SCIENTIFIC OPINION

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Safety and efficacy of secondary alicyclic saturated and unsaturated alcohols, ketones, ketals and esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols from chemical group 8 when used as flavourings for all animal species

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

Abstract

This opinion considers the safety and efficacy of 29 compounds belonging to chemical group 8. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) established the following conclusions: menthol [02.015] is safe at 25 mg/kg complete feed for all target species; menthyl acetate [09.016], *d*-carvone [07.146] and methyl dihydrojasmonate [09.520] at 5 mg/kg for all species; α-ionone [07.007], β-ionone [07.008] and *d,l*-isoborneol [02.059] at 5 mg/kg feed for salmonids, veal calves and dogs, and at 1 mg/kg feed for the remaining species; *d,l*-isobornyl acetate [09.218] at 5 mg/kg for all target species except chickens for fattening, laying hens, piglets and cats, for which 1 mg/kg is safe; *d,l*-borneol [02.016], fenchyl alcohol [02.038], α-irone [07.011], (*Z*)-β-damascone [07.083], β-damascenone [07.108], (*E*)-β-damascone [07.224], cyclohexyl acetate [09.027], carvyl acetate [09.215], dihydrocarvyl acetate [09.216] and fenchyl acetate [09.269] at 1 mg/kg for all target species; and *d,l*-isomenthone [07.078], nootkatone [07.089], *Z*-jasmone [07.094], 3-methyl-2-cyclopenten-1-one [07.112], isophorone [07.126], dihydrojasmone [07.140], *l*-carvone [07.147], *d*-fenchone [07.159], *trans*-menthone [07.176], *d*-camphor[07.215] and *d,l*-bornyl acetate [09.017] are safe only at concentrations below the proposed use levels (0.5 mg/kg for cattle, salmonids and non-food producing animals, and 0.3 mg/kg for pigs and poultry). No safety concern would arise for consumers from the use of these compounds as proposed in feeds. Hazards for skin and eye contact, and respiratory exposure are recognised for the majority of the compounds under application. Most are classified as irritating to the respiratory system. Use of the majority of the compounds in animal feed at the maximum safe level is considered safe for the environment. As all of the compounds are used in food as flavourings and their function in feed is essentially the same as that in food no demonstration of efficacy is necessary.

Keywords: sensory additives, feed flavourings, secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters, chemical group 8, safety

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Summary

Following a request from the European Commission, the European Food Safety Authority (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 32 compounds (secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols. Esters may contain aliphatic acyclic or alicyclic acid component) belonging to chemical group 8 when used as flavourings for all animal species. Because the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) has outstanding concerns about two of the compounds under application when used in food, the FEEDAP Panel will delay its assessment of these compounds until these issues have been resolved. During the assessment, the applicant expressed the intention to withdraw the application for DL-menthol [02.218]. The compound has been excluded from further assessment. Consequently, this opinion deals with only 29 of the 32 compounds for which application was made.

The use of menthol [02.015] in animal feed is safe for all target species at the proposed maximum use level of 25 mg/kg complete feed. Menthyl acetate [09.016], *d*-carvone [07.146] and methyl dihydrojasmonate [09.520] are safe for all target species at the proposed maximum use level of 5 mg/kg complete feed. α-Ionone [07.007] and β-ionone [07.008] are safe at the proposed normal use level of 5 mg/kg complete feed for salmonids, veal calves and dogs, and at the use level of 1 mg/kg complete feed for the remaining target species. *d,l*-isoborneol [02.059] is safe at the proposed maximum use level of 5 mg/kg complete feed for salmonids, veal calves, cattle for fattening and dogs, and at the normal use level of 1 mg/kg complete feed for the remaining target species. *d,l*-Isobornyl acetate [09.218] is safe at the proposed maximum use level of 5 mg/kg complete feed for all target species except chickens for fattening, laying hens, piglets and cats, for which the normal use level of 1 mg/kg complete feed is considered safe. *d,l*-Borneol [02.016], fenchyl alcohol [02.038], α-irone [07.011], (*Z*)-β-damascone [07.083], β-damascenone [07.108], (*E*)-β-damascone [07.224], cyclohexyl acetate [09.027], carvyl acetate [09.215], dihydrocarvyl acetate [09.216] and fenchyl acetate [09.269] are safe at the proposed normal use levels of 1 mg/kg complete feed for all target species. *d,l*-Isomenthone [07.078], nootkatone [07.089], *Z*-jasmone [07.094], 3-methyl-2-cyclopenten-1-one [07.112], isophorone [07.126], dihydrojasmone [07.140], *l*-carvone [07.147], *d*-fenchone [07.159], *trans*-menthone [07.176], *d*-camphor[07.215] and *d,l*-bornyl acetate [09.017] are safe only at concentrations below the proposed use levels (0.5 mg/kg complete feed for cattle, salmonids and non-food producing animals, and 0.3 mg/kg complete feed for pigs and poultry).

Secondary alcohols, ketones and esters with esters containing secondary alcohols are rapidly converted to innocuous substances. Mammals, birds and fish share a similar metabolic capacity to handle these compounds. Consequently, no safety concern would arise for the consumer from the use of these compounds up to the highest safe level in feeds.

No specific data on the safety for the user was provided. In the material safety data sheets, hazards for skin and eye contact, and respiratory exposure are recognised for the majority of the compounds under application. Most of them are classified as irritating to the respiratory system.

The concentrations considered safe for the target species are unlikely to have detrimental effects on the terrestrial and fresh water environment, with some exceptions. For five compounds, α-irone [07.011], (*Z*)-β-damascone [07.083], 3-methyl-2-cyclopenten-1-one [07.112], dihydrojasmone [07.140] and (*E*)-β-damascone [07.224], it was not possible to reach a conclusion on the safety for the terrestrial compartment. For cyclohexyl acetate [09.027] and methyl dihydrojasmonate [09.520], the proposed normal use level of 1 mg/kg feed would not cause an environmental risk. For the marine environment, the safe use level for all substances was estimated to be 0.05 mg/kg feed.

As all of the compounds under assessment are used in food as flavourings and their function in feed is essentially the same as that in food, no further demonstration of efficacy is necessary.

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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 also 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 32 substances (menthol, borneol, DL-menthol, fenchyl alcohol, isoborneol, α-ionone, β-ionone, 4-(2,5,6,6-tetramethyl-2-cyclohexenyl)-3-buten-2-one, isopulegone, *d,l*-isomenthone, β-damascone, nootkatone, 3-methyl-2(pent-2-enyl)cyclopent-2-en-1-one, β-damascenone, 3-methyl-2-cyclopenten-1-one, 3,5,5-trimethylcyclohex-2-en-1-one, α-damascone, 3-methyl-2-pentylcyclopent-2-en-1-one, *d*-carvone, *l*-carvone, *d*-fenchone, trans-menthone, (1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, *tr*-1-(2,6,6-tri-methyl-1-cyclohexen-1-yl)but-2-en-1-one, menthyl acetate, bornyl acetate, cyclohexyl acetate, carvyl acetate, dihydrocarvyl acetate, isobornyl acetate, fenchyl acetate and methyl 3-oxo-2-pentyl-1-cyclopentylacetate) belonging to chemical group (CG) 8, when used as a feed additive for all animal species (category: sensory additives; functional group: flavouring compounds). CG 8 for flavouring substances is defined in Commission Regulation (EC) No 1565/2000[3] as 'secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols. Esters may contain aliphatic acyclic or alicyclic acid component'. During the assessment, the applicant expressed the intention to withdraw the application for DL-menthol (EU Flavour Information System (FLAVIS) number) [02.218].[4] During the course of the assessment, this application was split and the present opinion covers 29 out of the 32 substances under application (see Section 1.2).

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 10(2) (re-evaluation of an authorised feed additive). During the course of the assessment, the applicant withdrew the application for the use of chemically defined flavourings in water for drinking.[5] 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 November 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 menthol, borneol, fenchyl alcohol, isoborneol, α-ionone, β-ionone, 4-(2,5,6,6-tetramethyl-2-cyclohexenyl)-3-buten-2-one, *d,l*-isomenthone, β-damascone, nootkatone, 3-methyl-2(pent-2-enyl)cyclopent-2-en-1-one, β-damascenone, 3-methyl-2-cyclopenten-1-one, 3,5,5-trimethylcyclohex-2-en-1-one, 3-methyl-2-pentylcyclopent-2-en-1-one, *d*-carvone, *l*-carvone, *d*-fenchone, trans-menthone, (1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, *tr*-1-(2,6,6-tri-methyl-1-cyclohexen-1-yl)but-2-en-1-one, menthyl acetate, bornyl acetate, cyclohexyl acetate, carvyl acetate, dihydrocarvyl acetate, isobornyl acetate, fenchyl acetate and methyl 3-oxo-2-pentyl-1-cyclopentylacetate, when used under the proposed conditions of use (see Section 3.1.3).

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

[2] On 13/03/2013, EFSA was informed by the applicant that FFAC EEIG was liquidated on 19/12/2012 and their rights as applicant were transferred to FEFANA Asbl (EU Association of Specialty Feed Ingredients and their Mixtures), Avenue Louise 130A, Box 1, 1050 Brussels, Belgium.

[3] Commission Regulation (EC) No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council. OJ L 180, 19.7.2000, p. 8.

[4] The applicant informed EFSA (12 September 2011) on the intention to withdraw the application for *d,l*-menthol [FLAVIS Number 02.218].

[5] On 10 March 2016, EFSA was informed by the European Commission on the withdrawal of the application for re-authorisation of chemically defined flavourings - use in water.

1.2. Additional information

All 32 compounds except *trans*-1-(2,6,6-tri-methyl-1-cyclohexen-1-yl)but-2-en-1-one [07.224] and methyl 3-oxo-2-pentyl-1-cyclopentylacetate [09.520] have been assessed by the Joint Food and Agriculture Organization of the United nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA; WHO, 2000, 2001, 2002, 2005) and considered safe for use in food without limit in most cases. Acceptable daily intake (ADI) values were specified for menthol [02.015], α-ionone [07.007] and β-ionone [07.008], and *d*-carvone [07.146].

The EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) assessed the same compounds and concluded that 29 were safe for consumer when used at the concentrations used for flavouring purposes (EFSA, 2008b,c, 2009a; EFSA CEF Panel, 2010, 2011, 2012a, 2014a,b,c, 2015). However, concerns were raised by the EFSA CEF Panel for two compounds. There was a genotoxicity alert for α-damascone [07.134] based on the presence of the α,β-unsaturated ketone (EFSA, 2009b; EFSA CEF Panel, 2014b). EFSA also requested additional toxicity data for isopulegone [07.067] (EFSA, 2009c). The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) will not proceed with an assessment of these two compounds until (geno)toxicity issues have been resolved. Since the applicant expressed the intention to withdraw the application for DL-menthol [02.218], this compound is also excluded from the present assessment.

(1*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one [07.215] (also known as *d*-camphor) has been evaluated by EFSA (2008c) and maximum use levels were proposed to ensure that exposure to camphor does not exceed 2 mg/kg body weight (bw) on a single day in any age group. Subsequently, specific conditions of use in food were set for *d*-camphor in Regulation (EC) 872/2012.

In its assessment of the safety of carvone considering all sources of exposure, the EFSA Scientific Committee (SC) established an ADI value of 0.6 mg/kg bw per day for *d*-carvone, based on a lower 95% confidence limits of the benchmark dose response of 10% ($BMDL_{10}$) of 60 mg/kg bw per day for an increase in relative liver weight in the rat 90-day studies and an uncertainty factor (UF) of 100. An ADI for *l*-carvone could not be established because of a lack of toxicological data for this enantiomer. The highest level of aggregated exposure to *d*-carvone was estimated to be 0.60 mg/kg bw and day, i.e. at the level of the ADI established for *d*-carvone. The highest level of aggregated exposure to *l*-carvone is threefold that of *d*-carvone (EFSA SC, 2014).

The current assessment concerns 29 substances, all of which are currently listed in the European Union database of flavouring substances[6] and thus authorised for use in food in the European Union. They are also listed as feed flavourings in the European Union Register of Feed Additives. They have not been previously assessed by EFSA as feed additives.

Regulation (EC) No 429/2008[7] allows substances already approved for use in human food to be assessed with a more limited procedure than for other feed additives. However, the use of this procedure is always subject to the condition that food safety assessment is relevant to the use in feed.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[8] in support of the authorisation request for the use of secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols. Esters may contain aliphatic acyclic or alicyclic acid component as a feed additive. The technical dossier was prepared following the provisions of Article 7 of Regulation (EC) No 1831/2003, Regulation (EC) No 429/2008 and the applicable EFSA guidance documents.

[6] 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.

[7] 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.

[8] FEED dossier reference: FAD-2010-0125.

The FEEDAP Panel has sought to use 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 and experts' knowledge, to deliver the present output.

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of flavourings from CG 8 – secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols. Esters may contain aliphatic acyclic or alicyclic acid component – in animal feed. The Executive Summary of the EURL report can be found in Annex A.[9]

2.2. Methodologies

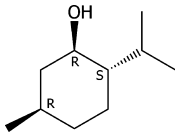
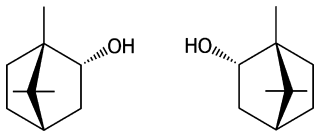
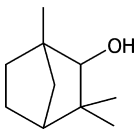
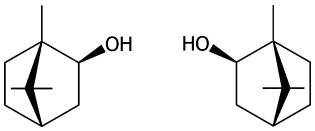
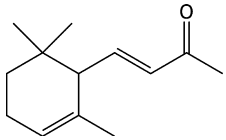
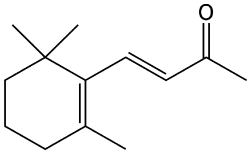
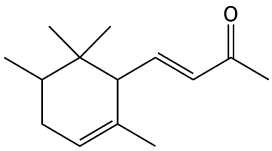
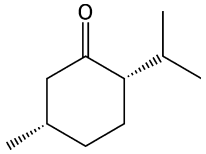
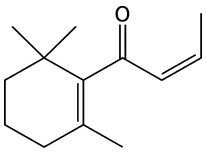
The approach followed by the FEEDAP Panel to assess the safety and the efficacy of the aliphatic and aromatic hydrocarbons is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance documents: Guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), Technical Guidance for assessing the safety of feed additives for the environment (EFSA 2008d), Guidance for the preparation of dossiers for additives already authorised for use in food (EFSA FEEDAP Panel, 2012b), Guidance for establishing the safety of additives for the consumer (EFSA FEEDAP Panel, 2012c), and Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012d).

3. Assessment

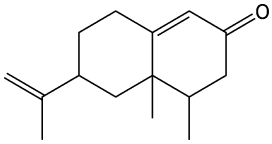
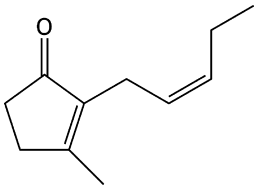
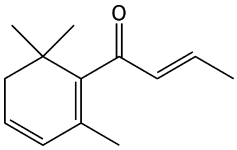
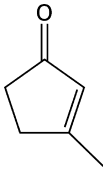
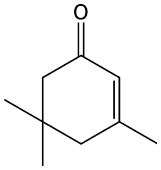
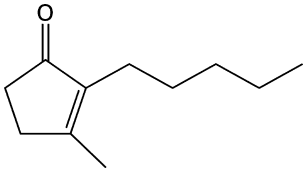
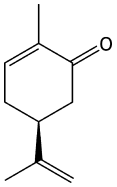
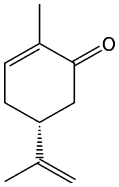
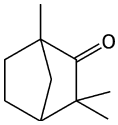
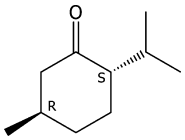
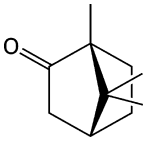
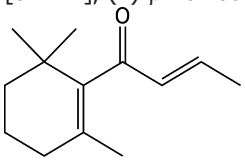
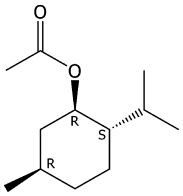
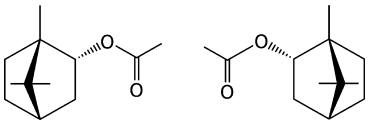
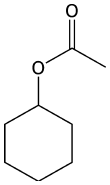
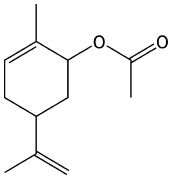
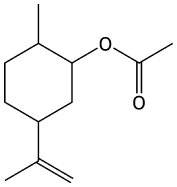
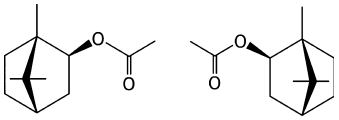
3.1. Characterisation

3.1.1. Characterisation of the flavouring additives

The molecular structures of the 29 additives under assessment are shown in Figure 1 and their physicochemical characteristics in Table 1.

Menthol[10] [02.015]  (-)-isomer shown	*d,l*-Borneol[11] [02.016] 	Fenchyl alcohol[12] [02.038] 
d,l-Isoborneol[13] [02.059] 	α-Ionone [07.007], *E*-isomer 	β-Ionone [07.008], *E*-isomer 
4-(2,5,6,6-Tetramethyl-2-cyclohexenyl)-3-buten-2-one [07.011] (α-Irone), *E*-isomer 	*d,l*-Isomenthone [07.078]  (-)-isomer shown	(*Z*)-β-Damascone [07.083], *Z*-isomer 

[9] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/default/files/FinRep-FAD-2010-0125.pdf
[10] The stereochemistry is not specified but the analytical data provided refer to (-)-menthol or *l*-menthol.
[11] Racemate (±) = DL-Borneol. CAS No refers to (1*R*,2*S*,4*R*)-rel. (EFSA CEF Panel, 2012a).
[12] Racemate (EFSA CEF Panel, 2012a).
[13] Racemate (±) = DL-isoborneol. CAS No in Register refers to (1*R*,2*R*,4*R*)-rel. (EFSA CEF Panel, 2012a).

Nootkatone[14] [07.089] 	3-Methyl-2(pent-2-enyl)cyclopent-2-en-1-one [07.094], (*Z*-jasmone) *Z*-isomer 	β-Damascenone [07.108], *E*-isomer 
3-Methyl-2-cyclopenten-1-one [07.112] 	3,5,5-Trimethylcyclohex-2-en-1-one [07.126] (Isophorone) 	3-Methyl-2-pentylcyclopent-2-en-1-one [07.140] (Dihydrojasmone) 
d-Carvone [07.146] 	*l*-Carvone [07.147] 	*d*-Fenchone[15] [07.159] 
trans-Menthone[16] [07.176]  (-)-isomer shown	(1*R*)-1,7,7-trimethylbicyclo[2.2.1] heptan-2-one [07.215], (*d*-Camphor) 	*trans*-1-(2,6,6-Trimethyl-1-cyclo hexen-1-yl)but-2-en-1-one [07.224], (*E*)-β-Damascone 
Menthyl acetate[17] [09.016] 	*d,l*-Bornyl acetate[18] [09.017] 	Cyclohexyl acetate [09.027] 
Carvyl acetate [09.215] 	Dihydrocarvyl acetate [09.216] 	*d,l*-Isobornyl acetate[19] [09.218] 

[14] (+)-Nootkatone which refers to the (4*R*,4a*S*,6*R*)-isomer (EFSA CEF Panel, 2014d).
[15] D-(+)-Fenchone. CAS No in Register refers to (1*S*,4*R*)-isomer (EFSA CEF Panel, 2012a).
[16] JECFA name: Menthone. CAS No in Register refers to cyclohexanone, 5-methyl-2-(1- methylethyl)-, (2*R*,5*S*)-rel-. (EFSA CEF Panel, 2014b).
[17] JECFA evaluated menthyl acetate (CAS No 16409-45-3 which does not specify isomer). In 2013, the CAS No in Register was replaced by 16409-45-3.
[18] Racemate (±) = DL-Bornyl acetate. CAS No in Register refers to (1*R*,2*S*,4*R*)-rel. (EFSA CEF Panel, 2012a).
[19] Racemate (±) = DL-Isobornyl acetate. CAS No in Register refers to (1*R*,2*R*,4*R*)-rel. (EFSA CEF Panel, 2012a).

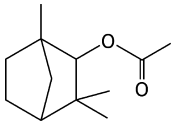
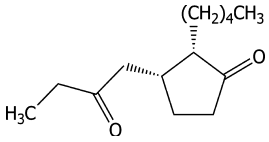
Fenchyl acetate[20] [09.269]	Methyl 3-oxo-2-pentyl-1- cyclopentylacetate [09.520],[21] (Methyl dihydrojasmonate)
	

Figure 1: Molecular structures, [FLAVIS numbers] and (trivial names) of the 29 flavouring compounds under assessment

Table 1: Chemical Abstracts Service (CAS) and FLAVIS numbers and some characteristics of 29 flavouring compounds under assessment

EU Register name	CAS no.	FLAVIS no.	Molecular formula	Molecular weight	Physical state	Log K_{ow}[(a)]
Menthol	89-78-1	02.015	$C_{10}H_{20}O$	156.27	Solid	3.4
d,l-Borneol	507-70-0	02.016	$C_{10}H_{18}O$	154.25	Solid	2.69
Fenchyl alcohol	1632-73-1	02.038	$C_{10}H_{18}O$	154.25	Solid	2.85
d,l-Isoborneol	124-76-5	02.059	$C_{10}H_{18}O$	154.25	Solid	3.24
α-Ionone	127-41-3	07.007	$C_{13}H_{14}O$	192.30	Liquid	3.85
β-Ionone	14901-07-6	07.008	$C_{13}H_{14}O$	192.30	Liquid	3.84
α-Irone	79-69-6	07.011	$C_{14}H_{22}O$	206.33	Liquid	4.71
d,l-Isomenthone	491-07-6	07.078	$C_{10}H_{18}O$	154.25	Liquid	2.87
(*Z*)-β-Damascone	23726-92-3	07.083	$C_{13}H_{20}O$	192.30	Liquid	4.40
Nootkatone	4674-50-4	07.089	$C_{15}H_{22}O$	218.35	Liquid	4.88
Z-Jasmone	488-10-8	07.094	$C_{11}H_{16}O$	164.25	Liquid	3.55
β-Damascenone	23696-85-7	07.108	$C_{13}H_{18}O$	190.28	Liquid	4.04
3-Methyl-2-cyclopenten-1-one	2758-18-1	07.112	C_6H_8O	96.12	Liquid	0.54
Isophorone	78-59-1	07.126	$C_9H_{14}O$	138.21	Liquid	2.07
Dihydrojasmone	1128-08-1	07.140	$C_{11}H_{18}O$	166.26	Liquid	3.25
d-Carvone	2244-16-8	07.146	$C_{10}H_{14}O$	150.22	Liquid	3.07
l-Carvone	6485-40-1	07.147	$C_{10}H_{14}O$	150.22	Liquid	2.71
d-Fenchone	4695-62-9	07.159	$C_{10}H_{16}O$	152.24	Liquid	3.04
trans-Menthone	89-80-5	07.176	$C_{10}H_{18}O$	154.25	Liquid	2.87
d-Camphor	464-49-3	07.215	$C_{10}H_{16}O$	152.24	Solid	3.04
(*E*)-β-Damascone	23726-91-2	07.224	$C_{13}H_{20}O$	192	Liquid	4.40
Menthyl acetate	29066-34-0[(b)]	09.016	$C_{12}H_{22}O_2$	198.31	Liquid	4.39
d,l-Bornyl acetate	76-49-3	09.017	$C_{12}H_{20}O_2$	196.29	Liquid	3.86
Cyclohexyl acetate	622-45-7	09.027	$C_8H_{14}O_2$	142.19	Liquid	2.64
Carvyl acetate	97-42-7	09.215	$C_{12}H_{18}O_2$	194.27	Liquid	3.36
Dihydrocarvyl acetate	20777-49-5	09.216	$C_{12}H_{20}O_2$	196.29	Liquid	3.89
d,l-Isobornyl acetate	125-12-2	09.218	$C_{12}H_{20}O_2$	196.29	Liquid	3.60
Fenchyl acetate	13851-11-1	09.269	$C_{12}H_{20}O_2$	196.29	Liquid	3.60
Methyl dihydrojasmonate	24851-98-7	09.520	$C_{13}H_{22}O_3$	226.31	Liquid	2.98[(c)]

EU: European Union; CAS no. Chemical Abstracts Service number; Flavis number: EU Flavour Information System numbers.
(a): Logarithm of octanol–water partition coefficient.
(b): In 2013, the CAS No in Register was replaced by 16409-45-3.
(c): Generated from EPI-Suite 4.01.

[20] Racemate. CAS No in Register refers to the racemate (EFSA CEF Panel, 2012a).
[21] Mixture of four stereoisomeric forms (*RR, RS, SR* and *SS*) in relatively equal ratios (approx. 25% each), (EFSA CEF Panel, 2014b).

The following compounds are hereafter referred to using the trivial names: 4-(2,5,6,6-tetramethyl-2-cyclohexenyl)-3-buten-2-one [07.011] as α-irone, 3-methyl-2(pent-2-enyl)cyclopent-2-en-1-one [07.094] as *Z*-jasmone, 3,5,5-trimethylcyclohex-2-en-1-one [07.126] as isophorone, 3-methyl-2-pentylcyclopent-2-en-1-one [07.140] as dihydrojasmone, (1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one [07.215] as *d*-camphor, *trans*-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)but-2-en-1-one [07.224] as (*E*)-β-damascone and methyl 3-oxo-2-pentyl-1-cyclopentylacetate [09.520] as methyl dihydrojasmonate.

All of the compounds under consideration except *d*-fenchone are produced by chemical synthesis and typical routes of synthesis are described for each compound.[22] *d*-Fenchone was isolated by distillation from cedar leaf oil (*Cedrum* spp).

Data were provided on the batch to batch variation in five batches of each additive except for *d,l*-isomenthone [07.078], nootkatone [07.089], *d*-fenchone [07.159] and dihydrocarvyl acetate [09.126], for which only one batch was available due to the low use volume (< 2 kg/year).[23] Four batches were available for isophorone [07.126] and dihydrojasmone [07.140]. The content of the active substance exceeded in all cases the JECFA specifications (Table 2).

Table 2: Identity of the substances and data on purity

EU Register name	FLAVIS no.	JECFA specification minimum %[(a)]	Assay %	
			Average	Range
Menthol	02.015	> 95[(b)]	99.8	99.6–100
d,l-Borneol	02.016	> 97[(c)]	98.0	97.6–99.0
Fenchyl alcohol	02.038	> 97[(d)]	98.6	97.0–99.0
d,l-Isoborneol	02.059	> 92[(e)]	97.4	95.5–98.5
α-Ionone	07.007	> 85[(f)]	95.6[(g)]	95.2–95.8
β-Ionone	07.008	> 95[(h)]	98.3	96.5–99.4
α-Irone	07.011	> 98	97.8	97.6–98.3
d,l-Isomenthone	07.078	> 98	98.9[(i)]	–
(*Z*)-β-Damascone	07.083	> 90 (*E*+*Z*)[(j)]	97.5	93.4–99.4
Nootkatone	07.089	> 93[(k)]	97.6[(i)]	–
Z-Jasmone	07.094	> 98 *cis*	99.7	99.2–99.9
β-Damascenone	07.108	> 98	99.4	99.2–99.6
3-Methyl-2-cyclopenten-1-one	07.112	> 98	99.1	98.9–99.4
Isophorone	07.126	> 97	98.8	98.1–99.5
Dihydrojasmone	07.140	> 99	99.2	99.0–99.4
d-Carvone	07.146	> 95	99.8	99.5–100
l-Carvone	07.147	> 97	99.6	99.3–99.7
d-Fenchone	07.159	> 97[(l)]	98.9[(i)]	–
trans-Menthone	07.176	> 96[(b)]	99.5	99.4–99.6
d-Camphor	07.215	> 96	99.4	98.3–100
(*E*)-β-Damascone	07.224	> 90 (*Z*+*E*)[(m)]	97.5	97.1–97.9
Menthyl acetate	09.016	> 97	99.5	98.2–99.9
d,l-Bornyl acetate	09.017	> 98[(n)]	98.1	99.9–99.9
Cyclohexyl acetate	09.027	> 98	99.8	98.2–100
Carvyl acetate	09.215	> 98	99.6	99.3–99.8
Dihydrocarvyl acetate	09.216	> 97[(o)]	98.2[(i)]	–
d,l-Isobornyl acetate	09.218	> 97[(p)]	98.2[(q)]	97.9–98.6
Fenchyl acetate	09.269	> 98	99.1	98.7–99.5

[22] Technical dossier/Section II.
[23] Technical dossier/Section II/Annex 2.1 and Supplementary information June 2011.

EU Register name	FLAVIS no.	JECFA specification minimum %[a]	Assay %	
			Average	Range
Methyl dihydrojasmonate	09.520	> 98[r]	99.0	98.0–99.4

EU: European Union; Flavis number: EU Flavour Information System numbers; JECFA: The Joint FAO/WHO Expert Committee on Food Additives.
(a): FAO (2006).
(b): Sum of two isomers.
(c): According to JECFA, 'Min. Assay value may include isoborneol, other isomers of borneol, trace amounts of fenchyl alcohol and other $C_{10}H_{18}O$ compounds' (EFSA CEF Panel, 2012a).
(d): According to JECFA, 'Min. Assay value is (97%) of $C_{10}H_{18}O$ which may include small amounts of borneol and isoborneol' (EFSA CEF Panel, 2012a).
(e): According to JECFA, 'Min. assay value is 92% and secondary components 3–5% borneol' (EFSA CEF Panel, 2012a).
(f): Applicant specifications: at least 70%, at least 95% sum of isomers.
(g): Sum of isomers.
(h): At least 97% total content of ionones.
(i): One batch, use of the product is 2 kg/year or less.
(j): At least 90%; secondary components 5–8% α- and δ-damascone.
(k): At least 93%; secondary components 3–4% dihydronootkatone.
(l): According to JECFA, 'Min. Assay value is 97% of $C_{10}H_{16}O$ which may include small amounts of *d*-camphor' (EFSA CEF Panel, 2012a).
(m): At least 90%; secondary components 2–4% α–damascone and 2–4% δ-damascone.
(n): According to JECFA, 'Min. Assay value is 98% and may include isobornyl acetate and other bornyl acetate isomers' (EFSA CEF Panel, 2012a).
(o): Sum of four isomers.
(p): According to JECFA, 'Min. Assay value may include small amounts of bornyl acetate' (EFSA CEF Panel, 2012a).
(q): Average of four batches. In a fifth batch, the content of isobornyl acetate (95%) only was determined.
(r): Secondary components: 9,11-methyl-epi-dihydrojasmonate.

Potential contaminants are considered as part of the product specification and are monitored as part of the hazard analysis and critical control point (HACCP) procedure applied by all consortium members. The parameters considered include residual solvents, heavy metals and other undesirable substances. However, no evidence of compliance was provided for these parameters.

3.1.2. Stability

The shelf life for the 29 compounds under assessment ranges from 18 to 36 months, when stored in closed containers under recommended conditions. This assessment is made on the basis of compliance with the original specification over this storage period.

3.1.3. Conditions of use

The applicant proposes the use of all of the 29 compounds in feed for all animal species without withdrawal. For menthol, α-ionone and β-ionone, the applicant proposes a normal use level of 5 mg/kg feed and a high use level of 25 mg/kg. For the remaining 26 additives, the applicant proposes a normal use level of 1 mg/kg feed and a high use level of 5 mg/kg.

3.2. Safety

The assessment of safety is based on the high use levels proposed by the applicant (25 mg/kg for *d,l*-menthol, α-ionone and β-ionone, and 5 mg/kg complete feed for the remaining compounds).

3.2.1. Absorption, distribution, metabolism and excretion (ADME) and residues studies

The majority of the compounds of CG 8 are terpenoids (alcohols, ketones and esters). As lipophilic compounds, they are well absorbed in the gastrointestinal tract.

The metabolic pathways of terpenes/terpenoids in mammals were identified by JECFA as (i) hydrolysis of esters, (ii) oxidation of alcohols and aldehydes, (iii) conjugation of alcohols, (iv) reduction of ketones, (v) reduction of double bonds, (vi) oxidation of side chains, (vii) oxidation of alicyclics, and (viii) conjugation with glutathione (WHO, 2000).

Alcohols are extensively conjugated with glucuronic acid and the derivatives eliminated in urine, as is the case of menthol (WHO, 2000). The major metabolic pathway for the ketones involves reduction

to the corresponding secondary alcohols, which are subsequently excreted, mainly as glucuronic acid conjugates. Some ketones, as carvone and ionone, may undergo ring hydroxylation. The endocyclic double bound of carvone can be reduced giving rise to dihydrocarvone and dihydrocarveol; the exocyclic double bound in β-ionone is reduced to dihydro-β-ionol. The resulting alcohols are conjugated with glucuronic acid and eliminated. The α,β-unsaturated ketones (e.g. carvone, isophorone, etc.), besides being reduced to alcohols and conjugated with glucuronic acid, can also be conjugated with glutathione and eliminated through the bile or in urine as mercapturic acids (WHO, 2000).

In the more lipophilic ketones (e.g. nootkatone) or in those with sterically hindered functional groups (e.g. *d*-camphor), oxidation of a ring position by cytochrome P450 (CYP450) may compete with reduction of the ketone group or oxidation of the alcohol group (WHO, 2005).

The pathways by which fused ring and macrocyclic ketones are detoxified are similar to those for the bridged bicyclic substances. Activated ring positions (e.g. tertiary and allylic positions) and ring substituents are oxidised primarily by CYP450 enzymes, introducing additional polar groups into the molecule. The resulting metabolites are conjugated and then excreted, mainly in the urine (WHO, 2005).

Metabolism studies in laboratory animals are available for a number of compounds belonging to CG 8.

In a recent review of the toxicokinetics of *d*- and *l*-carvone, the EFSA SC concluded that *in vivo* studies in humans and *in vitro* studies in rat resulted in different profiles of metabolites. Particularly, the main metabolites of *d*- and *l*-carvone identified in human volunteers were carvonic acid, dihydrocarvonic acid and uroterpenolone, with carveol and dihydrocarveol as minor products. However, this study did not assess the stereospecificity of the metabolism of carvone in humans (Engel, 2001). The evidence from *in vitro* studies in rat liver microsomes suggests that carveol is likely to be the main metabolite and that metabolic conversion of carvone to carveol in female rat liver is likely to be very slow compared to male rat. *In vitro* studies in rat liver microsomes indicate a steroselective reduction of carvone to carveol and stereospecific conjugation (only *l*-carveol is glucuronidated and with a fourfold higher rate in the rat compared with humans). Glucuronidation of *d*- and *l*-carvone and their other metabolites (carvonic acid, dihydrocarvonic acid and uroterpenolone, dihydrocarveol) has not been studied (EFSA SC, 2014).

Metabolism of *l*-menthol in rats was investigated both *in vitro* and *in vivo*. Rat liver microsomes readily converted *l*-menthol to *p*-menthane-3,8-diol in the presence of NADPH and O_2 (Hawthorn et al., 1988). After oral administration of *l*-menthol (800 mg/kg bw per day) to rats, the following metabolites were isolated and characterised from the urine: *p*-menthane-3,8-diol, *p*-menthane-3,9-diol, 3,8-oxy-*p*-menthane-7-carboxylic acid and 3,8-dihydroxy-*p*-menthane-7-carboxylic acid. *In vivo*, the major urinary metabolites were *p*-menthane-3,8-diol and 3,8-dihydroxy-*p*-menthane-7-carboxylic acid. Repeated oral administration of *l*-menthol to rats for 3 days resulted in the increase of both liver microsomal CYP450 content and NADPH-cytochrome c-reductase activity by nearly 80%. Further treatment (for 7 days total) did not change these levels. Studies with tritiated *l*-menthol in rats indicated about equal excretion in faeces and urine. The main metabolite identified was menthol-glucuronide. Additional metabolites are mono- or dihydroxylated menthol derivatives (EMEA, 2008). Similarly to rats, humans metabolise menthol primarily by conjugation with glucuronic acid and elimination in the urine. CYP450-mediated oxidation occurs in humans, yielding various alcohol and hydroxy acid derivatives, which would also be eliminated in the urine unchanged or conjugated with glucuronic acid (WHO, 1999).

Camphor is readily absorbed in the gastrointestinal tract. In rabbits, orally administered *d*- and *l*-camphor were shown to be oxidised to 5-*endo*- and 3-*endo*-hydroxycamphor, the former predominating. A reduction to borneol was also observed (Robertson and Hussain, 1969). In dogs, the major hydroxylation products of *d*- and *l*-camphor detected in urine after extraction and hydrolysis were 5-*endo*- and 5-*exo*-hydroxycamphor, and probably the *endo*-stereoisomer of 3-hydroxycamphor (Leibmann and Ortiz, 1973). *In vitro* studies with liver preparations from rats and rabbits demonstrated that these reactions occur in liver microsomes, where a small amount of 2,5-bornanedione was also formed (Leibmann and Ortiz, 1973). In humans acutely intoxicated after ingestion of 6–10 g camphor, hydroxylated metabolites in the positions 3, 5 and 8 (or 9) were identified in the urine. The metabolites 5-, 8- (or 9-) hydroxycamphor were subsequently oxidised to the corresponding ketones and carboxylic acids, the latter being conjugated with glucuronic acid (Köppel et al., 1982).

ADME data in general is not available for CG 8 compounds in target species and direct evidence of the specific metabolic pathways involved in their metabolism in animal species is limited. Because of the age of some studies, the information is considered indicative and maybe incomplete. Studies carried out in the rabbit with oral administration of terpenoid ketones, e.g. α-ionone and β-ionone (Prelog & Wursch, 1951 as quoted by WHO 1999), *d,l*-isomenthone (Williams, 1940 as quoted by

WHO, 1999), nootkatone (Asakawa et al., 1986 as quoted by WHO 2006), isophorone (Dutertre-Catella, 1978 as quoted by WHO 2003), carvone (Fischer & Bielig, 1940 as quoted by WHO 1999), camphor (Leibmann and Ortiz, 1973 as quoted by WHO, 2006), (+)-fenchone (Miyazawa and Kameoka as quoted by Scheline, 1991) and fenchyl alcohol (Hämäläinen, 1912 as quoted by WHO, 2006) showed oxidated and/or reduced metabolites (depending on the structure of the ketones), mainly eliminated as glucuronide derivatives in the urine. Orally administered *d,l*-bornyl acetate in rabbits and (+)-borneol in hens were excreted via the kidney as borneol glucuronide (Williams, 1959 as quoted by WHO, 2006; Pan and Fouts, 1978).

Terpenoids presented different stability after 24 h of incubation in an artificial rumen (Rusitec). Approximately 30% menthol was recovered, while menthone, camphor, fenchyl alcohol and fenchone proved to be more stable, with about 60% being recovered (Franz et al., 2010). This indicates that fractions of some terpenes are transformed in the rumen, reducing their bioavailability. Cow fresh rumen content was incubated in a Rusitec system with thuja twigs containing fenchone, camphor and bornyl acetate (Chizzola et al., 2004). Rumen overflow samples were analysed after 24 and 48 h as well as the rumen content at 48 h. Total recoveries were 18.9% of fenchone and 27.8% of camphor of that originally present. Borneol, the hydrolysis product of bornyl acetate, was identified in all fractions.

In a study made for feeding behaviour purposes, lambs were given camphor intraruminally at an increasing dose up to 125 mg/kg bw (Dziba et al., 2009). Absorption of camphor was very rapid, as was its elimination during the primary elimination phase as shown by the plasma concentration time curve. After 7 h, camphor was no longer detected in plasma (detection limit of the method not given).

High-juniper-consuming (HJC) goats and low-juniper-consuming (LJC) goats were intraruminally dosed with a cocktail of several terpenes including 50% of camphor, corresponding to 0.132 g/kg of this compound. The camphor C_{max} in plasma was 0.1 μg/mL in HJC and 0.64 μg/mL in LJC. Also, the area under the curve was significantly higher in LJC than in HJC, the T_{max} being similar in both groups (48 min, median value). The authors attribute those differences to the more extensive degradation of camphor in HJC gut resulting from an adaptive metabolism (Campbell et al., 2010).

The FEEDAP Panel notes that metabolism studies in target animals are scarce, usually nonquantitative, and dealing with only some of the compounds under assessment.

However, the enzymes involved in the biotransformation pathways of these compounds are present in all target species. Carboxylesterases, responsible for the hydrolysis of esters, are present in the gut especially of ruminants and liver of several animal species (cattle, pigs, broiler chicks, rabbits and horses), operating the hydrolysis of esters and originating the respective alcohols and acids (Gusson et al., 2006). Cytosolic carbonyl reductases that reduce ketones to secondary alcohols were characterised in liver and kidney of several animal species, namely chicken, rabbit, and sheep, as reviewed by Felsted and Bachur (1980). The CYP450 monooxygenase families, are present and have been characterised in a number of food-producing animals, including ruminants, horses, pigs (Nebbia et al., 2003; Ioannides, 2006), fish (Wolf and Wolfe, 2005) and birds (Blevins et al., 2012). Epoxide hydrolases, the enzymes involved in the detoxification of the epoxides via formation of diols, which are conjugated and eliminated, are present in mammals (Wisniewski et al., 1987; Marini et al., 1998), fish (Newman et al., 2001) and birds (Harris et al., 2006). All these species, also carry out conjugation reactions with sulfate and glucuronic acid (Watkins and Klaassen, 1986; James, 1987), producing water-soluble derivatives that are eliminated in urine. The FEEDAP Panel notes that for feline species the capacity for conjugation is limited (Court, 2013). Mammals (Watkins and Klaassen, 1986), fish (Espinoza et al., 2013) and birds (Blevins et al., 2012) possess glutathione transferases, which mediate the detoxication of the epoxides by conjugation with glutathione and elimination of the corresponding mercapturic derivatives. Also, the reactive α,β-unsaturated ketones can directly react with glutathione and be eliminated through bile or in urine as mercapturic acids. Therefore, mammals, fish and birds can also be assumed to have the ability to metabolise and excrete the flavouring substances present in CG 8.

Residue studies of the compounds under application in food-producing animals are scarce. However, the secretion of terpene compounds in milk is well demonstrated and varies depending on the nature of pasture and the season, among other factors. However, the most part of data concerns monoterpenes and sesquiterpenes, being data on oxygenated terpenoids (alcohols, ketones and esters) very scarce (Tornambé et al., 2006).

Cheese produced from total mixed ration (TMR)-fed or pasture-fed cows differed in terpenoid contents, for example, *l*-carvone identified in some pasture species and present in the respective cheese, was not found in the TMR-derived cheese (Carpino et al., 2004). Valdivielso et al. (2016) carried out an experiment on a commercial sheep flock under extensive mountain grazing. Although the compounds under assessment, e.g. camphor, bornyl acetate, *endo*-borneol, α-ionone and

β-ionone, were identified in the lyophilised grass, none of these compounds was detected either in milk or in cheese. The authors considered that biodegradation in the animal could explain their absence.

In another study bypassing the rumen, cows were infused into the duodenum with two essential oils, caraway or oregano oil, the first rich in carvone as compared with the second (200:1, based on peak area). Milk was collected and analysed for terpenes. Terpene contents (quantified as total) was significantly higher in milk collected 9 h after infusion of the oils, as compared with control, although returning to control values in the morning milk of the next day. The milk analysis did not discriminate between the compounds, but demonstrated that terpenoids were rapidly transferred to milk and rapidly disappeared on reversion to control diet (Lejonklev et al., 2013).

Different rearing systems (cocksfoot hay, freshly cut-green herbage or pasture, containing different amounts of terpenoids) resulted in similar contents of some terpenoids including menthol and bornyl acetate (in arbitrary units) in bull adipose tissues (Serrano et al., 2011).

These studies show that at least some of the CG 8 compounds are naturally present in different feedingstuffs and the animals, although ingesting different quantities of terpenoids, did not differently accumulate them.

3.2.2. Toxicological studies

Toxicological data (subchronic, repeated-dose studies, with multiple doses tested) could be found for menthol [02.015], α-ionone [07.007], β-ionone [07.008], *d*-carvone [07.146], *d,l*-isobornyl acetate [09.218] and methyl dihydrojasmonate [09.520].

In a study by the National Cancer Institute (NCI, 1979), two doses of (±)-menthol were given orally to rats in the diet (375 and 750 mg/kg bw per day) and mice (300 and 600 mg/kg bw per day) for 103 weeks. A small reduction in survival was seen in the treated female mice. An increase in incidence of mammary gland fibroadenomas or mammary adenocarcinomas was observed in female rats at the lower dose level, but this was not dose related. Overall, the authors concluded that (±)-menthol was not carcinogenic in rats and mice in the performed studies. From this study, a no observed adverse effect level (NOAEL) of 375 mg/kg bw per day in rat and a NOAEL of 600 mg/kg bw per day in mice were derived.

α-Ionone [07.007] and β-ionone [07.008] were given to rats in a 13-week study (Ford et al., 1983 as described in WHO, 1984, 1999). Groups of 15 males and 15 females were administered doses of 0, 10 and 100 mg/kg bw per day of one of the isomers via the diet. The following effects were observed in the high-dose group given α-ionone: reduced food intake (both sexes); reduced serum alkaline phosphatase in males and reduced blood glucose in females; and increased kidney weight (relative) and liver weight (relative and absolute) in males and desquamation of the thyroid in females. When β-ionone was supplied to rats, the effects observed in the high-dose group were as follows: reduced weight gain, food consumption, serum glucose, increased water intake and mild renal functional change. No histological changes in the kidneys and livers were observed. No adverse effects were observed in the low-dose groups given either isomers, and consequently, a NOAEL of 10 mg/kg bw per day was derived.

In another 13-week study in rats (15M/15F), three doses of *d,l*-isobornyl acetate [09.218] (0, 15, 90, 270 mg/kg bw per day) were administered by gastric intubation (Gaunt et al., 1971). No differences in body weight gain, food intake and haematological parameters were observed. Signs of nephrotoxicity (increased kidney weight and water intake, exfoliation and vacuolation of tubular cells, decrease in concentration ability) were seen starting from 90 mg/kg bw per day. Increased liver weight, vacuolation of the epithelium of the intrahepatic bile duct and enlargement of the caeca was seen in rats given the highest dose. From this study, a NOAEL of 15 mg/kg bw per day was derived.

The potential toxicity of methyl 3-oxo-2-pentyl-1-cyclopentylacetate (methyl dihydrojasmonate) [09.520] was examined in a 13-week study following the OECD 408 protocol (Kelly and Bolte, 2000). Sprague–Dawley CD rats (10M/10F per treatment) were administered the test substance with the diet at doses of 0, 10, 50 or 100 mg/kg bw per day. A full set of observations were made including motor activity, ophthalmology and functional activity. All animals were subject to a gross pathology and a histopathological examination was made of all tissues from animals in the control and top dose groups. One animal died from injury during the study, otherwise no deaths occurred. No treatment related differences were seen in food consumption, body weight, haematology, clinical chemistry, urinalysis or organ weights or after macro/microscopic examination of tissues. Consequently a NOAEL of 100 mg/kg bw per day, the top dose administered, can be derived from this study (EFSA CEF Panel, 2012b).

The EFSA SC established an ADI of 0.6 mg/kg bw per day for *d*-carvone, based on the $BMDL_{10}$ of 60 mg/kg bw per day for an increase in relative liver weight in the rat 90-day studies and an UF of 100 (EFSA SC, 2014).

3.2.3. Safety for the target species

The first approach to the safety assessment for target species takes account of the intended use levels in animal feed relative to the maximum reported exposure of humans on the basis of the metabolic body weight (kg $bw^{0.75}$). Human exposure in the European Union to the individual compounds ranges from 2.9 to 16,000 μg/person per day (EFSA, 2008a,b,c, 2009a,b,c,d,e; EFSA CEF Panel, 2014b; EFSA SC, 2014). This corresponds to 0.13–742 μg/$kg^{0.75}$ per day. A more recent estimate of the aggregated exposure to *d*-carvone [07.146] and *l*-carvone [07.147] from all sources resulted in 0.59 and 1.87 mg/kg bw per day, respectively (EFSA SC, 2014). According to these figures, human exposure to *d*- and *l*-carvone (34,500 and 122,200 μg/person per day corresponding to 1,558 and 5,204 μg/$kg^{0.75}$ per day). Table 3 summarises the result of the comparison with human exposure for representative target animals.

Table 3: Comparison of exposure of humans and target animals to the flavourings under application

EU register name	Use level in feed (mg/kg)	Human exposure (μg/kg $bw^{0.75}$ per day)[(a)]	Target animal exposure μg/kg $bw^{0.75}$ per day		
			Salmon	Piglet	Dairy cow
Menthol	25	742	588	2,632	3,855
d,l-Borneol	5	6.03	118	526	777
Fenchyl alcohol	5	2.55	118	526	777
d,l-Isoborneol	5	0.97	118	526	777
α-Ionone	25	12.5	588	2,632	3,855
β-Ionone	25	6.03	588	2,632	3,855
α-Irone	5	0.36	118	526	777
d,l-Isomenthone	5	n.a.	118	526	777
(*Z*)-β-Damascone	5	1.72	118	526	777
Nootkatone	5	6.03	118	526	777
Z-Jasmone	5	0.60	118	526	777
β-Damascenone	5	3.39	118	526	777
3-Methyl-2-cyclopenten-1-one	5	0.003	118	526	777
Isophorone	5	0.21	118	526	777
Dihydrojasmone	5	0.02	118	526	777
d-Carvone	5	1,558[(b)]	118	526	777
l-Carvone	5	5,204[(b)]	118	526	777
d-Fenchone	5	0.28	118	526	777
trans-Menthone	5	39.4	118	526	777
d-Camphor	5	2.69	118	526	777
(*E*)-β-Damascone	5	4.64	118	526	777
Menthyl acetate	5	12.5	118	526	777
d,l-Bornyl acetate	5	0.31	118	526	777
Cyclohexyl acetate	5	0.83	118	526	777
Carvyl acetate	5	0.19	118	526	777
Dihydrocarvyl acetate	5	0.45	118	526	777
d,l-Isobornyl acetate	5	41.3	118	526	777
Fenchyl acetate	5	0.13	118	526	777
Methyl dihydrojasmonate	5	35.7	118	526	777

EU: European Union.
(a): Metabolic body weight (kg $bw^{0.75}$) for a 60-kg person = 21.6.
(b): Refined intake data derived from the EFSA Scientific Committee opinion on the safety assessment of carvone, considering all sources of exposure (EFSA SC, 2014).

Table 3 shows that for all compounds except *d*-carvone [07.146] and *l*-carvone [07.147], the intake by the target animals greatly exceeds that of humans, resulting from use in food. However, for *d*-carvone [07.146] and *l*-carvone [07.147], the level of human exposure has not been established as safe and thus target animal safety cannot be assumed from a comparison of exposures. As a consequence, safety for the target species at the feed concentration applied for these compounds cannot be derived from the risk assessment for food use.

Toxicological data (subchronic, repeated-dose studies) could be found only for menthol [02.015], α-ionone [07.007], β-ionone [07.008], *d,l*-isobornyl acetate [09.218] and methyl dihydrojasmonate [09.520], from which a NOAEL value could be derived (see Section 3.2.2) and *d*-carvone [07.146] for which a $BMDL_{10}$ is available. The NOAELs for menthol and *d,l*-isobornyl acetate are considered also to apply, respectively, to menthyl acetate [09.016] and *d,l*-isoborneol [02.059], because the compounds share common metabolic pathways and are interconverted by hydrolysis reactions.

Applying an UF of 100 to these NOAELs and the $BMDL_{10}$, the maximum safe intake for the target species was derived following the EFSA Guidance for sensory additives (EFSA FEEDAP Panel, 2012b), and thus the maximum safe feed concentration was calculated for menthol and menthyl acetate, α- and β-ionone, *d*-carvone, *d,l*-isobornyl acetate and *d,l*-isoborneol, and methyl dihydrojasmonate. The results are summarised in Tables 4 and 5.

Table 4: Maximum safe concentration in feed for different target animals for (**A**) menthol [02.015] and menthyl acetate [09.016], (**B**) α-ionone [07.007] and β-ionone [07.008], (**C**) *d*-carvone [07.146]

Target animal	Default values		Maximum safe intake/feed concentration					
	Body weight (kg)	Feed intake (g/day)[a]	Intake (mg/day)			Concentration (mg/kg feed)[b]		
			A	B	C	A	B	C
Salmonids	2	40	7.5	0.2	1.2	189	5.0	30
Veal calves (milk replacer)	100	2,000	375	10	60	188	5.0	30
Cattle for fattening	400	8,000	1,500	40	240	165	4.4	26
Dairy Cows	650	20,000	2,437	62	390	107	2.9	17
Piglets	20	1,000	75	2.0	12	75	2.0	12
Pigs for fattening	100	3,000	375	10	60	125	3.3	20
Sows	200	6,000	750	20	120	125	3.3	20
Chickens for fattening	2	120	7.5	0.2	1.2	62	1.7	10
Laying hens	2	120	7.5	0.2	1.2	62	1.7	10
Turkeys for fattening	12	400	45	1.2	7.2	112	3.0	18
Dogs	15	250	56	1.5	9	198	5.3	32
Cats[c]	3	60	2.2	0.1	0.4	33	0.9	5.2

(a): Complete feed with 88% dry matter (DM), except milk replacer for veal calves (94.5% DM), and for cattle for fattening, dairy cows, dogs and cats for which the values are DM intake.
(b): Complete feed containing 88% DM, milk replacer 94.5% DM.
(c): The uncertainty factor for cats is increased by an additional factor of 5 because of the reduced capacity for glucuronidation.

Table 5: Maximum safe concentration in feed for different target animals for (**D**) *d,l*-isobornyl acetate [09.218] and (**E**) methyl dihydrojasmonate [09.520]

Target animal	Default values		Maximum safe intake/feed concentration			
	Body weight (kg)	Feed intake (g/day)[a]	Intake (mg/day)		Concentration (mg/kg feed)[b]	
			D	E	D	E
Salmonids	2	40	0.3	2	7.5	50
Veal calves (milk replacer)	100	2,000	15	100	7.5	50
Cattle for fattening	400	8,000	60	400	6.6	44
Dairy Cows	650	20,000	97.5	650	4.3	29

Target animal	Default values		Maximum safe intake/feed concentration			
	Body weight (kg)	Feed intake (g/day)[a]	Intake (mg/day)		Concentration (mg/kg feed)[b]	
			D	E	D	E
Piglets	20	1,000	3.0	20	3.0	20
Pigs for fattening	100	3,000	15	100	5.0	33
Sows	200	6,000	30	200	5.0	33
Chickens for fattening	2	120	0.3	2	2.5	17
Laying hens	2	120	0.3	2	2.5	17
Turkeys for fattening	12	400	1.8	12	4.5	30
Dogs	15	250	2.3	15	7.9	53
Cats[c]	3	60	0.1	0.6	1.3	8.8

(a): Complete feed with 88% dry matter (DM), except milk replacer for veal calves (94.5% DM), and for cattle for fattening, dairy cows, dogs and cats for which the values are DM intake.
(b): Complete feed containing 88% DM, milk replacer 94.5% DM.
(c): The uncertainty factor for cats is increased by an additional factor of 5 because of the reduced capacity for glucuronidation.

For *d,l*-isoborneol, taking into account that the NOAEL derives from the acetate and the relative molecular weights, safe levels in feed are reduced by approximately 20%. The resulting safe concentrations in feed (expressed as mg/kg complete feed) are 6 for salmonids and veal calves, 5 for cattle for fattening, 4 for pigs for fattening and sows, 3.4 for dairy cows, 3.6 for turkeys for fattening, 2.4 for piglets, 2.0 for chickens for fattening and laying hens, 6.3 for dogs and 1.0 for cats.

For the 21 remaining compounds, subchronic, repeated-dose studies performed with the additive under assessment were not available or were submitted only as a summary report. Therefore, the threshold of toxicological concern (TTC) approach was followed to derive the maximum safe feed concentration (EFSA FEEDAP Panel, 2012a).

For Cramer Class I compounds, namely *d,l*-borneol [02.016], fenchyl alcohol [02.038], α-irone [07.011], (Z)-β-damascone [07.083], β-damascenone [07.108], (*E*)-β-damascone [07.224], cyclohexyl acetate [09.027], carvyl acetate [09.215], dihydrocarvyl acetate [09.216] and fenchyl acetate [09.269], the calculated safe use level for these compounds is 1.5 mg/kg complete feed for cattle, salmonids and non-food producing animals and 1.0 mg/kg complete feed for pigs and poultry.

The remaining Cramer Class II compounds, namely *d,l*-isomenthone [07.078], nootkatone [07.089], *Z*-jasmone [07.094], 3-methyl-2-cyclopenten-1-one [07.112], isophorone [07.126], dihydrojasmone [07.140], *l*-carvone [07.147], *d*-fenchone [07.159], *trans*-menthone [07.176], *d*-camphor [07.215] and *d,l*-bornyl acetate [09.017] are considered safe at 0.5 mg/kg complete feed for cattle, salmonids and non-food producing animals and 0.3 mg/kg complete feed for pigs and poultry.

3.2.3.1. Conclusions on safety for the target species

The FEEDAP Panel concludes that:

- menthol [02.015] is safe at the proposed maximum use level (25 mg/kg complete feed) for all target species;
- menthyl acetate [09.016], *d*-carvone [07.146] and methyl dihydrojasmonate [09.520] are safe at the proposed maximum use level (5 mg/kg complete feed) for all target species;
- α-ionone [07.007] and β-ionone [07.008] are safe at the proposed normal use level (5 mg/kg complete feed) for salmonids, veal calves and dogs. For the remaining target species, the use level of 1 mg/kg complete feed is considered safe;
- *d,l*-isoborneol [02.059] is safe at the proposed maximum use level (5 mg/kg complete feed) for salmonids, veal calves, cattle for fattening and dogs. For the remaining target species, the normal use level of 1 mg/kg complete feed is considered safe;
- *d,l*-isobornyl acetate [09.218] is safe at the proposed maximum use level (5 mg/kg complete feed) for all target species except chickens for fattening, laying hens, piglets and cats. For these species, it is safe at the proposed normal use level of 1 mg/kg complete feed;
- *d,l*-borneol [02.016], fenchyl alcohol [02.038], α-irone [07.011], (*Z*)-β-damascone [07.083], β-damascenone [07.108], (*E*)-β-damascone [07.224], cyclohexyl acetate [09.027], carvyl

acetate [09.215], dihydrocarvyl acetate [09.216] and fenchyl acetate [09.269] are safe at the proposed normal use levels of 1 mg/kg complete feed for all animal species;

- *d,l*-isomenthone [07.078], nootkatone [07.089], *Z*-jasmone [07.094], 3-methyl-2-cyclopenten-1-one [07.112], isophorone [07.126], dihydrojasmone [07.140], *l*-carvone [07.147], *d*-fenchone [07.159], *trans*-menthone [07.176], *d*-camphor [07.215] and *d,l*-bornyl acetate [09.017] are safe only at concentrations below the proposed use levels (0.5 mg/kg complete feed for cattle, salmonids and non-food producing animals, and 0.3 mg/kg complete feed for pigs and poultry).

3.2.4. Safety for the consumer

All compounds are currently authorised in the European Union as food flavourings.[6] ADI values have been set for menthol (4 mg/kg bw per day), α-ionone and β-ionone (group ADI: 0.1 mg/kg bw per day) and *d*-carvone (0.6 mg/kg bw per day), and specific conditions apply for the use of *d*-camphor in food (Regulation (EC) No 872/2012).[6]

The consumers are exposed to the compounds under assessment due to their natural occurrence in food and use as food flavours. Animals consuming plant-based diets are also naturally exposed to the majority of the compounds under assessment with evidence of their presence in tissues and products (including milk). The additional exposure of consumers via products from animals given flavours cannot be calculated because much of the available data is only qualitative in nature. However, considering the data on metabolism and the toxicity of the compounds under consideration and the proposed use levels, the FEEDAP Panel concludes that supplementation of animals diets with any of the compounds under assessment would not raise concerns for consumer safety.

3.2.5. Safety for the user

No specific data on the safety for the user was provided. In the material safety data sheets,[24] hazards for skin and eye contact, and respiratory exposure are recognised for the majority of the compounds under application. Most of them are classified as irritating to the respiratory system.

3.2.6. Safety for the environment

The additions of naturally occurring substances that will not result in a substantial increase in the concentration in the environment are exempt from further assessment. Examination of the published literature shows that this applies to menthol [02.015], *d,l*-borneol [02.016], fenchyl alcohol [02.038], *d,l*-isoborneol [02.059], α-ionone [07.007], β-ionone [07.008], *d,l*-isomenthone [07.078], nootkatone [07.089], Z-jasmone [07.094], β-damascenone [07.108], isophorone [07.126], *d*-carvone [07.146], *l*-carvone [07.147], *d*-fenchone [07.159], *trans*-menthone [07.176], *d*-camphor [07.215], menthyl acetate [09.016], *d,l*-bornyl acetate [09.017], carvyl acetate [09.215], dihydrocarvyl acetate [09.216], *d,l*-isobornyl acetate [09.218] and fenchyl acetate [09.269], which occur in the environment at levels above the maximum application rate (data taken from the TNO database Volatile Compounds in Food *ver.* 14.1; Burdock, 2009).[25] They were excluded from further consideration.

For the other seven compounds, α-irone [07.011], (*Z*)-β-damascone [07.083], 3-methyl-2-cyclopenten-1-one [07.112], dihydrojasmone [07.140], (*E*)-β-damascone [07.224], cyclohexyl acetate [09.027] and methyl dihydrojasmonate [09.520], there is no or insufficient data on natural occurrence in the European environment or they occur at levels below the application rate identified as safe (ranging from 0.5 to 5 mg/kg feed). These substances are therefore assessed in a predicted environmental concentration (PEC) calculation for soil (PEC_{soil}) arising from the application rate. The calculations performed according to the EFSA guidance (EFSA, 2008b) using the most conservative value obtained (lamb manure) are shown in Table 6.

Table 6: PEC values of the flavourings of CG 8 under assessment

EU Register name	CAS no.	Dose (mg/kg)	PEC_{soil} (μg/kg)	$PEC_{pore\ water}$ (μg/L)	$PEC_{surface\ water}$ (μg/L)
α-Irone	79-69-6	1.5	32	1.6	0.5
(*Z*)-β-Damascone	23726-92-3	1.5	32	2.5	0.8

[24] Technical dossier/Section II/Annex II.3.
[25] Technical dossier/Supplementary information September 2011.

EU Register name	CAS no.	Dose (mg/kg)	PEC_{soil} (μg/kg)	$PEC_{pore\ water}$ (μg/L)	$PEC_{surface\ water}$ (μg/L)
3-Methyl-2-cyclopenten-1-one	2758-18-1	0.5	11	27.5	9.2
Dihydrojasmone	1128-08-1	0.5	11	2.0	0.7
(*E*)-β-Damascone	23726-91-2	1.5	32	2.5	0.8
Cyclohexyl acetate	622-45-7	1.5	32	26.0	8.7
Methyl dihydrojasmonate	24851-98-7	5	107	38.2	12.8

EU: European Union; CAS No: Chemical Abstracts Service; PEC: predicted environmental concentration.

All values are above the threshold of 10 μg/kg (EFSA, 2008b). The PEC for pore water, however, is dependent on the sorption, which is different for each compound. For these calculations, the substance-dependent constants organic carbon sorption constant (K_{oc}), molecular weight, vapour pressure and solubility are needed. These were estimated from the Simplified Molecular Input Line Entry Specification (SMILES) notation of the chemical structure using EPIWEB 4.1 (Table 7).[26] This program was also used to derive the SMILES notation from the CAS numbers. The K_{oc} value derived from the first-order molecular connectivity index was used, as recommended by the EPIWEB program.

Table 7: Physicochemical properties predicted by EPIWEB 4.1

EU Register name	CAS no.	Predicted by EPIWEB 4.1				
		DT_{50}[(a)] (days)	Molecular weight (g/mol)	Vapour pressure (Pa)	Solubility (mg/L)	K_{oc}[(b)] (L/kg)
α-Irone	79-69-6	27	206.33	1.96	3.85	1104
(*Z*)-β-Damascone	23726-92-3	25	192.30	1.7	7.986	713
3-Methyl-2-cyclopenten-1-one	2758-18-1	9	96.13	490	10,200	15
Dihydrojasmone	1128-08-1	6	166.27	3.97	38.82	295
(*E*)-β-Damascone	23726-91-2	25	192.30	1.7	7.986	713
Cyclohexyl acetate	622-45-7	8	142.20	180	453.8	63
Methyl dihydrojasmonate	24851-98-7	6	226.32	0.158	91.72	151

EU: European Union; CAS No: Chemical Abstracts Service.
(a): DT_{50}, half-life of the additive (by BioWin3).
(b): K_{oc}, organic carbon sorption constant.

The half-life (DT_{50}) was calculated using BioWin3 (Ultimate Survey Model), which gives a rating number. This rating number (*r*) was translated into a half-life using the formula of Arnot et al. (2005):

$$DT_{50} = 10^{(-r\times 1.07+4.12)}$$

This is the general regression used to derive estimates of aerobic environmental biodegradation half-lives from BioWin3 model output.

The seven substances in Table 5 have a $PEC_{pore\ water}$ above 0.1 μg/L and PEC_{soil} above 10 μg/kg. Therefore, they are subjected to phase II risk assessment.

In the absence of experimental data, the phase II risk assessment was performed using ECOSAR v1.11, which estimates the half-maximal effective concentration (EC_{50}) or lethal concentration (LC_{50}) for earthworms, fish, algae and *Daphnia* from the SMILES notation of the substance. The predicted no effect concentration (PNEC) for terrestrial environment ($PNEC_{soil}$) was determined by dividing the LC_{50} earthworm by a UF of 1,000. The corresponding PNEC for aquatic compartment ($PNEC_{aquatic}$) was derived from the lowest toxicity value for freshwater environment by applying a UF of 1,000.

For five compounds, it was not possible to derive the LC_{50} for the earthworms using ECOSAR, therefore it is not possible to reach a conclusion on the safety for the terrestrial compartment (Table 8). For the remaining two compounds, the ratio PEC/PNEC for soil was < 1, indicating that there is no risk for the terrestrial environment at the use levels considered safe for target species.

[26] Available online: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm

Table 8: Phase II environmental risk assessment of soil and aquatic compartments for CG 8 compounds used as feed additives for terrestrial farm animals (Exposure and effect data were modelled using EPIWEB 4.1 and ECOSAR 1.11)

EU Register name Soil	LC_{50}[(a)] Earthworm (mg/kg)			$PNEC_{soil}$ (µg/kg)	PEC_{soil} (µg/kg)	PEC/PNEC
α-Irone	–			–	32	–
(*Z*)-β-Damascone	–			–	32	–
3-Methyl-2-cyclopenten-1-one	–			–	11	–
Dihydrojasmone	–			–	11	–
(*E*)-β-Damascone	–			–	32	–
Cyclohexyl acetate	1,152			1,152	32	0.005
Methyl dihydrojasmonate	1,431			1,431	107	0.074
Aquatic	**LC_{50} Fish (mg/L)**	**LC_{50} *Daphnia* (mg/L)**	**EC_{50}[(b)] Algae (mg/L)**	**PNEC aquatic (µg/L)**	**PEC_{sw} (µg/L)**	**PEC/ PNEC**
α-Irone	1.794	0.513	0.519	0.513	0.5	0.975
(*Z*)-β-Damascone	2.772	0.867	0.828	0.828	0.8	0.966
3-Methyl-2-cyclopenten-1-one	361.419	303.068	154.146	154	9.2	0.060
Dihydrojasmone	7.586	2.911	2.44	2.44	0.7	0.286
(*E*)-β-Damascone	2.772	0.867	0.828	0.828	0.8	0.966
Cyclohexyl acetate	8.011	15.544	5.975	5.975	8.7	1.456
Methyl dihydrojasmonate	8.155	15.272	5.569	5.569	12.75	2.289

EU: European Union.
(a): LC_{50}, the concentration of a test substance which results in a 50% mortality of the test species.
(b): EC_{50}, the concentration of a test substance which results in 50% of the test animals being adversely affected (i.e. both mortality and sublethal effects).

The PEC/PNEC for surface water was < 1 for all compounds with the exception of cyclohexyl acetate and methyl dihydrojasmonate indicating that there is no risk to the fresh water environment at the doses considered safe for target species. For cyclohexyl acetate a dose of 1.5 mg/kg feed resulted in a PEC_{sw}/PNEC ratio of 1.45. For methyl dihydrojasmonate a dose of 5 mg/kg feed resulted in a PEC_{sw}/PNEC ratio of 2.29. For cyclohexyl acetate [09.027] and methyl dihydrojasmonate [09.520], the proposed normal use level of 1 mg/kg feed would not cause an environmental risk.

The use of all additives in fish feed land-based aquaculture systems does not give a predicted environmental concentration of the additive (parent compound) in surface water (PEC_{swaq}) above the trigger value of 0.1 µg/L when calculated according to the guidance. For sea cages, a dietary concentration of 0.047 mg/kg would ensure that the threshold for the PEC_{sed} of 10 µg/kg is not exceeded when calculated according to the EFSA guidance (EFSA, 2008b).

3.2.6.1. Conclusions on safety for the environment

The concentrations considered safe for the target species (see Section 3.2.3) are unlikely to have detrimental effects on the terrestrial and fresh water environment, with some exceptions. For five compounds, α-irone [07.011], (*Z*)-β-damascone [07.083], 3-methyl-2-cyclopenten-1-one [07.112], dihydrojasmone [07.140] and (*E*)-β-damascone [07.224], it was not possible to reach a conclusion on the safety for the terrestrial compartment. For cyclohexyl acetate [09.027] and methyl dihydrojasmonate [09.520], the proposed normal use level of 1 mg/kg feed would not cause an environmental risk. For the marine environment, the safe use level for all substances is estimated to be 0.05 mg/kg feed.

3.3. Efficacy

As all 29 compounds are used in food as flavourings,[6] and their function in feed is essentially the same as that in food, no further demonstration of efficacy is necessary.

4. Conclusions

The use of menthol [02.015] in animal feed is safe for all target species at the proposed maximum use level of 25 mg/kg complete feed. Menthyl acetate [09.016], *d*-carvone [07.146] and methyl dihydrojasmonate [09.520] are safe for all target species at the proposed maximum use level of 5 mg/kg complete feed. α-Ionone [07.007] and β-ionone [07.008] are safe at the proposed normal use level of 5 mg/kg complete feed for salmonids, veal calves and dogs, and at the use level of 1 mg/kg complete feed for the remaining target species. *d,l*-isoborneol [02.059] is safe at the proposed maximum use level of 5 mg/kg complete feed for salmonids, veal calves, cattle for fattening and dogs, and at the normal use level of 1 mg/kg complete feed for the remaining target species. *d,l*-Isobornyl acetate [09.218] is safe at the proposed maximum use level of 5 mg/kg complete feed for all target species except chickens for fattening, laying hens, piglets and cats, for which the normal use level (1 mg/kg complete feed) is considered safe. *d,l*-Borneol [02.016], fenchyl alcohol [02.038], α-irone [07.011], (*Z*)-β-damascone [07.083], β-damascenone [07.108], (*E*)-β-damascone [07.224], cyclohexyl acetate [09.027], carvyl acetate [09.215], dihydrocarvyl acetate [09.216] and fenchyl acetate [09.269] are safe at the proposed normal use levels of 1 mg/kg complete feed for all target species. *d,l*-Isomenthone [07.078], nootkatone [07.089], *Z*-jasmone [07.094], 3-methyl-2-cyclopenten-1-one [07.112], isophorone [07.126], dihydrojasmone [07.140], *l*-carvone [07.147], *d*-fenchone [07.159], *trans*-menthone [07.176], *d*-camphor[07.215] and *d,l*-bornyl acetate [09.017] are safe only at concentrations below the proposed use levels (0.5 mg/kg complete feed for cattle, salmonids and non-food producing animals and 0.3 mg/kg complete feed for pigs and poultry).

Secondary alcohols, ketones and esters with esters containing secondary alcohols are rapidly converted to innocuous substances. Mammals, birds and fish share a similar metabolic capacity to handle these compounds. Consequently, no safety concern would arise for the consumer from the use of these compounds up to the highest safe level in feeds.

Hazards for skin and eye contact, and respiratory exposure are recognised for the majority of the compounds under application. Most are classified as irritating to the respiratory system.

The concentrations considered safe for the target species are unlikely to have detrimental effects on the terrestrial and fresh water environment, with some exceptions. For five compounds, α-irone [07.011], (*Z*)-β-damascone [07.083], 3-methyl-2-cyclopenten-1-one [07.112], dihydrojasmone [07.140] and (*E*)-β-damascone [07.224], it was not possible to reach a conclusion on the safety for the terrestrial compartment. For cyclohexyl acetate [09.027] and methyl dihydrojasmonate [09.520], the proposed normal use level of 1 mg/kg feed would not cause an environmental risk. For the marine environment, the safe use level for all substances was estimated to be 0.05 mg/kg feed.

As all of the compounds under assessment are used in food as flavourings and their function in feed is essentially the same as that in food, no further demonstration of efficacy is necessary.

Documentation provided to EFSA

1) Chemically defined flavourings from Flavouring Group 08 - secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols. Esters may contain aliphatic acyclic or alicyclic acid component (CDG 08). October 2010. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
2) Chemically defined flavourings from Flavouring Group 08 - secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols. Esters may contain aliphatic acyclic or alicyclic acid component (CDG 08). Supplementary information. September 2011. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
3) Chemically defined flavourings from Flavouring Group 08 - secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols. Esters may contain aliphatic acyclic or alicyclic acid component (CDG 08). Supplementary information. July 2012. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
4) Evaluation report of the European Union Reference Laboratory for Feed Additives on the Methods(s) of Analysis for Chemically defined flavourings from Flavouring Group 8.
5) Comments from Member States.

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Abbreviations

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and excretion
$BMDL_{10}$	lower 95% confidence limits of the benchmark dose response of 10%
bw	body weight
$bw^{0.75}$	metabolic 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
DT_{50}	half life of additive (by BioWin3)
EC_{50}	half-maximal effective concentration
EEIG	European Economic Interest Grouping
EURL	European Union Reference Laboratory
FAO	Food Agriculture Organization of the United Nations
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	EU Flavour Information System
GC–MS	gas chromatography–mass spectrometry
HACCP	hazard analysis and critical control points
HJC	high-juniper-consuming
LC_{50}	half-maximal lethal concentration
JECFA	Joint FAO/WHO Expert Committee on Food Additives
K_{oc}	organic carbon sorption constant
LJC	low-juniper-consuming
Log K_{ow}	logarithm of octanol–water partition coefficient
NOAEL	no observed adverse effect level
PEC	predicted environmental concentration
PECsoil	predicted environmental concentration for soil
$PEC_{pore\ water}$	predicted environmental concentration for pore water
$PEC_{surface\ water}$	predicted environmental concentration for surface water
PEC_{swaq}	predicted environmental concentration of the additive (parent compound) in surface water
PNEC	predicted no effect concentration
$PNEC_{aquatic}$	predicted no effect concentration for aquatic compartment
$PNEC_{soil}$	predicted no effect concentration for terrestrial environment
RTL	retention time locking
SC	Scientific Committee
SMILES	simplified molecular input line entry specification
TMR	total mixed ration
TTC	threshold of toxicological concern
UF	uncertainty factor
WHO	World Health Organization

Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis for Secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols

The *chemically defined flavourings - Group 08* (*Secondary alicyclic saturated and unsaturated alcohols/ketones/ketals/esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols*) in this application comprises 32 substances, for which authorisation as feed additives is sought under the category 'sensory additives', functional group 2(b) 'flavouring compounds', according to the classification system of Annex I of Regulation (EC) No 1831/2003.

In the current application submitted according to Article 4(1) and Article 10(2) of Regulation (EC) No 1831/2003, the authorisation for all species and categories is requested. The flavouring compounds of interest have a purity ranging from 90% to 99% and 85% for methyl 3-oxo-2-pentyl-1-cyclopentylacetate.

Mixtures of flavouring compounds are intended to be incorporated only into *feedingstuffs* or drinking *water*. The Applicant suggested no minimum or maximum levels for the different flavouring compounds in *feedingstuffs*.

For the identification of volatile chemically defined flavouring compounds *CDG08* in the *feed additive,* the Applicant submitted a qualitative multianalyte gas chromatography–mass spectrometry (GC–MS) method, using retention time locking (RTL), which allows a close match of retention times on GC–MS. By making an adjustment to the inlet pressure, the retention times can be closely matched to those of a reference chromatogram. It is then possible to screen samples for the presence of target compounds using a mass spectral database of RTL spectra. The Applicant maintained two FLAVOR2 databases/libraries (for retention times and for MS spectra) containing data for more than 409 flavouring compounds. These libraries were provided to the European Union Reference Laboratory (EURL). The Applicant provided the typical chromatogram for the *CDG08* of interest.

In order to demonstrate the transferability of the proposed analytical method (relevant for the method verification), the Applicant prepared a model mixture of flavouring compounds on a solid carrier to be identified by two independent expert laboratories. This mixture contained 20 chemically defined flavourings belonging to 20 different chemical groups to represent the whole spectrum of compounds in use as feed flavourings with respect to their volatility and polarity. Both laboratories properly identified all the flavouring compounds in all the formulations. As the substances of *CDG08* are within the volatility and polarity range of the model mixture tested, the Applicant concluded that the proposed analytical method is suitable to determine qualitatively the presence of the substances from *CDG08* in the *mixture of flavouring compounds.*

Based on the satisfactory experimental evidence provided, the EURL recommends for official control for the qualitative identification in the *feed additive* of the individual (or mixture of) *flavouring compounds* of interest (*) the GC–MS–RTL (Agilent specific) method submitted by the Applicant. However, the method is not able to discriminate between [menthol and D-menthol] or [β-damascone and *tr*-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)but-2-en-1-one] or the two isomers [*d*-Carvone and *l*-Carvone].

As no experimental data were provided by the Applicant for the identification of the *active substance(s)* in *feedingstuffs* and *water*, no methods could be evaluated. Therefore, the EURL is unable to recommend a method for the official control to identify the *active substance(s)* of interest (*) in *feedingstuffs* or *water*.

Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by Article 10 (Commission Regulation (EC) No 378/2005) is not considered necessary.