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SCIENTIFIC OPINION

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Safety and efficacy of a feed additive consisting of an essential oil derived from the aerial parts of *Mentha × piperita* L. (peppermint oil) for use in all animal species (FEFANA asbl)

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The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts

Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of an essential oil from the aerial parts of *Mentha × piperita* L. (peppermint oil) when used as a sensory additive in feed and in water for drinking for all animal species. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concluded that that peppermint oil is safe for all animal species at the maximum use level of 12 mg/kg complete feed. The FEEDAP Panel considered that the use of peppermint oil in water for drinking is safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed. No concerns for consumers and the environment were identified following the use of the additive up to the maximum proposed use level in feed. Regarding user safety, the essential oil under assessment should be considered as an irritant to skin and eyes and as a dermal and respiratory.

KEYWORDS

efficacy, flavouring compounds, *Mentha × piperita* L., menthol, menthone, peppermint oil, 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 the Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)[2] for authorisation/re-evaluation of 41 additives (king of bitter extract, thyme leaved gratiola tincture, devils claw extract, devils claw tincture, lavender oil, lavender tincture, spike lavender oil, melissa oil, balm leaves extract, mentha arvensis/corn mint oil, pennyroyal oil, spearmint oil, peppermint oil, peppermint tincture, basil oil, basil tincture, olive extract, marjoram oil, oregano oil, oregano tincture, patchouli oil, rosemary oil, rosemary oleoresin, rosemary extract, rosemary tincture, Spanish sage oil, sage oil, sage tincture, clary sage oil, savoury summer oil, savoury summer tincture, Pau darco tincture, thymus origanum oil, thyme oil, thyme oleoresin, thyme extract, thyme tincture, lilac chastetree extract, lilac chastetree tincture, Spanish marjoram oil and wild thyme tincture) belonging to botanically defined group (BDG) 01 – Lamiales, when used as a feed additive for all animal species (category: sensory additives; functional group: flavouring compounds). During the assessment, the applicant withdrew the applications for nine additives.[3] These additives were deleted from the register of feed additives.[4] In addition, during the course of the assessment, the application was split and the present opinion covers only one out of the remaining 32 additives under application: peppermint oil from *Mentha* × *piperita* L.[5] for use in all animal species.

The remaining 31 additives belonging to botanically defined group (BDG) 01 – Lamiales, under application are assessed in separate opinions.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority deleted (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 1 June 2011.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the feed additive consisting of peppermint oil from *Mentha* × *piperita* (aerial parts), when used under the proposed conditions of use (see Section 3.3.3).

1.2 | Additional information

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

2 | DATA AND METHODOLOGIES

2.1 | Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[6] in support of the authorisation request for the use of peppermint oil from *Mentha* × *piperita* as a feed additive. The dossier was received on 19 June 2024 and the general information and supporting documentation is available at https://open.efsa.europa.eu/questions/EFSA-Q-2024-00405.[7]

[1]Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2]On 13/03/2013, EFSA was informed by the applicant that the applicant company changed to FEFANA asbl, Avenue Louise 130 A, Box 1, 1050 Brussels, Belgium.
[3]Thyme leaves gratiola tincture, spike lavender oil, melissa oil, pennyroyal oil, basil oil and savoury summer oil (27 February 2019); Spanish majoram oil (28 September 2023); lilac chastetree extract and savoury summer tincture (8 July 2024).
[4]Register of feed additives, Annex II, withdrawn by OJ L162, 10.05.2021, p. 5.
[5]Accepted name: *Mentha* × *piperita* L., basionym *M. aquatica* × *M. spicata* L.
[6]Dossier reference: FAD-2010-0137.
[7]The original application EFSA-Q-2010-0137 was split on 19/06/2024 and a new EFSA-Q-2024-00405 was generated.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers, other scientific reports and experts' knowledge, to deliver the present output.

Many of the components of the essential oil under assessment have been already evaluated by the FEEDAP Panel as chemically defined flavourings (CDGs). The applicant submitted a written agreement to reuse the data submitted for the assessment of chemically defined flavourings (dossiers, publications and unpublished reports) for the risk assessment of additives belonging to BDG 01, including the current one under assessment.[8]

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the phytochemical markers in the additive. The evaluation report is related to the methods of analysis for each feed additive included in the group BDG 01 – Lamiales. During the assessment, upon request of EFSA, the EURL issued a partial report,[9] which included the additive under assessment. In particular, the EURL recommended a method based on gas chromatography with flame ionisation detection (GC-FID) for the quantification of the phytochemical markers *menthol* and *menthone* in *peppermint oil*.[10]

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of peppermint oil from *Mentha* × *piperita* is in line with the principles laid down in Regulation (EC) No 429/2008[11] and the relevant guidance documents: Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA Scientific Committee, 2009), Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements (EFSA, 2012), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a), Guidance on the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017c), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018), Guidance on the assessment of the safety of feed additives for the users (EFSA FEEDAP Panel, 2023), Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019), Statement on the genotoxicity assessment of chemical mixtures (EFSA Scientific Committee, 2019), Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (EFSA Scientific Committee, 2019).

3 | ASSESSMENT

The additive under assessment, peppermint oil, is an essential oil obtained from the aerial parts of *Mentha* × *piperita* 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

Mentha × *piperita* L., commonly referred to as peppermint, is a perennial herb belonging to the Lamiaceae family. It is a sterile hybrid resulting from a cross between *Mentha aquatica* L. (watermint) and *Mentha spicata* L. (common mint, spearmint), which is itself a hybrid. Both parents are native to Europe and widely distributed. *Mentha* × *piperita* was not recognised until 1696, but due to its perceived culinary and medicinal value, has been extensively propagated by vegetative means and is now found worldwide. It should be noted that plant sources described as Chinese or Japanese mint/peppermint and the essential oils obtained from the aerial parts of such plants are different species (*Mentha arvensis* L. or *Mentha canadensis* L.).

The additive is extracted from the aerial parts (the leaves with or without the flowers) of *Mentha* × *piperita* L. by steam distillation. The volatile constituents are condensed and then separated from the aqueous phase by decantation.

[8]Technical dossier/Supplementary information August 2024/Letter dated 27/08/2024.

[9]Additives included in the partial report: Spanish sage oil, peppermint oil, thymus origanum oil, patchouli oil, clary sage oil, lavender oil and sage oil.

[10]Evaluation report available on the EU Science Hub https://joint-research-centre.ec.europa.eu/eurl-fa-eurl-feed-additives/eurl-fa-authorisation/eurl-fa-evaluation-reports_en.

[11]Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

3.2 | Uses other than feed flavouring

There is no specific EU authorisation for any *Mentha* × *piperita* preparation when used to provide flavour in food. However, according to Regulation (EC) No 1334/2008[12] flavouring preparations produced from food, may be used without an evaluation and approval as long as 'they do not, on the basis of the scientific evidence available, pose a safety risk to the health of the consumer, and their use does not mislead the consumer.'

'Peppermint leaf (Menthae piperitae folium)' and 'Peppermint oil (Menthae piperitae aetheroleum)' from *Mentha*× *piperita* L. are described in monographs of the European Pharmacopoeia 11.0 (PhEur, 2022a, 2022b) and of the European Medicines Agency (EMA, 2020a, 2020b, 2020c, 2020d, 2020e) for medicinal uses.

3.3 | Characterisation

3.3.1 | Characterisation of peppermint oil

The essential oil is obtained from the aerial parts of *Mentha* × *piperita* L. sourced from the USA and India and is a clear, almost colourless to pale yellow, mobile liquid with a characteristic minty, sweet odour. Peppermint oil is identified with the single Chemical Abstracts Service (CAS) number 8006-90-4, the European Inventory of Existing Commercial Chemical Substances (EINECS) number 308-770-2, the Flavor Extract Manufacturers Association (FEMA) number 2848 and the Council of Europe (CoE) number 282. In 10 batches of the additive, the refractive index (20°C) fell within the range of 1.457–1.461. In eight batches the density (20°C) ranged between 902 and 904 kg/m^3, and the optical rotation (20°C) between –25.72° and –24.96°.[13]

For peppermint oil, the specifications used by the applicant are based on the standard developed by the International Organisation for Standardization (ISO) 856:2006 for oil of peppermint (*Mentha* × *piperita* L.),[14] which were adapted to reflect the concentrations of selected volatile components. Five components contribute to the specifications as shown in Table 1, with menthol and menthone selected as the phytochemical markers. Analysis of 10 batches of the additive showed compliance with the specifications when analysed by GC-FID and expressed as percentage of gas chromatographic peak area (% GC area).[15]

TABLE 1 Constituents of peppermint oil defined by specifications, and batch to batch variation based on the analysis of 10 batches by gas chromatography with flame ionisation detector (GC-FID). The content of each constituent is expressed as the area per cent of the corresponding chromatographic peak (% GC area), assuming the sum of chromatographic areas of all detected peaks as 100%.

Constituent			% GC area		
EU register name	**CAS no**	**FLAVIS no**	**Specifications[1]**	**Mean**	**Range**
Menthol[2]	89-78-1	02.015	30–55	43.42	42.51–45.54
Menthone[3]	10458-14-7	07.059	13–32	21.62	17.49–24.32
d,l-Isomenthone[4]	491-07-6	07.078	1.5–10	6.35	6.21–6.50
Menthyl acetate[5]	16409-45-3	09.016	2–10	3.61	3.61–6.30
1,8-Cineole	470-83-6	03.001	2–8	4.27	2.40–5.27
Total				75.5[6]	71.8–80.5[7]

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

[1]Specification defined based on GC-FID analysis.

[2]Menthol [02.105]: The stereochemistry is not specified but the analytical data provided refer to (–)-menthol (= *l*-menthol) which is the natural one (EFSA FEEDAP Panel, 2016b). The same FLAVIS number [02.015] can be used to identify the racemate *d,l*-menthol and its isomeric forms (EFSA FEEDAP Panel, 2020).

[3]*p*-Menthan-3-one (menthone): The stereochemistry of menthone [07.059] is not specified. EFSA evaluated a mixture of four diastereoisomers: (+)-menthone and (–)-menthone (in *trans*-configuration [07.176]) in co-occurrence with their two diastereoisomers (+)-isomenthone and (–)-isomenthone (in *cis*-configuration [07.078]), the mixture containing approximately 25% of each (EFSA CEF Panel, 2012).

[4]*d,l*-Isomenthone [07.078]: mixture of two stereoisomers (+)-isomenthone and (–)-isomenthone in *cis*-configuration.

[5]Stereochemistry not indicated.

[6]The value given for the Total (mean) is the mean of the sum of the constituents in the individual batches analysed.

[7]The values given for the Total (range) are the lowest and the highest values of the sum of the constituents in the individual batches analysed.

[12]Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Regulation (EC) No 1601/91 of the Council, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34.

[13]Technical dossier/Supplementary information May 2023/ Annex_II_SIn_reply_peppermint_oil_CoAs_chromatograms.

[14]Technical dossier/Supplementary information May 2023/ Annex_V_SIn_reply_peppermint_oil_ISO.

[15]Technical dossier/Supplementary information May 2023/Annex_III_Sin_reply_peppermint_oi_composition.

The applicant provided a full analysis of the same 10 batches by gas chromatography–mass spectrometry (GC–MS).[16] In total, up to 117 peaks were detected in the chromatograms, all of which were identified and accounted for on average of 99.6% (99.2%–99.9%) of the % GC area. The five specified compounds accounted on average for 75.3% (range 72.0%–79.6%) of the % GC area when measured with GC–MS (Table 2). In addition to the five compounds indicated in the product specifications, 23 compounds were detected at individual levels of >0.2% and are also listed in Table 2. These 28 compounds together accounted on average for 96.2% (range 95.6%–97.6%) of the % GC area. The remaining 89 compounds (ranging between 0.2% and 0.002%), accounting for 3.4% of the GC area are listed in the footnote.[17] Based on these data, peppermint oil is considered a fully defined mixture (EFSA Scientific Committee, 2019).

TABLE 2 Constituents of peppermint oil accounting for >0.2% of the composition: Batch to batch variation based on the analysis of 10 batches by gas chromatography–mass spectrometry (GC–MS). The content of each constituent is expressed as the area per cent of the corresponding chromatographic peak (% GC area), assuming the sum of chromatographic areas of all detected peaks as 100%.

Constituent			% GC area	
EU register name	**CAS no**	**FLAVIS no**	**Mean**	**Range**
Menthol[1]	89-78-1	02.015	37.99	35.64–45.80
Menthone[2]	10458-14-7	07.059	21.60	18.22–24.18
d,l-Isomenthone[3]	491-07-6	07.078	3.81	2.99–6.18
Menthyl acetate[4]	16409-45-3	09.016	6.71	4.50–8.58
1,8-Cineole	470-82-6	03.001	5.17	2.49–6.36
Neomenthol[4]	491-01-0	–	3.51	3.11–3.99
Menthofuran[5]	494-90-6	13.035	3.31	2.29–4.54
β-Caryophyllene	87-44-5	01.007	2.70	0.67–3.62
d-Limonene[6]	5989-27-5	01.045	2.37	1.70–3.23
Pulegone[5]	89-82-7	–	1.28	0.48–1.72
β-Pinene (pin-2(10)-ene)	127-91-3	01.003	1.08	0.92–1.17
Germacra-1(10),4(14),5-triene	23986-74-5	01.042	0.88	0.09–1.96
α-Pinene (pin-2(3)-ene)	80-56-8	01.004	0.78	0.64–0.93
p-Menth-1-en-3-one	89-81-6	07.175	0.77	0.48–1.13
4-Terpinenol	562-74-3	02.072	0.53	0.35–0.76
Neoisomenthol[4]	491-02-1	–	0.51	0.16–0.79
trans-Sabinene hydrate	17699-16-0	–	0.41	0.02–1.11
Sabinene (4(10)-thujene)	3387-41-5	01.059	0.39	0.30–0.46
α-Terpineol	98-55-5	02.014	0.38	0.20–0.54
Isomenthol	490-99-3	–	0.36	0.18–0.80
β-Bourbonene	5208-59-3	01.024	0.33	0.17–0.44
γ-Terpinene	99-85-4	01.020	0.28	0.04–0.60
Isopulegol	89-79-2	02.067	0.27	0.12–0.67
trans-3(10)-Caren-2-ol	–	–	0.25	0.21–0.30
Octan-3-ol	589-98-0	02.098	0.24	0.12–0.36
Bicyclogermacrene	67650-90-2	–	0.23	0.09–0.41
Neomenthyl acetate	2230-87-7	–	0.22	0.05–0.47

[16]Technical dossier/Supplementary information May 2023/Annex_VII_Sin_reply_peppermint_oil_safety_target_species.

[17]Additional constituents: constituents ($n=30$) between <0.2% and ≥0.05%: linalool, myrcene, dihydroterpineol, δ-terpineol, 1-isopropyl-4-methylbenzene (*p*-cymene), α-terpinene, isomenthyl acetate, β-farnesene, β-elemene, decan-1-ol, *cis*-3,7-dimethyl-1,3,6-octatriene (*cis*-β-ocimene), β-cubebene, isocaryophyllene-5,6-epoxide, viridiflorol, 3-methylcyclohexanone, terpinolene, 2-*tert*-butylcyclohexanone, 4-hydroxy-menthone, carvone (stereochemistry not indicated), bicycloelemene, camphene, β-caryophyllene epoxide, 3-methylbutyl 3-methylbutyrate, octan-1-ol, thymol, δ-cadinene, oct-1-en-3-ol, α-copaene, 2-methylbutyl isovalerate, 3-octyl acetate, *cis*-p-2-menthen-1-ol; constituents ($n=30$) between <0.05% and ≥0.002%: 2-methylbutyl 2-methylbutyrate, longifolene, citronellol, myrtenol, dihydroedulan II, α-ylangene, *trans*-3,7-dimethyl-1,3,6-octatriene (*trans*-β-ocimene), γ-muurolene, *trans*-carveol,α-cubebene, *cis*-3-hexenyl isovalerate, pseudolimonene, 4-hydroxy-4-methylpentan-2-one, α-phellandrene, octan-3-one, α-thujene, *p*-mentha-3,8-diene, p-mentha-1,8(10)-dien-9-yl acetate, *1R,2S,5R*-isopulegyl acetate, hex-2*(trans)*-enal, *trans*-1-methyl-4-(1-methylvinyl)cyclohex-2-en-1-ol, β-copaene, para-3-menthene, *(E)*-α-bergamotene, cyclosativene, 3-methyl-cyclohexanol, menthofurolactone, 2,5-diethyltetrahydrofuran, nonan-3-ol, alloaromadendrene; constituents ($n=28$) between <0.02% and ≥0.002%: isothujol, α-muurolene, hex-3*(cis)*-en-1-ol, isocaryophyllene, aromadendrene, linalool oxide, eugenol, γ-cadinene, *(E)*-2-hexen-1-ol, carvenone, carvotan acetone, β-thujone, *p*-mentha-1,4(8)-dien-3-one, tetrahydrolinalool, 2-phenylethan-1-ol, hexan-1-ol, 3-methyl-2(pent-2-enyl)cyclopent-2-en-1-one, δ-3-carene, *p*-1-menthene, oct-1-en-3-yl-acetate, spathulenol, β-terpinyl acetate, 2,4-thujadiene, mint sulfide, benzaldehyde, 2,6-dimethylocta-2,4,6-triene, 3-methylcyclohex-2-en-1-one, heptan-3-ol.

TABLE 2 (Continued)

Constituent			% GC area	
EU register name	**CAS no**	**FLAVIS no**	**Mean**	**Range**
3,7,10-Humulatriene	6753-98-6	01.043	0.21	0.07–0.38
Total			96.2[7]	95.6–97.4[8]

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

[1]Menthol [02.105]: The stereochemistry is not specified but the analytical data provided refer to (–)-menthol (= *l*-menthol) which is the natural one (EFSA FEEDAP Panel, 2016b). The same FLAVIS number [02.015] can be used to identify the racemate *d,l*-menthol and its isomeric forms (EFSA FEEDAP Panel, 2020).

[2]*p*-Menthan-3-one (menthone): The stereochemistry of menthone [07.059] is not specified. EFSA evaluated a mixture of four diastereoisomers, (+)-menthone and (–)-menthone (in *trans*-configuration [07.176]) in co-occurrence with their two diastereoisomers (+)-isomenthone and (–)-isomenthone (in *cis*-configuration [07.078]), the mixture containing approximately 25% of each (EFSA CEF Panel, 2012).

[3]*d,l*-Isomenthone [07.078]: two diastereoisomers (+)-isomenthone and (–)-isomenthone in *cis*-configuration.

[4]Stereochemistry not indicated.

[5]Substance which shall not be added as such to food (Annex III), maximum level in food is set by Regulation (EC) No 1334/2008, including dairy products (20 mg/kg), meat products (15 mg/kg), fish products (10 mg/kg), soups and sauces (60 mg/kg), ready-to eat savouries (20 mg/kg) and non-alcoholic beverages (1 mg/kg).

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

[7]The value given for the Total (mean) is the mean of the sum of the constituents in the individual batches analysed.

[8]The values given for the Total (range) are the lowest and the highest values of the sum of the constituents in the individual batches analysed.

The applicant carried out an extensive database search (no time limits) to identify data related to the chemical composition and the safety of preparations obtained from *Mentha* × *piperita* L.[18] 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 keywords used covered different aspects of safety and the inclusion and exclusion criteria were provided by the applicant. The literature search on the chemical composition of *Mentha* × *piperita* L. and its preparations was aimed at identifying the presence of any recognised substances of concern. The EFSA Compendium of botanicals (EFSA, 2012)[19] reports the presence of following substances of possible concern: menthofuran, pulegone, 1,8-cineole and coumarin in the essential oil from the aerial parts of *Mentha* × *piperita* L. 1,8-Cineole, menthofuran and pulegone are constituents of the essential oil under assessment (Table 2). The oil also contains trace amounts of β-thujone (≤ 0.015%), which is included in the list of substances which shall not be added as such to food according to Annex III of Regulation (EC) No 1334/2008, and for which maximum levels in food are set by Regulation (EC) No 1334/2008.[20] A few references reported the presence of estragole in peppermint oil at concentrations ranging from 0.05% to 0.89% (Abdellatief et al., 2017; Dolghi et al., 2022; Giunti et al., 2021). Coumarin and estragole were not detected by GC–MS in the 10 batches of essential oil under assessment (limit of detection (LOD), 0.001%).

3.3.1.1 | *Impurities*

The applicant referred to the 'periodic testing' of some representative flavourings premixtures for mercury, cadmium, lead, arsenic, fluoride, dioxins and polychlorinated biphenyls (PCBs), organo-chlorine pesticides, organo-phosphorous pesticides, aflatoxins (B1, B2, G1, G2) and ochratoxin A. However, no data were provided on the presence of these impurities.

3.3.2 | Shelf-life

The shelf-life of peppermint 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).[21] However, no data supporting this statement were provided.

3.3.3 | Conditions of use

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

[18]Technical dossier/Supplementary information March 2023/Literature search_peppermint_oil.

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

[20]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 Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34.

[21]Technical dossier/Section II.

TABLE 3 Maximum proposed use levels of peppermint oil in complete feed.

Animal category	Maximum use level (mg/kg complete feed)
Chickens for fattening	150
Laying hens	150
Turkeys for fattening	150
Piglets	150
Pigs for fattening	150
Sows	150
Veal calves (milk replacers)	35
Cattle for fattening	35
Dairy cows	35
Sheep/goats	35
Horses	65
Rabbits	25
Salmonids	25
Dogs	25
Cats	25
Ornamental fish	25
Other species	25

3.4 | Safety

The assessment of the safety of peppermint oil is based on the maximum use levels in complete feed proposed by the applicant (Table 3).

No studies to support the safety for target animals, consumers and users were performed with the additive under assessment.

Many of the individual components of the essential oil have been already assessed as chemically defined flavourings for use in feed and food by the FEEDAP Panel, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), the EFSA Panel on Food Additives and Flavourings (FAF) and/or by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The flavouring compounds currently authorised for food[22] and/or feed[23] use, together with the EU Flavour Information System (FLAVIS) number, the chemical group as defined in Commission Regulation (EC) No 1565/2000[24] and the corresponding EFSA opinion are listed in Table 4.

TABLE 4 Flavouring compounds already assessed by EFSA and/or by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) 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/JECFA opinion.

CG	Chemical group	Product (EU register name)	FLAVIS no	EFSA/JECFA opinion,* year
01	Straight-chain primary aliphatic alcohols/ aldehydes/acids, acetals and esters with esters containing saturated alcohols and acetals containing saturated aldehydes	Hexan-1-ol	02.005	2013
		Octan-1-ol	02.006	
		Decan-1-ol	02.024	
02	Branched-chain primary aliphatic alcohols/ aldehydes/ acids, acetals and esters with esters containing branched-chain alcohols and acetals containing branched-chain aldehydes	3-Methyl 3-methylbutyrate	09.463	2012a
		2-Methylbutyl isovalerate (2-methyl 3-methylbutyrate)	09.531	
		2-Methylbutyl 2-methylbutyrate[1]	09.516	WHO, 2002

[22]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.

[23]European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. https://ec.europa.eu/food/sites/food/files/safety/docs/animal-feed-eu-reg-comm_register_feed_additives_1831-03.pdf.

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

TABLE 4 (Continued)

CG	Chemical group	Product (EU register name)	FLAVIS no	EFSA/JECFA opinion,* year
03	a, ß-Unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/ acids, acetals and esters	*(E)*-2-Hexen-1-ol[2]	02.020	2019b
		Hex-2(*trans*)-enal	05.073	
04	Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols, aldehydes, acids, acetals and esters	Citronellol	02.011	2016a
		Hex-3(*cis*)-en-1-ol	02.056	
05	Saturated and unsaturated aliphatic secondary alcohols, ketones and esters with esters containing secondary alcohols	Nonan-3-ol	02.190	2010a, CEF
		Octan-3-ol	02.098	2015a, 2023b
		Octan-3-one	07.062	
		Oct-1-en-3-ol	02.023	2020
		Isopulegol	02.067	
		Oct-1-en-3-yl acetate	09.281	
		Heptan-3-ol	02.044	WHO, 2000
		3-Octyl acetate[1]	09.254	
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	
		3,7-Dimethyloctan-3-ol (tetrahydrolinaool)	02.028	WHO, 2000
07	Primary alicyclic saturated and unsaturated alcohols/aldehydes/acids/acetals/esters with esters containing alicyclic alcohols	Myrtenol[1]	02.091	2017a, 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	Menthol[3]	02.015	2016b, 2020
		cis-p-Menthan-3-one (*d,l*-isomenthone)[4,5]	07.078	2016b, 2023c
		d-Carvone	07.146	2016b
		l-Carvone	07.147	
		Menthyl acetate	09.016	
		d-Neomenthol	02.063	WHO, 2000
		p-Menthan-3-one[1,5]	07.059	2012, CEF
		trans-p-Menthan-3-one[1,5,6] (*trans*-menthone)	07.176	
		3-Methylcyclohex-2-en-1-one[1]	07.098	2014a, CEF
		p-Menth-1-en-3-one[1]	07.175	
		3-Methylcyclohexanone[1]	07.180	WHO, 2002
		Carvone[1]	07.012	2014, SC
		(1R,2S,5R)-Isopulegyl acetate[1]	09.219	2017b, CEF
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[1]	07.165	2011a, CEF
13	Furanones and tetrahydrofurfuryl derivatives	2,5-Diethyltetrahydrofuran[1]	13.095	2016, CEF
		Linalool oxide[7]	13.140	2012c
15	Phenyl ethyl alcohols, phenylacetic acids, related esters, phenoxyacetic acids and related esters	2-Phenylethan-1-ol	02.019	2012d
16	Aliphatic and alicyclic ethers	1,8-Cineole	03.001	2012e, 2021
18	Allylhydroxybenzenes	Eugenol	04.003	2011
23	Benzyl alcohols/aldehydes/ acids/esters/acetals	Benzaldehyde	05.013	2012f
25	Phenol derivatives containing ring-alkyl, ring-alkoxy and side-chains with an oxygenated functional group	Thymol	04.006	2012g

(Continues)

TABLE 4 (Continued)

CG	Chemical group	Product (EU register name)	FLAVIS no	EFSA/JECFA opinion,* year
31	Aliphatic and aromatic hydrocarbons and acetals containing saturated aldehydes	1-Isopropyl-4-methylbenzene (*p*-Cymene)	01.002	2015b
		Terpinolene	01.005	
		α-Phellandrene	01.006	
		α-Terpinene	01.019	
		γ-Terpinene	01.020	
		d-Limonene	01.045	
		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[1,8]	01.021	2011b, CEF
		β-Cubebene[1,8]	01.030	
		Germacra-1(10),4(14),5-triene δ-Germacrene[1,8]	01.042	
		3,7,10-Humulatriene[1,8]	01.043	
		Longifolene[1,8]	01.047	
		α-Muurulene[1,8]	01.052	
		2,6-Dimethylocta-2,4,6-triene	01.035	2015a, CEF
		4(10)-Thujene (sabinene)[1]	01.059	
		cis-3,7-Dimethyl-1,3,6-octatriene (*cis*-β-Ocimene)[1,9]	01.064	
		β-Bourbonene[1]	01.024	2015b, CEF
		β-Farnesene[1]	01.041	
32	Epoxides	β-Caryophyllene epoxide[1]	16.043	2014b, CEF

*FEEDAP opinion unless otherwise indicated.

[1]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.

[2]Hex-2-en-1-ol [02.020]: evaluated by JECFA as a mixture of isomers. Min. assay value is '95% (sum of cis/trans isomers)'. Subsequently, EFSA evaluated *(E)*-Hex-2-en-1-ol or hex-2(*trans*)-en-1-ol. The chemical name should be changed to Hex-*(2E)*-en-1-ol and the CAS number to 928-95-0, according to the specifications provided (EFSA FAF Panel, 2020).

[3]Menthol [02.105]: The stereochemistry is not specified but the analytical data provided refer to (–)-menthol (= *l*-menthol) (EFSA FEEDAP Panel, 2016b). The same FLAVIS number [02.015] can be adequately used to identify the racemate and its isomeric forms (EFSA FEEDAP Panel, 2020).

[4]*d,l*-Isomenthone [07.078]: two diastereoisomers (+)-isomenthone and (–)-isomenthone in *cis*-configuration.

[5]*p*-Menthan-3-one (menthone): The stereochemistry of menthone [07.059] is not specified. It possesses two chiral centres. (5): EFSA evaluated a mixture of (+)-menthone and (–)-menthone (in *trans*-configuration [07.176]) in co-occurrence with their two diastereoisomers (+)-isomenthone and (–)-isomenthone (in *cis*-configuration [07.078]), containing approximately 25% of each (EFSA CEF Panel, 2012).

[6]*trans*-Menthone [07.176]: menthone exists only as *trans*-isomer. Referred in the opinion to as menthone (JECFA name).

[7]Linalool oxide [13.140]: A mixture of *cis*- and *trans*-linalool oxide (5-ring) was evaluated [13.140] (EFSA FEEDAP Panel, 2012c).

[8]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, 2010b). No longer authorised for use as flavours in food.

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

As shown in Table 4, a number of components of peppermint oil, accounting for about 92% of the % GC peak areas, have been previously assessed by EFSA and/or JECFA and considered safe for use as flavourings. They are currently authorised for use in food[25] without limitations and for use in feed[26] at individual use levels higher than those resulting from the intended use in feed of the essential oil under assessment. Subsequently, *d,l*-isomenthone [07.078] was assessed in tolerance studies with a mixture of flavourings referred to as 'Herbal mixture' in chickens for fattening, piglets, cattle for fattening and salmons. The tolerance studies showed that *d,l*-isomenthone was safe up to 5 mg/kg complete feed. Based on the structural and metabolic similarity, the conclusions reached for *d,l*-isomenthone were extrapolated to menthone [07.176] by applying read-across (EFSA FEEDAP Panel, 2023c).

[25]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.

[26]European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. https://ec.europa.eu/food/sites/food/files/safety/docs/animal-feed-eu-reg-comm_register_feed_additives_1831-03.pdf.

Six compounds listed in Table 4; δ-cadinene [01.021], β-cubebene [10.030], δ-germacrene [01.042], 3,7,10-humulatriene [01.043], longifolene [01.047] and α-muurulene [01.052] have been evaluated in Flavouring Group Evaluations 25 Revision 2 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, 2010b). 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 these data, the CEF Panel was unable to complete its assessment (EFSA CEF Panel, 2015a). As a result, these compounds are no longer authorised for use as flavours in food. For these compounds, in the absence of toxicity data, the FEEDAP Panel applies the threshold of toxicological concern (TTC) approach or read-across from structurally related substances, as recommended in the Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019).

Fifty-three volatile compounds have not been previously assessed for use as flavourings. The FEEDAP Panel notes that 32 of them[27] accounting for 6.1% of the GC–MS area are aliphatic monoterpenes or sesquiterpenes structurally related to flavourings already assessed in CG 4, 6, 8, 31 and 32 and a similar metabolic and toxicological profile is expected. Because of their lipophilic nature, they are expected to be rapidly absorbed from the gastro-intestinal tract, oxidised to polar oxygenated metabolites, conjugated and excreted, and no significant accumulation in animal tissues and products is expected (EFSA CEF Panel, 2014b; EFSA FEEDAP Panel, 2012b, 2015b, 2016a, 2016b, 2016c).

The oil under assessment contains up to 4.54% menthofuran and 1.72% pulegone, which have been evaluated by the FEEDAP Panel as characteristic components of buchu leaf oil (EFSA FEEDAP Panel, 2022). Peppermint oil also contains trace amounts of β-thujone (≤ 0.015%) previously evaluated in the opinion on expressed lemon oil (EFSA FEEDAP Panel, 2021).

Additionally, 18 compounds[28] have not been previously assessed or are structurally related to flavourings previously assessed.

The following sections focus on these 18 compounds and on substances of concern, pulegone and its metabolite menthofuran, based on the evidence provided by the applicant in the form of quantitative structure–activity relationship (QSAR) analysis and literature searches. For β-thujone, reference is made to the FEEDAP opinion on expressed lemon oil (EFSA FEEDAP Panel, 2021).

3.4.1 | Absorption, distribution, metabolism and excretion

Pulegone

Pulegone is highly absorbed after oral administration, extensively metabolised, broadly distributed and rapidly excreted mainly in urine in the form of several metabolites. As summarised by the EMA in the public statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA, 2016) and described in detail in a previous opinion by the FEEDAP Panel (EFSA FEEDAP Panel, 2022), the metabolism of pulegone and menthofuran has been elucidated in detail in in vitro and in vivo studies. The biotransformation of pulegone is very complex and involves several metabolic pathways, including the reduction to menthone and isomenthone, which are hydroxylated in ring or side chain and subsequently conjugated with glucuronic acid. In another pathway, pulegone can be biotransformed into menthofuran, which in turn is bioactivated to unstable reactive metabolites (see section on *Menthofuran*). There is some evidence that conjugation reactions predominate over the menthofuran pathway at low doses of pulegone (Chen et al., 2001). Menthofuran was not detected in the Chen et al. (2001) study in rats given single or multiple 80 mg/kg body weight (bw) oral doses of pulegone. Piperitone formed by hydroxylation of pulegone followed by dehydration is subsequently hydroxylated at several positions. These hydroxylated metabolites are conjugated with glucuronic acid and excreted. Pulegone can also be directly conjugated with glutathione.

Menthofuran

Rats were given by gavage a single dose of [2-^{14}C]menthofuran at 6 or 60 mg/kg bw, 40 μCi/kg (Chen et al., 2003). Urine was collected at several time points, up to 72 h after administration. Radioactivity excreted in urine within 24 h ranged from 36% to 49% of the dose administered.

Menthofuran is metabolised to a reactive intermediate, such as an epoxide and a γ-ketoenal derivative. The latter, after several reactions including hydration, 1,4-dehydration and rearrangement, leads to the formation of mintlactones. Some mintlactones and other metabolites were identified in the urine: 7a-hydroxymintlactone, 6,7a-dihydroxymintlactone, 7a-hydroxymintlactone glucuronide, 2-[2-keto-4-methylcyclohexyl]propionic acids, octahydro-3,6-dimethyl-7a-hydroxybenzofuran glucuronide, hexahydro-3,6-dimethyl-7a-hydroxy-2(3H)-benzofuranone glucuronide and 2-(2-hydroxy-4-methylphenyl)propionic acid.

[27] *cis*-3-Hexenyl isovalerate (CG 4); δ-terpineol, β-terpinyl acetate, *trans*-sabinene hydrate (CG 6); neomenthol, neoisomenthol, isomenthol, *trans*-carveol, neomenthyl acetate, isomenthyl acetate (CG 8); *trans*-3,7-dimethyl-1,3,6-octatriene, *p*-3-menthene, pseudolimonene, *p*-1-menthene, *p*-mentha-3,8-diene, β-elemene, α-thujene, α-cubebene, bicycloelemene, cyclosativene, α-ylangene, α-copaene, isocaryophyllene, β-cubebene, *(E)*-α-bergamotene, aromadendrene, alloaromadendrene, β-copaene, γ-muurolene, bicyclogermacrene, α-muurolene, γ-cadinene, δ-cadinene, 2,4-thujadiene (CG 31); and isocaryophyllene-5,6-epoxide (CG 32).

[28] *(E)*-2-Hexen-1-ol, *trans*-1-methyl-4-(1-methylvinyl)cyclohex-2-en-1-ol, *cis-p*-2-menthen-1-ol, dihydroterpineol, spathulenol, viridiflorol, *p*-mentha-1,8(10)-dien-9-yl acetate, 3-methyl cyclohexanol, 2-*tert*-butylcyclohexanone, isothujol, *trans*-3(10)-caren-2-ol, carvotan acetone, carvenone, *p*-mentha-1,4(8)-dien-3-one, 4-hydroxymenthone, menthofurolactone, dihydroedulan II and mint sulfide.

Four of these metabolites are identical to those identified in the rat by the same authors after administration of pulegone. In addition, three sulfonic acid metabolites of menthofuran were identified: hexahydro-3,6-dimethyl-1-(2 sulfoethyl)-2H-indol-2-one, hexahydro-3,6-dimethyl-7a-sulfo 2(3H)-benzofuranone and 2-sulfomenthofuran. No menthofuran was detected in urine. The formation of the sulfonic metabolites may result from the conjugation with glutathione to the ketone or the aldehyde of the γ-ketoenal with subsequent loss of the two amino acids glutamic acid and glycine, and acetylation of the cysteine residue, the addition of taurine, the direct addition of the sulfite ion to the ketone or the aldehyde of the γ-ketoenal.

3.4.2 | Toxicology

3.4.2.1 | *Genotoxicity and carcinogenicity*

For fully defined mixtures, the EFSA Scientific Committee (EFSA SC) recommends applying a component-based approach, i.e. assessing all components individually for their genotoxic potential (EFSA Scientific Committee, 2019).

The genotoxic potential of 18 compounds (*(E)*-2-hexen-1-ol, *trans*-1-methyl-4-(1-methylvinyl)cyclohex-2-en-1-ol, *cis-p*-2-menthen-1-ol, dihydroterpineol, spathulenol, viridiflorol, *p*-mentha-1,8(10)-dien-9-yl acetate, 3-methyl cyclohexanol, 2-tert-butylcyclohexanone, isothujol, *trans*-3(10)-caren-2-ol, carvotan acetone, carvenone, *p*-mentha-1,4(8)-dien-3-one, 4-hydroxy-menthone, menthofurolactone, dihydroedulan II, mint sulfide) was predicted by the applicant using the Organisation for Economic Co-operation and Development (OECD) QSAR Toolbox.[29] No alerts were identified for in vitro mutagenicity, genotoxic and non-genotoxic carcinogenicity or other toxicity endpoints for the following eight compounds: dihydroterpineol, spathulenol, viridiflorol, 3-methyl cyclohexanol, 2-tert-butylcyclohexanone, isothujol, 4-hydroxy-menthone and mint sulfide. For the remaining compounds, structural alerts were due to the presence of (i) the vinyl/allyl alcohol group for (*E*)-2-hexen-1-ol, *trans*-1-methyl-4-(1-methylvinyl)cyclohex-2-en-1-ol, *cis*-para-2-menthen-1-ol and *trans*-3(10)-caren-2-ol; (ii) the α,β-unsaturated/vinyl allyl ketone group for carvotan acetone, carvenone and *p*-mentha-1,4(8)-dien-3-one; (iii) the vinyl/allyl ester group for menthofurolactone and dihydroedulan II; and (iv) the ester group for *p*-mentha-1,8(10)-dien-9-yl acetate. For all substances, predictions of mutagenicity by Ames test (with and without S9) were made by 'read-across' analyses of data available for similar substances to the target compounds (i.e. analogues obtained by categorisation). Read-across-based predictions were found consistently negative for all categories of analogues. On this basis, the alerts raised were discounted by the FEEDAP Panel.[30]

Pulegone and menthofuran

The genotoxicity studies of pulegone and its metabolite menthofuran have been reviewed by EMA (2016) and the International Agency for Research on Cancer (IARC, 2018). In vitro studies were generally negative, with few (weak) positive findings in the Ames test. IARC regarded pulegone as non-mutagenic in vitro (IARC, 2018). EMA considered the genotoxic potential of pulegone and menthofuran in vitro unlikely. Pulegone, menthofuran and peppermint oil were tested in vivo in female rats, in a combined micronucleus test and Comet assay (with liver, kidney and urinary bladder urothelium as target organs) (EMA, 2016). The results were consistently negative, except for menthofuran which was slightly positive in the Comet assay in liver cells, most probably due to high-dose cytotoxicity. Overall, EMA concluded that 'pulegone is devoid of genotoxic potential also in those studies in which the production of short-lived reactive intermediates and their scavenging by cellular protection mechanisms has been taken into consideration. A slight increase in tail intensity by high-dose menthofuran in the Comet assay is most likely due to cytotoxicity. Despite some (weak) positive findings in some studies the overall conclusion is that pulegone and menthofuran do not possess genotoxic potential' (EMA, 2016).

The carcinogenicity of pulegone was investigated in a 2-year carcinogenicity study in mice and rats (NTP, 2011a) which is described in more detail in a previous opinion by the EFSA FEEDAP Panel (2022). Dose-related, statistically significant increases of hepatocellular adenoma and/or carcinoma were observed in female mice, and urinary bladder papillomas were observed in female rats. Both NTP (2011a) and the International Agency for Research on Cancer (IARC, 2018) concluded that there is clear evidence of carcinogenicity of pulegone and its metabolite menthofuran in male and female mice. IARC classified pulegone and menthofuran as possibly carcinogenic to humans (2B). Based on a weight of evidence approach, EMA as well as IARC concluded that cell cytotoxicity and regenerative proliferation are driven by reactive metabolites (see Section 3.4.1) and GSH depletion as a probable mechanism of action, with the overall conclusion that toxicity and carcinogenicity of pulegone have a thresholded mode of action (EMA, 2016).

Peppermint oil

The available genotoxicity studies on peppermint oil were evaluated by EMA (EMA, 2020e). Negative results for the induction of gene mutations were reported from in vitro mutagenesis assays in bacteria and mammalian cells. In addition, negative results were observed in an unscheduled DNA synthesis assay in rat hepatocytes (Nair, 2001). Weak and inconsistent positive

[29]Technical dossier/Supplementary information March 2023/BDG-01-SIn-reply_peppermint oil.

[30]Technical dossier/Supplementary information March 2023/Annex_VIII_Sin_reply peppermint_oil_QSAR.

responses were reported in non-validated tests, i.e. on sister chromatid exchanges (SCEs) in human lymphocytes and on somatic mutations and recombination in *Drosophila* melanogaster (Lazutka et al., 2001). Peppermint oil was negative when tested in the in vivo combined micronucleus test and Comet assay in female rats as described above.

A carcinogenicity study with peppermint oil is described by EMA (2020e). The study involved groups of 52 male mice treated by gavage with 0, 4 or 16 mg peppermint oil/kg body weight per day and a group of 260 male mice receiving the vehicle (toothpaste base) on 6 days each week for 80 weeks with a follow-up period of 16–24 weeks. No significant treatment relationship was reported in the overall incidence of malignant neoplasms or the incidence of neoplasms of kidney or lung. As the study was confined to one sex and does not detail specific tumour incidences, it cannot be used for a definitive conclusion about the carcinogenicity of peppermint oil but may be considered as supporting evidence for a lack of carcinogenicity. A similar view applies to the report of another study (Roe et al., 1979) where hepatic cell tumour incidence for peppermint oil-dosed mice (25%) was comparable to the incidence for mice of the vehicle-control group (27%).

3.4.2.2 | *Repeated dose toxicity studies*

Pulegone

Pulegone was tested in the framework of the NTP of the US Department of Health and Human Services (NTP, 2011a). For pulegone and menthofuran, the FEEDAP Panel retained a no observed adverse effect level (NOAEL) of 9.38 mg/kg bw derived from a 14-week study in F344/N rats, based on a dose-dependent reduction of red blood cells starting at 18.75 mg/kg bw (EFSA FEEDAP Panel, 2022).

Menthone

Menthol and menthone are major constituents of peppermint oil. In a 28-day toxicity study, rats were orally administered 0, 200, 400 or 800 mg menthone/kg bw per day. Menthone was found to cause a dose-dependent increase in alkaline phosphatase and bilirubin in plasma, as well as a decrease in plasma creatinine. In addition, cyst-like spaces were observed in the white matter of the cerebellum of rats at the two highest doses tested (Madsen et al., 1986, reviewed in EMA, 2020e). No NOAEL could be established from this study.

3.4.3 | Safety for the target species

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

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

As the additive under assessment is a fully defined mixture (the identified components represent 99.6% of the % GC area, see Section 3.3.1), the FEEDAP Panel applied a component-based approach to assess the safety for target species of the essential oil. The oil under assessment contains by specification up to 32% of menthone [07.176] and up to 10% of *d,l*-isomenthone [07.078], which are assessed separately from the other components of the oil.

d,l-Isomenthone and menthone

The tolerance trials in chickens for fattening, piglets, cattle for fattening and salmons with a mixture of flavourings containing *d,l*-isomenthone [07.078] ('Herbal mixture') showed that *d,l*-isomenthone [07.078] was safe up to 5 mg/kg complete feed for all animal species with a margin of safety of 10 (EFSA FEEDAP Panel, 2023). The FEEDAP Panel considered that the conclusions reached for *d,l*-isomenthone could be extrapolated to menthone [07.176], by applying read-across.

At the proposed conditions of use for peppermint oil (see Section 3.3.3), the concentration of the sum of menthone and *d,l*-isomenthone in feed would range from 10.5 to 63 mg/kg complete feed, considering that menthone and *d,l*-isomenthone are present in the essential oil under assessment at the highest specification of 32% and 10%, respectively (see Table 5).

Considering that *d,l*-isomenthone is safe up to 5 mg/kg complete feed and considering a concentration of the sum of menthone and *d,l*-isomenthone in peppermint oil corresponding to the highest specifications of 32% and 10%, the FEEDAP Panel concludes that the use of peppermint oil is safe at a maximum use level of 12 mg/kg complete feed for all animal species, with regard to the presence of menthone and *d,l*-isomenthone.

TABLE 5 Concentration of the sum of menthone and *d,l*-isomenthone in complete feed resulting from the use of peppermint oil at the proposed conditions of use and calculated maximum safe concentrations of peppermint oil in complete feed (mg/kg) to ensure a safe level of menthone and *d,l*-isomenthone for the different target animal categories.

Animal category	Daily feed intake (g DM/kg bw)	proposed use level (mg/kg complete feed)[1]	Concentration of menthone and *d,l*-isomenthone (mg/kg complete feed)[2]	Maximum safe use level (mg/kg complete feed)[1,3]
Chickens for fattening	79	150	63.0	12
Laying hens	53	150	63.0	12
Turkeys for fattening	59	150	63.0	12
Pig for fattening	44	150	63.0	12
Piglets	37	150	63.0	12
Sows lactating	30	150	63.0	12
Veal calves (milk replacer)	19	35	14.7	12
Cattle for fattening	20	35	14.7	12
Dairy cows	31	35	14.7	12
Sheep/goats	20	35	14.7	12
Horses	20	65	27.3	12
Rabbits	50	25	10.5	12
Salmonids	18	25	10.5	12
Dogs	17	25	10.5	12
Cats	20	25	10.5	12
Ornamental fish	5	25	10.5	12

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

[2]Based on the highest proposed specification of menthone (32% of the GC area) and *d,l*-isomenthone (10% of the GC area) in the additive.

[3]Maximum safe use level calculated to ensure a maximum concentration of 5 mg/kg complete feed for the sum of menthone and *d,l*-isomenthone.

Components other than d,l-isomenthone and menthone

Based on considerations related to structural and metabolic similarities, the components were allocated to 19 assessment groups, corresponding to the chemical groups (CGs) 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 13, 15, 16, 18, 23, 25, 30, 31 and 32, as defined in Annex I of Regulation (EC) No 1565/2000. 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, 2015b, 2015c). The allocation of the components to the (sub-)assessment groups is shown in Table 6 and in the corresponding footnote.

For hazard characterisation, each component of an assessment group was first assigned to the structural class according to Cramer classification using Toxtree (version 3.1.0, May 2018[31]). For some components in the assessment group, toxicological data were available to derive no observed adverse effect levels (NOAEL). 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 several compounds in CG 1 (EFSA FEEDAP Panel, 2013), for the representative compound 2-ethylhexan-1-ol [02.082] in CG 2 (EFSA FEEDAP Panel, 2012a), for hex-2(*trans*)-enal [05.073] in CG 3 (EFSA FEEDAP Panel, 2019), hex-3(*cis*)-en-1-ol [02.056] and citronellol [02.011] in CG 4 (EFSA FEEDAP Panel, 2016a), isopulegol [02.067] and oct-1-en-3-one [07.081] in CG 5 (EFSA FEEDAP Panel, 2020), linalool [02.013] in CG 6 (EFSA FEEDAP Panel, 2012b), menthol [02.015] in CG 8 (EFSA FEEDAP Panel, 2016b), 1,8-cineole [03.001] in CG 16 (EFSA FEEDAP Panel, 2021), eugenol [04.003] in CG 18 (EFSA FEEDAP Panel, 2011), benzaldehyde [05.013] in CG 23 (Andersen, 2006), myrcene [01.008], *p*-cymene [01.002] and β-caryophyllene [01.007] in CG 31 (EFSA FEEDAP Panel, 2015b, 2016c) and β-caryophyllene epoxide [16.043] in CG 32 (EFSA CEF Panel, 2014b). For α-terpinene [01.019], the FEEDAP Panel identified a NOAEL of 60 mg/kg bw per day based on maternal toxicity (reduced body weight gain) in a teratogenicity study in rats (Araujo et al., 1996; also reported in ECHA, 2018). The NOAEL of 60 mg/kg bw per day was dividded by a factor of 2 to take into account the nature of the study.

The FEEDAP Panel applied a $BMDL_{10}$ of 8 mg/kg bw per day for α-thujone (EFSA FEEDAP Panel, 2021), which is also extended to β-thujone despite its lower neurotoxicity. The FEEDAP Panel applied a $BMDL_{10}$ of 8 mg/kg bw per day for β-thujone, and a NOAEL of 9.38 mg/kg bw per day for pulegone and its metabolite menthofuran in the same assessment group (EFSA FEEDAP Panel, 2022).

[31]Toxtree includes both the original Cramer rule base with the 33 structural rules (Cramer et al., 1978) and an extended rule base with five additional rules which were introduced to overcome misclassification (in Class I or Class II) of several substances with low NOAELs. https://toxtree.sourceforge.net/.

For CG 1, a group NOAEL of 120 mg/kg per day was derived from the toxicological data available and was used as a group NOAEL for all the compounds belonging to CG 1, hexan-1-ol [02.005], octan-1-ol [02.006] and decan-1-ol [02.024]. The NOAEL of 50 mg/kg bw per day for the representative compound 2-ethylhexan-1-ol [02.082] was extrapolated to 2-methylbutyl isovalerate [09.531] in CG 2. Similarly, the NOAEL of 6.7 mg/kg bw per day for oct-1-en-3-one [07.081] was applied to the structurally related compounds oct-1-en-3-ol [02.023] and oct-1-en-3-yl-acetate [09.281] in CG 5. The NOAEL of 38 mg/kg bw per day for isopulegol [02.067] in CG 5 was applied to *(1R,2S,5R)*-isopulegyl acetate [09.219] in CG 8.

For the subgroup of terpinyl derivatives in CG 6, i.e. α-terpineol [02.014], 4-terpinenol [02.072], β-terpinyl acetate and δ-terpineol, the NOAEL of 250 mg/kg bw per day for terpineol [02.230] was selected as the reference point. The NOAEL of 250 mg/kg bw per day was divided by a factor of 2 to take into account the short duration of the study (35 days) with terpineol (EFSA FEEDAP Panel, 2012b).

The NOAEL of 375 mg/kg bw per day for menthol [02.015] has been already applied to menthyl acetate [09.016] in CG 8 (EFSA FEEDAP Panel, 2016b). In the current assessment, the NOAEL is also extrapolated to neomenthol, neoisomenthol, isomenthol, neomenthyl acetate and isomenthyl acetate in CG 8. The $BMDL_{10}$ of 60 mg/kg bw per day for *d*-carvone [07.146] was applied to carvone [07.012] (stereochemistry not indicated), *trans*-carveol and to *p*-menth-1-en-3-one [07.175] (EFSA FEEDAP Panel, 2016b, 2023d; EFSA Scientific Committee, 2014).

For thymol [04.006] in CG 25, a NOAEL of 36 mg/kg bw per day was extrapolated from benzene-1,3-diol [04.047] (EFSA FEEDAP Panel, 2012g).

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

Considering the structural and metabolic similarities, the NOAELs for the representative compounds in CG 31, myrcene [01.008], *d*-limonene [01.045] and β-caryophyllene [01.007] were applied, respectively, using read-across to the compounds within sub-assessment groups II (β-farnesene [01.041], *(Z)*-β-ocimene [01.064], *(E)*-β-ocimene and 2,6-dimethylocta-2,4,6-triene [01.035]), III (γ-terpinene [01.020], β-elemene, terpinolene [01.005], *p*-mentha-3,8-diene and *p*-1-menthene) and V (β-pinene [01.003], α-pinene [01.004], sabinene [01.059], β-bourbonene [01.024], bicyclogermacrene, bicycloelemene, longifolene, α-yanglene, β-cubebene [01.030], α-copaene, δ-cadinene [01.021], camphene [01.009], γ-muurolene, α-cubebene, β-copaene, isocaryophyllene, α-thujene, *(E)*-α-bergamotene, alloaromadendrene, α-muurolene [01.052], γ-cadinene, δ-3-carene [01.029], cyclosativene and aromadendrene),[32] respectively (EFSA CEF Panel, 2015b; 2016c). In the current assessment, the NOAEL of 60 mg/kg bw per day for α-terpinene [01.019] is applied to α-phellandrene, divided by a factor of 2 to take into account the nature of the study carried out with α-terpinene.

The NOAEL of 222 mg/kg bw per day for β-caryophyllene [01.007] was also applied to *trans*-sabinene hydrate, viridiflorol and spathulenol in CG 6, 3,7,10-humulatriene [01.043] in CG 31, VI. For viridiflorol and spathulenol, the NOAEL of β-caryophyllene [01.007] was divided by a factor of 2 because of differences in the structures (the presence of an additional cyclopropane ring). Similarly for 3,7,10-humulatriene, the NOAEL of β-caryophyllene was divided by a factor of 2 take into account the differences in the structure (extrapolation from a tricyclic to a macrocyclic non-aromatic compound) (EFSA FEEDAP Panel, 2023). The NOAEL of 109 mg/kg bw per day for β-caryophyllene epoxide [16.043] was used for isocaryophyllene-5,6-epoxide in CG 32.

For the remaining compounds,[33] 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, 2017b; EFSA Scientific Committee, 2019).

As the result of the hazard characterisation, a reference point was identified for each component in the assessment group based on the toxicity data available (NOAEL from in vivo toxicity study or read-across) or from the 5th percentile of the distribution of NOAELs of the corresponding Cramer Class (i.e. 3, 0.91 and 0.15 mg/kg bw per day, respectively, for Cramer Class I, II and III compounds, Munro et al., 1996). Reference points selected for each compound are shown in Table 6.

For each component in the assessment group, exposure in target animals was estimated considering the use levels in feed, the percentage of the component in the oil and the default values for feed intake according to the guidance on the safety of feed additives for target species (EFSA FEEDAP Panel, 2017b). For those compounds covered by specifications (menthol, menthone, *d,l*-isomentone, menthyl acetate and 1,8-cineole, see Table 1), the maximum limit is used for the calculation of exposure. For the other components, the highest analysed concentration is used. Default values for body

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

[33]CC I (3 mg/kg bw per day): 2-methylbutyl 2-methylbutyrate [09.516], 3-methylbutyl 3-methylbutyrate [09.463] (CG 2), (*E*)-2-hexen-1-ol (CG 3); *cis*-3-hexenyl isovalerate (CG 4); heptan-3-ol [02.044], octan-3-ol [02.098], nonan-3-ol [02.190], 3-octyl acetate [09.254] (CG 5); tetrahydrolinalool [02.028], *trans*-1-methyl-4-(1-methylvinyl) cyclohex-2-en-1-ol, *cis-p*-2-menthen-1-ol, dihydroterpineol (CG 6); myrtenol [02.091], *p*-mentha-1,8(10)-dien-9-yl acetate [09.809] (CG 7); isothujol, *trans*-3(10)-caren-2-ol (CG 8); 4-hydroxy-4-methylpentan-2-one [07.165] (CG 10); 2-phenylethan-1-ol [02.019] (CG 15); *p*-3-menthene, pseudolimonene, germacra-1(10),4(14),5-triene [01.042] (CG 31); CC II (0.91 mg/kg bw per day): octan-3-one [07.062] (CG 5); 3-methyl cyclohexanol, 3-methylcyclohexanone [07.180], 3-methylcyclohex-2-en-1-one, 2-*tert*-butylcyclohexanone, carvotan acetone, carvenone, 3-methyl-2(pent-2-enyl)cyclopent-2-en-1-one [07.094], *p*-mentha-1,4(8)-dien-3-one [07.127] (CG 8); 4-hydroxymenthone (CG 10); 2,5-diethyltetrahydrofuran [13.095], linalool oxide [13.140] (CG 13); CC III (0.15 mg/kg bw per day): menthofurolactone (CG 11); dihydroedulan II (CG 16); 2,4-thujadiene (CG 31); mint sulfide (CG 30).

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/bw per day, are shown in Table 6.

For risk characterisation, the margin of exposure (MOE) was calculated for each component as the ratio between the reference point and the exposure. For each assessment group, the combined (total) margin of exposure (MOET) was calculated as the reciprocal of the sum of the reciprocals of the MOE of the individual substances (EFSA Scientific Committee, 2019). 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 (except β-thujone, which is a substance of concern) were not further considered in the assessment group as their contribution to the MOE(T) is negligible. They are listed in the footnote.[34]

The approach to the safety assessment of peppermint oil for the target species is summarised in Table 6. The calculations were done for chickens for fattening, the species with the highest ratio of feed intake/body weight and represent the worst-case scenario at the use level of 12 mg/kg complete feed, considered safe based on the presence of menthone and *d,l*-isomenthone.

TABLE 6 Compositional data, intake values (calculated for chickens for fattening at 12 mg/kg complete feed), reference points and margin of exposure (MOE) for the individual components of additive 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.**	**Daily intake[1]**	**Cramer Class[2]**	**NOAEL[3]**	**MOE[4]**	**MOET[5]**
Constituent	**–**	**%**	**mg/kg**	**mg/kg bw per day**	**–**	**mg/kg bw per day**	**–**	**–**
CG 2								
2-Methylbutyl isovalerate	09.531	0.12	0.014	0.0013	(I)	50	39,037	
2-Methylbutyl 2-methylbutyrate	09.516	0.08	0.010	0.0009	I	*3*	3285	
3-Methylbutyl 3-methylbutyrate	09.463	0.08	0.010	0.0009	I	*3*	3285	
MOET CG 2								1576
CG 3								
(*E*)-2-Hexen-1-ol	–	0.02	0.002	0.0002	I	*3*	13,833	
CG 4								
cis-3-Hexenyl isovalerate	–	0.04	0.005	0.0004	I	*3*	6941	
CG 5								
Isopulegol	02.067	0.67	0.081	0.0073	(I)	38	5234	
Octan-3-ol	02.098	0.36	0.044	0.0039	I	*3*	765	
Oct-1-en-3-ol	02.023	0.11	0.013	0.0012	(I)	6.7	5700	
3-Octyl acetate	09.254	0.11	0.013	0.0012	I	*3*	2590	
Octan-3-one	07.062	0.07	0.008	0.0007	II	*0.91*	1300	
Nonan-3-ol	02.190	0.03	0.003	0.0003	I	*3*	10,164	
MOET CG 5								342
CG 6								
trans-Sabinene hydrate	–	1.11	0.133	0.0119	(III)	222	18,614	
4-Terpinenol	02.072	0.76	0.091	0.0082	(I)	125[6]	15,324	
α-Terpineol	02.014	0.54	0.065	0.0058	(I)	125[6]	21,480	
Linalool	02.013	0.39	0.046	0.0041	(I)	**117**	28,199	
Dihydroterpineol	–	0.20	0.024	0.0022	I	*3*	1394	
cis-p-2-Menthen-1-ol	–	0.11	0.013	0.0012	I	*3*	2590	

[34]Compounds included in the assessment groups but not reported in the table: decan-1-ol [02.024], octan-1-ol [02.006], hexan-1-ol [02.005] (CG 1); hex-2*(trans)*-enal [05.073] (CG 3); citronellol [02.011], hex-3*(cis)*-en-1-ol (CG 4); oct-1-en-3-yl-acetate [09.281], nonan-3-ol [02.044] (CG 5); δ-terpineol, viridiflorol, spathulenol, β-terpinyl acetate (CG 6); *trans*-carveol, *(1R,2S,5R)*-isopulegyl acetate, neomenthyl acetate, isomenthyl acetate (CG 8); eugenol (CG 18); benzaldehyde (CG 23); *(E)*-β-ocimene and 2,6-dimethylocta-2,4,6-triene (CG 31,II); *p*-cymene (CG 31,IVe); bicycloelemene, α-ylangene, bicyclogermacrene, longifolene [01.047], β-cubebene [01.030], α-copaene, δ-cadinene [01.021], camphene [01.009], γ-muurolene, α-cubebene, β-copaene, isocaryophyllene, α-thujene, *(E)*-α-bergamotene, alloroaromadendrene, α-muurolene [01.052], γ-cadinene, δ-3-carene [01.029], cyclosativene, aromadendrene (CG 31, V); isocaryophyllene, 5,6-epoxide and β-caryophyllene epoxide [16.043] (CG 32).

TABLE 6 (Continued)

Essential oil composition			Exposure		Hazard characterisation		Risk characterisation	
Assessment group	**FLAVIS-no**	**Highest conc. in the oil**	**Highest feed conc.**	**Daily intake[1]**	**Cramer Class[2]**	**NOAEL[3]**	**MOE[4]**	**MOET[5]**
Constituent	**–**	**%**	**mg/kg**	**mg/kg bw per day**	**–**	**mg/kg bw per day**	**–**	**–**
Tetrahydrolinalool	02.028	0.04	0.005	0.0005	I	*3*	6263	
trans-1-Methyl-4-(1-methyl vinyl)cyclohex-2-en-1-ol	–	0.03	0.003	0.0003	I	*3*	9603	
MOET CG 6								638
CG 7								
Myrtenol	02.091	0.05	0.006	0.0006	I	*3*	5774	
p-Mentha-1,8(10)-dien-9-yl acetate	09.809	0.04	0.005	0.0005	I	*3*	6723	
MOET CG 7								3106
CG 8								
Menthol	02.015	55	6.600	0.5925	(I)	**375**	633	
Menthyl acetate	09.016	10	1.200	0.1077	(I)	375	3481	
Neomenthol	–	3.99	0.478	0.0429	(I)	375	8735	
p-Menth-1-en-3-one	07.175	1.13	0.136	0.0122	(II)	60	4919	
Isomenthol	–	0.80	0.096	0.0086	(I)	375	43,731	
Neoisomenthol	–	0.79	0.095	0.0085	(I)	375	44,089	
trans-3(10)-Caren-2-ol	–	0.30	0.036	0.0032	I	*3*	928	
3-Methylcyclohexanone	07.180	0.20	0.024	0.0022	II	*0.91*	418	
Carvone	07.012	0.16	0.019	0.0017	(II)	60	34,594	
2-*tert*-Butylcyclohexanone	-	0.10	0.012	0.0011	II	*0.91*	828	
3-Methyl cyclohexanol	–	0.04	0.005	0.0005	II	*0.91*	1964	
Isothujol	–	0.03	0.004	0.0003	I	*3*	8798	
3-Methylcyclohex-2-en-1-one	07.098	0.01	0.001	0.0001	II	*0.91*	16,321	
Carvotan acetone	–	0.01	0.002	0.0002	II	*0.91*	6061	
Carvenone	–	0.01	0.002	0.0001	II	*0.91*	6074	
3-Methyl-2(pent-2-enyl) cyclopent-2-en-1-one	07.094	0.01	0.002	0.0001	II	*0.91*	6484	
p-Mentha-1,4(8)-dien-3-one	07.127	0.01	0.002	0.0001	II	*0.91*	6485	
MOET CG 8								121
CG 10								
4-Hydroxy-menthone	–	0.09	0.011	0.0010	II	*0.91*	939	
4-Hydroxy-4-methylpentan-2-one	07.165	0.04	0.004	0.0004	I	*3*	7865	
MOET CG 10								839
CG 11								
Menthofurolactone	–	0.03	0.004	0.0003	III	*0.15*	440	
CG 13								
2,5-Diethyltetrahydrofuran	13.095	0.04	0.004	0.0004	II	*0.91*	2414	
Linalool oxide	13.140	0.02	0.002	0.0002	II	*0.91*	4066	
MOET CG 13								1515
CG 15								
2-Phenylethan-1-ol	02.019	0.02	0.002	0.0002	I	*3*	17,733	
CG 16								
1,8-Cineole	03.001	8	0.960	0.0862	(II)	**100**	1160	
Dihydroedulan II	–	0.06	0.007	0.0006	III	*0.15*	245	

(Continues)

TABLE 6 (Continued)

Essential oil composition			Exposure		Hazard characterisation		Risk characterisation	
Assessment group	**FLAVIS-no**	**Highest conc. in the oil**	**Highest feed conc.**	**Daily intake[1]**	**Cramer Class[2]**	**NOAEL[3]**	**MOE[4]**	**MOET[5]**
Constituent	**–**	**%**	**mg/kg**	**mg/kg bw per day**	**–**	**mg/kg bw per day**	**–**	**–**
MOET CG 16								202
CG 25								
Thymol	04.006	0.09	0.011	0.0010	(I)	36	35,637	
CG 30								
Mint sulfide	–	0.00	0.001	0.0001	III	*0.15*	2963	
CG 31, II (Acyclic alkanes)								
Myrcene	01.008	0.32	0.039	0.0035	(I)	**44**	12,684	
β-Farnesene	01.041	0.29	0.035	0.0032	(I)	44	13,867	
(Z)-β-Ocimene	01.064	0.24	0.029	0.0026	(I)	44	16,802	
MOET CG 31, II								4751
CG 31, III (Cyclohexene hydrocarbons)								
d-Limonene	01.046	3.23	0.388	0.0348	(I)	**250**	7176	
γ-Terpinene	01.020	0.60	0.072	0.0064	(I)	250	38,814	
α-Terpinene	01.019	0.32	0.039	0.0035	(I)	**30**[7]	8673	
Pseudolimonene	–	0.06	0.008	0.0007	II	*3*	4311	
α-Phellandrene	01.006	0.06	0.008	0.0007	(I)	30[7]	43,107	
p-3-Menthene	–	0.03	0.004	0.0004	II	*3*	7971	
								1513
CG 31, V (Bi-, tricyclic, non-aromatic hydrocarbons)								
β-Caryophyllene	01.007	3.62	0.434	0.0389	(I)	**222**	5701	
β-Pinene	01.003	1.17	0.140	0.0126	(I)	222	17,613	
α-Pinene	01.004	0.93	0.112	0.0100	(I)	222	22,159	
Sabinene	01.059	0.46	0.056	0.0050	(I)	222	44,320	
β-Bourbonene	01.024	0.44	0.053	0.0047	(I)	222	46,806	
2,4-Thujadiene	–	0.01	0.001	0.0001	III	*0.15*	2172	
MOET CG 31, V								1279
CG 31, VI (Macrocyclic non-aromatic hydrocarbons)								
Germacra-1(10),4(14),5-triene	01.042	1.96	0.235	0.0211	I	*3*	142	
3,7,10-Humulatriene	01.043	0.38	0.046	0.0041	(I)	111[8]	27,103	
MOET CG 31, VI								141
Pulegone and menthofuran								
Menthofuran	13.035	4.54	0.544	0.0489	(II)	9.38	192	
Pulegone	–	1.72	0.206	0.0185	(II)	**9.38**	507	
								139
β-Thujone	–	0.01	0.002	0.0002	(III)	8	50,835	

[1]Intake calculations for the individual components are based on the use level of 12 mg/kg in feed for chickens for fattening, the species with the highest ratio of feed intake/body weight.

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

[3]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.

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

[5]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.

[6]A factor of 2 was applied to the NOAEL of 250 mg/kg bw per day for terpineol because of theshort duration of the study.

[7]A factor of 2 was applied to the NOAEL of 60 mg/kg bw per day for α-terpinene because of thenature of the study.

[8]A factor of 2 was applied to the NOAEL of 222 mg/kg bw per day for β-caryophyllene because of differences in the structures.

As shown in Table 6, for all assessment groups, the MOET calculated for chickens for fattening at the reduced use level of 12 mg/kg complete feed was > 100. The lowest MOET was calculated for CG 8, the assessment group which includes the major components menthol and menthone. From the lowest MOET of 121 for chickens for fattening, the MOET for CG 8 compounds was calculated for the other target species at 12 mg/kg complete feed and considering the respective daily feed intake. The results are summarised in Table 7.

TABLE 7 Combined margin of exposure (MOET) for the assessment group CG 8 calculated for the different target animal categories at the use level of 12 mg/kg complete feed (considered safe based on the presence of menthone and *d,l*-isomenthone) and maximum safe use level in feed.

Animal category	Daily feed intake (g DM/kg bw)	Use level (mg/kg complete feed)[1]	Lowest MOET CG 8	Maximum safe use level (mg/kg complete feed)[1]
Chickens for fattening	79	12	121	–[2]
Laying hens	53	12	180	–
Turkeys for fattening	59	12	162	–
Piglets	44	12	217	–
Pigs for fattening	37	12	258	–
Sows lactating	30	12	319	–
Veal calves (milk replacer)	19	12	543	–
Cattle for fattening	20	12	478	–
Dairy cows	31	12	308	–
Sheep/goats	20	12	478	–
Horses	20	12	478	–
Rabbits	50	12	191	–
Salmonids	18	12	531	–
Dogs	17	12	562	–
Cats[3]	20	12	478	11.5
Ornamental fish	5	12	1912	–

[1]Complete feed containing 88% DM, milk replacer 94.5% DM.
[2]For the species for which the MOET is > 100, the use level of 12 mg/kg complete feed is considered safe.
[3]The MOET for cats is increased to 500 because of the reduced capacity of glucuronidation.

At the reduced use level of 12 mg/kg complete feed, the MOET exceeds the value of 100 for all animal species. Because glucuronidation is an important metabolic pathway to facilitate the excretion of the components of the essential oil and considering that cats have an unusually low capacity for glucuronidation, particularly for aromatic compounds (Court & Greenblatt, 1997; Lautz et al., 2021), the use of peppermint oil as an additive in cat feed needs a wider margin of exposure. A MOET of 500 is considered adequate for cats, the resulting maximum safe level in complete feed is 11.5 mg/kg, which is rounded to 12 mg/kg. For all the species listed in Table 6, peppermint oil is considered safe when used as feed additive at 12 mg/kg complete feed. These levels are extrapolated to physiologically related minor species. For the other species not considered, the level of 12 mg/kg complete feed is applied.

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

3.4.3.1 | *Conclusions on safety for the target species*

The FEEDAP Panel concludes that peppermint oil is safe for all animal species at the maximum use level of 12 mg/kg complete feed.

The FEEDAP Panel considers that the use in water for drinking alone or in combination with the use in feed should not exceed the daily amount that is considered safe when consumed via feed alone.

3.4.4 | Safety for the consumer

Peppermint oil is added to a wide range of food categories for flavouring purposes. Fenaroli's handbook reports use levels for the oil ranging from 6 to 1200 in mg/kg in food and beverages. Although individual consumption figures are not available, the Fenaroli's handbook of flavour ingredients (Burdock, 2009) cites intake values of 1.175 mg/kg per day for peppermint oil (FEMA 2848).

Most of the individual constituents of the essential oil under assessment are currently authorised as food flavourings without limitations and have been already assessed for consumer safety when used as feed additives in animal production (see Table 4, Section 3.3).

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 peppermint oil are expected to be extensively metabolised and excreted in the target species. For the major components, menthol, menthone, *d,l*-isomenthone and menthyl acetate, the available data in laboratory animals and humans indicate that they are absorbed, metabolised by oxidation and excreted and are not expected to accumulate in animal tissues and products (EFSA FEEDAP Panel, 2016b). Consequently, relevant residues in food products are unlikely.

Considering the above and the reported human exposure due to the direct use of peppermint oil in food (Burdock, 2009), the FEEDAP Panel considers that it is unlikely that the consumption of products from animals given peppermint oil at the proposed maximum use level would increase human background exposure. The use of peppermint oil in animal nutrition under the proposed conditions of use is safe for human consumers of animal products.

3.4.5 | 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[35] for peppermint oil, where hazards for users have been identified.

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

3.4.6 | Safety for the environment

Mentha × *piperita* L. occurs wild and is native to and widely distributed over Europe and cultivated in many European countries. The use of peppermint oil in animal feed under the proposed conditions of use is not expected to pose a risk to the environment.

3.5 | Efficacy

Peppermint oil from *Mentha* × *piperita* is listed in Fenaroli's Handbook of Flavour Ingredients (Burdock, 2009) and by FEMA with the reference number 2848.

Since peppermint 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

Peppermint oil from *Mentha* × *piperita* L. may be produced from plants of different geographical origins and by various processes resulting in preparations with different composition and toxicological profiles. Thus, the following conclusions apply only to peppermint oil which contains ≤ 1.72% pulegone, ≤ 4.54% menthofuran and ≤ 0.01% β-thujone, and for which coumarin and estragole are not detected (LOD, 0.001%).

The FEEDAP Panel concludes that peppermint oil is safe for all animal species at the maximum use level of 12 mg/kg complete feed.

The FEEDAP Panel considers that the use in water for drinking alone or in combination with the use in feed should not exceed the daily amount that is considered safe when consumed via feed alone.

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

Regarding user safety, the essential oil under assessment should be considered as irritant to skin and eyes, and as a dermal and respiratory sensitiser.

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

Since peppermint 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.

[35]Technical dossier/Supplementary information March 2023/ Annex_IX_Sin_reply_peppermint_oil_MSDS. Acute toxicity (oral) (H302, category 4), skin corrosion/irritation (H315, category 2), sensitization (H317, category 1), May cause an allergic skin reaction (H317B, category 1B), Causes skin irritation (H315) in accordance with the criteria outlined in Annex I of 1272/2008/EC (CLP/EU-GHS).

5 | RECOMMENDATION

The specification should ensure that the concentrations of pulegone is ≤ 1.72%, menthofuran is ≤ 4.54%, and that coumarin and estragole are not detected (LOD, 0.001%).

6 | DOCUMENTATION PROVIDED TO EFSA/CHRONOLOGY

Date	Event
23/11/2010	Dossier received by EFSA. Botanically defined flavourings from Botanical Group 01 – Lamiales for all animal species and categories. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)
03/01/2011	Reception mandate from the European Commission
06/01/2011	Application validated by EFSA – Start of the scientific assessment
01/04/2011	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: analytical methods*
08/01/2013	Reception of supplementary information from the applicant - Scientific assessment remains suspended
26/02/2013	EFSA informed the applicant (EFSA ref. 7,150,727) that, in view of the workload, the evaluation of applications on feed flavourings would be re-organised by giving priority to the assessment of the chemically defined feed flavourings, as agreed with the European Commission
24/06/2015	Technical hearing during risk assessment with the applicant according to the 'EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products': data requirement for the risk assessment of botanicals
27/02/2019	Partial withdrawal by applicant (EC was informed) for the following additives: Thyme leaves gratiola tincture, spike lavender oil, melissa oil, pennyroyal oil, basil oil and savoury summer oil
30/06/2021	EFSA informed the applicant that the evaluation process restarted
08/07/2021	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterisation, safety for target species, safety for the consumer, safety for the user and environment*
05/05/2023	Reception of supplementary information from the applicant (partial dataset: peppermint oil) - Scientific assessment remains suspended
28/09/2023	Partial withdrawal of the application for the following additive: Spanish majoram oil
19/06/2024	The application was split and a new EFSA-Q-2024-00405 was assigned to the additive included in the present assessment
08/07/2024	Partial withdrawal of the application for the following additives: lilac chastetree extract and savory summer tincture
26/08/2024	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives. Scientific assessment re-started for the additive included in the present assessment
27/08/2024	Reception of supplementary information from the applicant (letter of agreement)
16/10/2024	Opinion adopted by the FEEDAP Panel on peppermint oil (EFSA-Q-2024-00405)
27/11/2024	Opinion readopted by the FEEEDAP Panel. End of the Scientific assessment for the additive included in the present assessment. The assessment of other additives in BGD 01 is still ongoing

ABBREVIATIONS

BW Body weight
BDG Botanically defined group
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
CLP Classification, Labelling and Packaging
CoE Council of Europe
DM dry matter
ECHA European Chemicals Agency
EINECS European Inventory of Existing Chemical Substances
EMA European Medicines Agency
EURL European Union Reference Laboratory
FEEDAP EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
FFAC Feed Flavourings authorisation Consortium of FEFANA (EU Association of Specialty Feed Ingredients and their Mixtures)
FEMA Flavour Extract Manufacturers Association
FGE food group evaluation
FLAVIS The EU Flavour Information System

FL-no	FLAVIS number
GC-MS	Gas chromatography-mass spectrometry
GC-FID	Gas chromatography-flame ionisation detection
ISO	International Organisation for Standardization
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LOD	Limit of detection
MOE	Margin of Exposure
MOET	Total Margin of Exposure
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PhEur	European Pharmacopoeia
QSAR	Quantitative Structure Activity Relationship
SCF	Scientific Committee on Food
TTC	threshold of toxicological concern
UF	uncertainty factor
WHO	World Health Organization

REQUESTOR

European Commission

QUESTION NUMBER

EFSA-Q-2010-01307 (new EFSA-Q-2024-00405)

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