-4-methylpentan-2-one (CG 10); octane (CG 31, I); *m*-xylene and 1-isopropenyl-4-methylbenzene (CG 31, IV); germacrene B (CG 31, VI).

[37]δ-Terpineol, γ-eudesmol, cubenol, cubebol, 4-epi-cubebol and neointermedeol (CG 6); *(Z)*-cinnamaldehyde (CG 22); benzaldehyde, 4-isopropylbenzyl alcohol (CG 23); β-elemene (CG 31, III); α-ylangene, aromadendrene, sabinene, α-panasinsene, δ-3-carene, γ-cadinene, (4aR,8aS)-4a-methyl-1-methylene-7-(propan-2-ylidene) decahydronaphthalene, alloaromadendrene, α-gurjunene, α-muurolene, camphene (CG 31, V).

TABLE 5 (Continued)

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**
β-Eudesmol	–	0.20	0.100	0.0090	(I)	250	27,848	
Linalool	02.013	0.19	0.095	0.0085	(I)	**117**	13,719	
Ledol	–	0.06	0.030	0.0027	I	*3*	1114	
MOET CG 6								59
CG 10								
4-Hydroxy-4-methylpentan-2-one	07.165	0.16	0.080	0.0072	I	*3*		418
CG 16								
1,8-Cineole	03.001	63.40	31.70	2.8458	(II)	100		35
CG 31, I								
Octane	–	0.04	0.020	0.0018	I	*3*		1671
CG 31, II								
Myrcene	01.008	0.76	0.380	0.0341	(I)	**44**	1290	
trans-3,7-Dimethyl-1,3,6-octatriene	–	0.10	0.050	0.0045	(I)	44	9803	
MOET CG 31, II								1140
CG 31, III								
d-Limonene	01.045	6.68	1.403	0.1259	(I)	**250**	834	
γ-Terpinene	01.020	3.50	0.171	0.0154	(I)	250	1591	
Terpinolene	01.005	1.42	0.060	0.0054	(I)	250	3922	
α-Terpinene	01.019	0.51	0.173	0.0155	(I)	250	10,921	
α-Phellandrene	01.006	0.22	0.203	0.0182	(I)	250	25,316	
MOET CG 31, III								452
CG 31, IV								
m-Cymene	–	1.56	0.780	0.0700	(I)	154	2199	
m-Xylene	–	0.40	0.200	0.0180	I	*3*	167	
1-Isopropenyl-4-methylbenzene	01.010	0.02	0.010	0.0009	I	*3*	3342	
MOET CG 31, IV								148
CG 31, V								
α-Pinene	01.004	3.94	1.970	0.1769	(I)	222	1255	
β-Caryophyllene	01.007	3.71	1.855	0.1665	(I)	222	1333	
β-Pinene	01.003	1.98	0.990	0.0889	(I)	222	2498	
β-Selinene	–	1.62	0.810	0.0727	(I)	222	3053	
1(5),11-Guaiadiene	01.023	1.31	0.655	0.0588	(I)	222	3775	
β-Thujene	–	0.57	0.285	0.0256	(I)	222	8677	
α-Amorphene	–	0.26	0.130	0.0117	(I)	222	19,022	
δ-Amorphene	–	0.22	0.110	0.0099	(I)	222	22,481	
epi-β-Caryophyllene	–	0.19	0.095	0.0085	(I)	222	26,031	
α-Cadinene	–	0.18	0.090	0.0081	(I)	222	27,477	
Isoledene	–	0.18	0.090	0.0081	(I)	222	27,477	
δ-Cadinene	01.021	0.12	0.060	0.0054	(I)	222	41,215	
4a,8-Dimethyl-2-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalene	–	0.11	0.055	0.0049	(I)	222	44,962	
MOET CG 31, V								344
CG 31, VI								
3,7,10-Humulatriene	01.043	1.80	0.900	0.0808	(I)	111[d]	37	
Germacrene B	–	0.14	0.070	0.0063	I	*3*	477	
MOET CG 31, VI								354

(Continues)

TABLE 5 (Continued)

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**
CG 32								
β-Caryophyllene epoxide	16.043	0.16	0.080	0.0072	(III)	**109**	15,177	
Humulene oxide II	–	0.05	0.025	0.0022	(III)	109	48,567	
MOET CG 32								11,564

[a]Intake calculations for the individual components are based on the use level of 50 mg/kg in feed for chickens for fattening, the species with the highest ratio of feed intake/bw. 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 222 mg/kg bw per day for β-caryophyllene was halved to take into account the uncertainty in read-across.

As shown in Table 5, for chickens for fattening at the proposed use level of 50 mg/kg complete feed an MOE of 35 was calculated for the major component 1,8-cineole in CG 16. From this lowest MOE of 35 for chickens for fattening, the MOE for 1,8-cineole (CG 16) was calculated for the other target species, considering the respective daily feed intake and conditions of use. The results are summarised in Table 6.

TABLE 6 Margin of exposure (MOE) for the assessment group CG 16 calculated for the different target animal categories at the proposed use level and maximum safe use level in feed.

Animal category	Daily feed intake (g DM/kg bw)	Proposed use level (mg/kg complete feed)[a]	Lowest MOE CG 16	Maximum safe use level (mg/kg complete feed)[a]
Chicken for fattening	79	50	35	18
Laying hen	53	50	52	26
Turkey for fattening	59	50	47	23
Pig for fattening	44	50	75	37
Piglet	37	50	63	31
Sow lactating	30	30	154	–
Veal calf (milk replacer)	19	235	31	78
Cattle for fattening	20	150	46	69
Dairy cow	31	50	89	45
Sheep/goat	20	150	46	69
Horse	20	50	138	–
Rabbit	50	50	55	28
Salmon	18	40	192	–
Dog	17	30	271	–
Cat[b]	20	5	1383	–
Ornamental fish	5	50	553	–

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

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

At the proposed use levels in complete feed, the MOE exceeds the value of 100 for sows, horses, salmon, dogs, cats and ornamental fish indicating that the proposed maximum use levels for these species are safe. For the other species, the maximum safe use levels in feed were calculated to ensure an MOET ≥ 100. Because glucuronidation is an important metabolic reaction to facilitate the excretion of the components of the essential oil and considering that cats have an unusually low capacity for glucuronidation (Court & Greenblatt, 1997; Lautz et al., 2021), the use of cajuput oil as an additive in cat feed needs a wider margin of exposure. An MOET of 500 is considered adequate. The maximum use levels proposed by the applicant of 30 mg/kg for sows, 50 mg/kg for horses, 40 mg/kg for salmonids, 30 mg/kg for dogs, 5 mg/kg for cats and 50 mg/kg for ornamental fish are safe. For the other species/categories, the calculated maximum safe levels are shown in Table 6.

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

3.3.1.1 | *Conclusions on safety for the target species*

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

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

Animal categories	Safe concentration (mg/kg complete feed)[a]
Turkeys for fattening	23
Chickens for fattening, other poultry for fattening or reared for laying/reproduction and ornamental birds	18
Laying hens and other laying/reproductive birds	26
Pigs for fattening	37
Piglets and other Suidae species for meat production or reared for reproduction	31
Sows and other Suidae species for reproduction	30
Veal calves (milk replacer)	78
Sheep/goat	69
Cattle for fattening, other ruminants for fattening or reared for milk production/reproduction and camelids at the same physiological stage	69
Dairy cows and other ruminants and camelids for milk production or reproduction	45
Horses and other Equidae	50
Rabbits	28
Salmonids and minor fin fish	40
Dogs	30
Cats	5
Ornamental fish	50
Other species	5

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

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

3.3.2 | Safety for the consumer

Cajuput oil is added to food of different categories for flavouring purposes. Although individual consumption figures are not available, the Fenaroli's handbook of flavour ingredients (Burdock, 2009) estimates daily exposure values of 0.00014 mg/kg per day for cajuput oil from *M. leucadendron* and other *Melaleuca* species. Fenaroli's handbook reports use levels ranging from 0.20 and 9.90 mg/kg in several food categories.

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 4, Section 3.3).

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 cajuput oil are expected to be extensively metabolised and excreted in the target species. For the major component, 1,8-cineole, the available data in laboratory animals and humans indicate that it is absorbed, metabolised by oxidation and excreted and it is not expected to accumulate in animal tissues and products (EFSA FEEDAP Panel, 2012b). The FEEDAP Panel considers that it is unlikely that the consumption of products from animals given cajuput oil at the proposed maximum use level would substantially increase human background exposure. Thus, no safety concern would be expected for the consumer from the use of cajuput oil up to the highest safe use level in feed for the target animals.

3.3.3 | Safety for the user

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

The applicant provided a safety data sheet[38] for cajuput oil, which identified concerns for dermal and eye irritation and dermal and respiratory sensitisation.

[38]Technical dossier/Supplementary information April 2023/Annex VII_SIn_reply_melaleuca_cajuputi_MSDS. Hazard for skin irritation (H315, Category 1), Aspiration hazard (H304, Category 1), May cause an allergic skin reaction (H317), in accordance with the criteria outlined in Annex I of 1272/2008/EC (CLP/EU-GHS).

The applicant made a literature search aimed at retrieving studies related to the safety of preparations obtained from *M. cajuputi* and *M. leucadendra* for users.[39] Seventeen references were found, none of which reported issues for user safety.

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

3.3.4 | Safety for the environment

M. cajuputi and *M. leucadendra* are not species native to Europe. Therefore, the safety for the environment is assessed based on the individual components of the essential oil.

The major components (1,8-cineole, α-terpineol and d-limonene) and 23 additional components (see Table 4) accounting together for about 94% of the % GC area have been evaluated by EFSA as sensory additives for animal feed. The three major components are present at high concentrations in plants native to Europe (EFSA FEEDAP Panel, 2012a, 2012b, 2015). Therefore, no risk to the environment is expected for these compounds from the use of cajuput oil in animal feed. Concerning the other components evaluated as feed additives, they were considered to be safe for the environment at individual use levels higher than those resulting from the use of the essential oil at the maximum safe levels in feed (see Table 4, Section 3.3).

The remaining identified constituents of the essential oil, which were not evaluated for use in feed, are chemically related to the substances evaluated by EFSA in CG 6, 22, 31 and 32 (EFSA FEEDAP Panel, 2012b, 2015, 2016, 2017d), for which EFSA concluded that they were extensively metabolised by the target species (see Section 3.3) and excreted as metabolites or carbon dioxide. Therefore, no risk for the safety for the environment is foreseen.

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

3.4 | Efficacy

Cajuput oil is listed in Fenaroli's Handbook of Flavour Ingredients (Burdock, 2009) and by FEMA with the reference number 2225.

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

4 | CONCLUSIONS

Cajuput oil from the fresh leaves of *Melaleuca cajuputi* Powell and *Melaleuca leucadendra* (L.) L may be produced from plants of different geographical origins, resulting in preparations with different composition and toxicological profiles. Thus, the following conclusions apply only to cajuput oil in which methyleugenol, estragole and safrole are not detected (LOD 0.01 mg/kg), and for which 1,8-cineole, α-terpineol and d-limonene are the main constituents.

The conclusions of the FEEDAP Panel on the safe levels of cajuput oil in complete feed for the respective target species are summarised as follows:

Animal categories	Safe concentration (mg/kg complete feed)[a]
Turkeys for fattening	23
Chickens for fattening, other poultry for fattening or reared for laying/reproduction and ornamental birds	18
Laying hens and other laying/reproductive birds	26
Pigs for fattening	37
Piglets and other Suidae species for meat production or reared for reproduction	31
Sows and other Suidae species for reproduction	30
Veal calves (milk replacer)	78
Sheep/goat	69
Cattle for fattening, other ruminants for fattening or reared for milk production/reproduction and camelids at the same physiological stage	69
Dairy cows and other ruminants and camelids for milk production or reproduction	45
Horses and other Equidae	50
Rabbits	28

[39]Technical dossier/Supplementary information January 2023/Literature search_melaleuca_cajuputi oil.

Animal categories	Safe concentration (mg/kg complete feed)[a]
Salmonids and minor fin fish	40
Dogs	30
Cats	5
Ornamental fish	50
Other species	5

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

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

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

Cajuput oil should be considered as an irritant to skin and eyes, and as a dermal and respiratory sensitiser.

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

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

5 | RECOMMENDATION

The specification should ensure that methyleugenol, estragole and safrole are not detected (LOD 0.01 mg/kg) in cajuput oil from *Melaleuca cajuputi* Powell and *Melaleuca leucadendra* (L.) L.

6 | DOCUMENTATION PROVIDED TO EFSA/CHRONOLOGY

Date	Event
28/10/2010	Dossier received by EFSA. Botanically defined flavourings from Botanical Group 07 – Geraniale, Myrtales, Poales for all animal species and categories. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)
09/11/2010	Reception mandate from the European Commission
21/12/2010	Application validated by EFSA – Start of the scientific assessment
22/03/2011	Comments received from Member States
01/04/2011	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: analytical methods*
08/01/2013	Reception of supplementary information from the applicant – Scientific assessment remains suspended
26/02/2013	EFSA informed the applicant (EFSA ref. 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
20/01/2014	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
27/02/2019	Partial withdrawal by applicant (EC was informed) for the following additive: broom teatree oil, geranium oil, bay oil and vetiveria oil
12/12/2019	EFSA informed the applicant that the evaluation process restarted
18/12/2019	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*
18/11/2022	Partial withdrawal by applicant (EC was informed) for the following additive: bambusa tincture and allspice oil
14/04/2023	Reception of supplementary information from the applicant (partial dataset: melaleuca cajuputi oil) – Scientific assessment remains suspended
06/06/2023	Reception of an amendment of the Evaluation report of the European Union Reference Laboratory for Feed Additives related to geranium rose oil, eucalyptus oil, lemongrass oil and clove oil
28/02/2024	The application was split and a new EFSA-Q-2024-00118 was assigned to the additive included in the present assessment. Scientific assessment re-started for the additive included in the present assessment
01/03/2024	Reception of an amendment of the Evaluation report of the European Union Reference Laboratory for Feed Additives related to citronella oil, melaleuca oil, tea tree oil, eucalyptus tincture, clove tincture
13/03/2024	Opinion adopted by the FEEDAP Panel on melaleuca cajuputi oil (EFSA-Q-2024-00118). End of the Scientific assessment for the additive included in the present assessment. The assessment of other additives in BGD 07 is still ongoing

ABBREVIATIONS

ADI	acceptable daily intake
BDG	botanically defined group
bw	body weight
CAS	Chemical Abstracts Service
CDG	chemically defined group
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CG	chemical group
DM	dry matter
EEIG	European Economic Interest Grouping
EINECS	European Inventory of Existing Chemical Substances
EURL	European Union Reference Laboratory
FAF	EFSA Scientific Panel on Food Additives and Flavourings
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 with flame ionisation detection
GC-MS	gas chromatography-mass spectrometry
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LOD	limit of detection
MOE	margin of exposure
MOET	combined margin of exposure
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
QSAR	Quantitative Structure Activity Relationship
SC	EFSA Scientific Committee
TTC	threshold of toxicological concern
UF	uncertainty factor
WHO	World Health Organization

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CONFLICT OF INTEREST

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

REQUESTOR

European Commission

QUESTION NUMBER

EFSA-Q-2010-01282 (new EFSA-Q-2024-00118)

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REFERENCES

Andersen, A. (2006). Final report on the safety assessment of benzaldehyde. *International Journal of Toxicology*, *25*(Suppl 1), 11–27. https://doi.org/10.1080/10915810600716612

Brophy, J. J. (1999). *Potentially commercial Melaleucas*. https://doi.org/10.4324/9780203303603_CHAPTER_16

Burdock, G. A. (2009). *Fenaroli's handbook of flavor ingredients* (6th ed., p. 736). CRC press. Taylor & Francis Group. https://doi.org/10.1201/9781439847503

Carson, C. F., & Riley, T. V. (2001). Safety, efficacy and provenance of tea tree (*Melaleuca alternifolia*) oil. *Contact Dermatitis*, *45*, 65–67. https://doi.org/10.1034/j.1600-0536.2001.045002065.x

Court, M. H., & Greenblatt, D. J. (1997). Molecular basis for deficient acetaminophen glucuronidation in cats. An interspecies comparison of enzyme kinetics in liver microsomes. *Biochemical Pharmacology*, *53*, 1041–1047. https://doi.org/10.1016/s0006-2952(97)00072-5

Cramer, G. M., Ford, R. A., & Hall, R. L. (1978). Estimation of toxic hazard–a decision tree approach. *Food and Cosmetics Toxicology*, *16*, 255–276. https://doi.org/10.1016/s0015-6264(76)80522-6

EFSA (European Food Safety Authority). (2012). Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements. *EFSA Journal*, *10*(5), 2663. https://doi.org/10.2903/j.efsa.2012.2663

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids). (2010). Guidance on the data required for the risk assessment of flavourings to be used in or on foods. *EFSA Journal*, *8*(6), 1623. https://doi.org/10.2093/j.efsa.2010.1623

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids). (2011a). Scientific opinion on Flavouring Group Evaluation 11, Revision 2 (FGE.11Rev2): Aliphatic dialcohols, diketones, and hydroxyketones from chemical groups 8 and 10. *EFSA Journal*, *9*(2), 1170. https://doi.org/10.2903/j.efsa.2011.1170

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids). (2011b). Scientific opinion on Flavouring Group Evaluation 25, Revision 2 (FGE.25Rev2): Aliphatic hydrocarbons from chemical group 31. *EFSA Journal*, *9*(6), 2177. https://doi.org/10.2903/j.efsa.2011.2177

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids). (2014). Scientific opinion on Flavouring Group Evaluation 82, Revision 1 (FGE.82Rev1): Consideration of epoxides evaluated by the JECFA (65th meeting). *EFSA Journal*, *12*(6), 3708. https://doi.org/10.2903/j.efsa.2014.3708

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids). (2015a). Scientific opinion on Flavouring Group Evaluation 25, Revision 3 (FGE.25Rev3): Aliphatic hydrocarbons from chemical group 31. *EFSA Journal*, *13*(4), 4069. https://doi.org/10.2903/j.efsa.2015.4069

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids). (2015b). Scientific opinion on Flavouring Group Evaluation 78, Revision 2 (FGE.78Rev2): Consideration of aliphatic and alicyclic and aromatic hydrocarbons evaluated by JECFA (63rd meeting) structurally related to aliphatic hydrocarbons evaluated by EFSA in FGE.25Rev3. *EFSA Journal*, *13*(4), 4067. https://doi.org/10.2903/j.efsa.2015.4067

EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes, M., Aquilina, G., Castle, L., Engel, K.-H., Fowler, P., Fürst, P., Gürtler, R., Gundert-Remy, U., Husøy, T., Mennes, W., Moldeus, P., Oskarsson, A., Shah, R., Waalkens-Berendsen, I., Wölfle, D., Boon, P., Crebelli, R., Di Domenico, A., … Frutos Fernandez, M. J. (2019). Scientific opinion on the re-evaluation of benzyl alcohol (E 1519) as food additive. *EFSA Journal*, *17*(10), 5876. https://doi.org/10.2903/j.efsa.2019.5876

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2012a). Guidance for the preparation of dossiers for sensory additives. *EFSA Journal*, *10*(1), 2534. https://doi.org/10.2903/j.efsa.2012.2534

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2012b). Scientific opinion on the safety and efficacy of aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters with esters containing tertiary alcohols ethers (chemical group 6) when used as flavourings for all animal species. *EFSA Journal*, *10*(11), 2966. https://doi.org/10.2903/j.efsa.2012.2966

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2012c). Scientific opinion on the safety and efficacy of aliphatic and alicyclic ethers (chemical group 16) when used as flavourings for all animal species. *EFSA Journal*, *10*(11), 2967. https://doi.org/10.2903/j.efsa.2012.2967

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2012d). Scientific opinion on the safety and efficacy of benzyl alcohols, aldehydes, acids, esters and acetals (chemical group 23) when used as flavourings for all animal species. *EFSA Journal*, *10*(7), 2785. https://doi.org/10.2903/j.efsa.2012.2785

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2015). Scientific opinion on the safety and efficacy of aliphatic and aromatic hydrocarbons (chemical group 31) when used as flavourings for all animal species. *EFSA Journal*, *13*(3), 4053. https://doi.org/10.2903/j.efsa.2015.4053

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2016). Scientific opinion on the safety and efficacy of aliphatic and aromatic hydrocarbons (chemical group 31) when used as flavourings for all animal species and categories. *EFSA Journal*, *14*(1), 4339. https://doi.org/10.2903/j.efsa.2016.4339

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen, G., Aquilina, G., Azimonti, G., Bampidis, V., Bastos, M. L., Bories, G., Chesson, A., Cocconcelli, P. S., Flachowsky, G., Gropp, J., Kolar, B., Kouba, M., López-Alonso, M., López Puente, S., Mantovani, A., Mayo, B., Ramos, F., Saarela, M., … Innocenti, M. L. (2017a). Guidance on the identity, characterisation and conditions of use of feed additives. *EFSA Journal*, *15*(10), 5023. https://doi.org/10.2903/j.efsa.2017.5023

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen, G., Aquilina, G., Azimonti, G., Bampidis, V., Bastos, M. L., Bories, G., Chesson, A., Cocconcelli, P. S., Flachowsky, G., Gropp, J., Kolar, B., Kouba, M., López-Alonso, M., López Puente, S., Mantovani, A., Mayo, B., Ramos, F., Saarela, M., … Martino, L. (2017b). Guidance on the assessment of the safety of feed additives for the target species. *EFSA Journal*, *15*(10), 5021. https://doi.org/10.2903/j.efsa.2017.5021

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen, G., Aquilina, G., Azimonti, G., Bampidis, V., Bastos, M. L., Bories, G., Chesson, A., Cocconcelli, P. S., Flachowsky, G., Gropp, J., Kolar, B., Kouba, M., López-Alonso, M., López Puente, S., Mantovani, A., Mayo, B., Ramos, F., Saarela, M., … Innocenti, M. L. (2017c). Guidance on the assessment of the safety of feed additives for the consumer. *EFSA Journal*, *15*(10), 5022. https://doi.org/10.2903/j.efsa.2017.5022

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen, G., Aquilina, G., Azimonti, G., Bampidis, V., Bastos, M. L., Bories, G., Cocconcelli, P. S., Flachowsky, G., Gropp, J., Kolar, B., Kouba, M., López Puente, S., López-Alonso, M., Mantovani, A., Mayo, B., Ramos, F., Saarela, M., Villa, R. E., … Chesson, A. (2017d). Scientific opinion on the safety and efficacy of aryl-substituted primary alcohol, aldehyde, acid, ester and acetal derivatives belonging to chemical group 22 when used as flavourings for all animal species. *EFSA Journal*, *15*(2), 4672 10.2903/j.efsa.2017.4672.

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen, G., Aquilina, G., Azimonti, G., Bampidis, V., Bastos, M. L., Bories, G., Chesson, A., Cocconcelli, P. S., Flachowsky, G., Gropp, J., Kolar, B., Kouba, M., López-Alonso, M., López Puente, S., Mantovani, A., Mayo, B., Ramos, F., Saarela, M., … Martino, L. (2018). Guidance on the assessment of the efficacy of feed additives. *EFSA Journal*, *16*(5), 5274. https://doi.org/10.2903/j.efsa.2018.5274

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis, V., Bastos, M., Christensen, H., Dusemund, B., Kouba, M., Kos Durjava, M., López-Alonso, M., López Puente, S., Marcon, F., Mayo, B., Pechová, A., Petkova, M., Ramos, F., Sanz, Y., Villa, R. E., Woutersen, R., Brock, T., de Knecht, J., … Azimonti, G. (2019). Guidance on the assessment of the safety of feed additives for the environment. *EFSA Journal*, *17*(4), 5648. https://doi.org/10.2903/j.efsa.2019.5648

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). (2021). Scientific opinion on the safety and efficacy of feed additives consisting of expressed lemon oil and its fractions from *Citrus limon* (L.) Osbeck and of lime oil from *Citrus aurantiifolia* (Christm.) Swingle for use in all animal species. *EFSA Journal*, *19*(4), 6548. https://doi.org/10.2903/j.efsa.2021.6548

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis, V., Azimonti, G., Bastos, M. L., Christensen, H., Durjava, M., Dusemund, B., Kouba, M., López-Alonso, M., López Puente, S., Marcon, F., Mayo, B., Pechová, A., Petkova, M., Ramos, F., Villa, R. E., Woutersen, R., Brantom, P., Chesson, A., … Galobart, J. (2023a). Guidance on the assessment of the safety of feed additives for the users. *EFSA Journal*, *21*(12), e8469.

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis, V., Azimonti, G., Bastos, M. L., Christensen, H., Durjava, M., Kouba, M., López-Alonso, M., López Puente, S., Marcon, F., Mayo, B., Pechová, A., Petkova, M., Ramos, F., Sanz, Y., Villa, R. E., Woutersen, R., Brantom, P., Chesson, A., … Dusemund, B. (2023b). Safety and efficacy of feed additives consisting of essential oils derived from the flower buds or the leaves of *Syzygium aromaticum* (L.) Merr. & L.M. Perry (clove bud oil and clove leaf oils) for all animal species (FEFANA asbl). *EFSA Journal*, *21*(7), 1–43. https://doi.org/10.2903/j.efsa.2023.8183

EFSA SC (EFSA Scientific Committee). (2009). Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. *EFSA Journal*, *7*(9), 1249. https://doi.org/10.2093/j.efsa.2009.1249

EFSA SC (EFSA Scientific Committee), More, S. J., Hardy, A., Bampidis, V., Benford, D., Bennekou, S. H., Bragard, C., Boesten, J., Halldorsson, T. I., Hernandez-Jerez, A. F., Jeger, M. J., Knutsen, H. K., Koutsoumanis, K. P., Naegeli, H., Noteborn, H., Ockleford, C., Ricci, A., Rychen, G., Schlatter, J. R., … Hogstrand, C. (2019a). Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. *EFSA Journal*, *17*(3), 5634. https://doi.org/10.2903/j.efsa.2019.5634

EFSA SC (EFSA Scientific Committee), More, S., Bampidis, V., Benford, D., Boesten, J., Bragard, C., Halldorsson, T., Hernandez-Jerez, A., Hougaard-Bennekou, S., Koutsoumanis, K., Naegeli, H., Nielsen, S. S., Schrenk, D., Silano, V., Turck, D., Younes, M., Aquilina, G., Crebelli, R., Gürtler, R., … Schlatter, J. (2019b). Statement on the genotoxicity assessment of chemical mixtures. *EFSA Journal*, *17*(1), 5519. https://doi.org/10.2903/j.efsa.2019.5519

EFSA SC (EFSA Scientific Committee), More, S. J., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T. I., Hernandez-Jerez, A. F., Hougaard, B. S., Koutsoumanis, K. P., Machera, K., Naegeli, H., Nielsen, S. S., Schlatter, J. R., Schrenk, D., Silano, V., Turck, D., Younes, M., Gundert-Remy, U., Kass, G. E. N., … Wallace, H. M. (2019c). Guidance on the use of the threshold of toxicological concern approach in food safety assessment. *EFSA Journal*, *17*(6), 5708. https://doi.org/10.2903/j.efsa.2019.5708

Farag, R. S., Shalaby, A. S., El-Baroty, G. A., Ibrahim, N. A., Ali, M. A., & Hassan, E. M. (2004). Chemical and biological evaluation of the essential oils of different Melaleuca species. *Phytotherapy Research*, *18*(1), 30–35. https://doi.org/10.1002/ptr.1348

Lautz, L. S., Jeddi, M. Z., Girolami, F., Nebbia, C., & Dorne, J. L. C. M. (2021). Metabolism and pharmacokinetics of pharmaceuticals in cats (*Felix sylvestris* catus) and implications for the risk assessment of feed additives and contaminants. *Toxicology Letters*, *338*, 114–127. https://doi.org/10.1016/j.toxlet.2020.11.014

Monzote, L., Scherbakov, A. M., Scull, R., Satyal, P., Cos, P., Shchekotikhin, A. E., Gille, L., & Setzer, W. N. (2020). Essential oil from *Melaleuca leucadendra*: Antimicrobial, antikinetoplastid, antiproliferative and cytotoxic assessment. *Molecules*, *25*, 5514. https://doi.org/10.3390/molecules25235514

Munro, I. C., Ford, R. A., Kennepohl, E., & Sprenger, J. G. (1996). Correlation of structural class with no-observed-effect levels: A proposal for establishing a threshold of concern. *Food and Chemical Toxicology*, *34*, 829–867. https://doi.org/10.1016/s0278-6915(96)00049-x

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