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Safety and efficacy of non-conjugated and accumulated unsaturated straight-chain and branched-chain, aliphatic primary alcohols, aldehydes, acids, acetals and esters belonging to chemical group 4 when used as flavourings for all animal species

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

Abstract

Following a request from the European Commission, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety and efficacy of 24 compounds belonging to chemical group 4 (non-conjugated and accumulated unsaturated straight-chain and branched-chain, aliphatic primary alcohols, aldehydes, acids, acetals and esters). This opinion concerns 23 compounds from this group. They are currently authorised as flavours in food. The FEEDAP Panel established the following conclusions: hex-3(*cis*)-en-1-ol [02.056], (*Z*)-non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094], non-6(*cis*)-enal [05.059], hex-3(*cis*)-enal [05.075], (*Z*)-hept-4-enal [05.085], hex-3(*cis*)-enyl acetate [09.197], hex-3(*cis*)-enyl formate [09.240], hex-3-enyl butyrate [09.270], hex-3-enyl hexanoate [09.271] and hex-3(*cis*)-enyl isobutyrate [09.563] are safe at the proposed maximum use level of 5 mg/kg complete feed for all target species; citronellol [02.011], (-)-3,7-dimethyl-6-octen-1-ol [02.229], citronellal [05.021], 2,6-dimethylhept-5-enal [05.074], citronellic acid [08.036], citronellyl acetate [09.012], citronellyl butyrate [09.049], citronellyl formate [09.078] and citronellyl propionate [09.129] are safe at the maximum use level of 5 mg/kg for all species, except cats for which the proposed normal use level of 1 mg/kg is considered safe; undec-10-enal [05.035], 1-ethoxy-1-(3-hexenyloxy)ethane [06.081] and hex-3-enyl isovalerate [09.505] are safe at the normal use levels of 1 mg/kg for all species. 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 use of the majority of the compounds in animal feed at the maximum safe level is considered safe for the environment. As all the compounds under assessment are used in food as flavourings, and their function in feed is essentially the same as in food, no further demonstration of efficacy is necessary.

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Keywords: sensory additives, flavourings, unconjugated straight-chain and branched-chain aliphatic primary alcohols, aldehydes, acids and esters, chemical group 4

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003¹ 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 and in addition, Article 10(2) of that Regulation specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, within a maximum of 7 years after the entry into force of this Regulation.

The European Commission received a request from Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)² for authorisation of 24 substances belonging to chemical group (CG) 4 (citronellol, hex-3(cis)-en-1-ol, non-6-en-1-ol, oct-3-en-1-ol, hex-4(cis)-en-1-ol, (-)-3,7-dimethyl-6-octen-1-ol, citronellal, undec-10-enal, non-6(cis)-enal, 2,6-dimethylhept-5-enal, hex-3(cis)-enal, hept-4-enal, 1-ethoxy-1-(3-hexenyloxy)ethane, citronellic acid, citronellyl acetate, citronellyl butyrate, citronellyl formate, citronellyl propionate, hex-3(cis)-enyl acetate, hex-3(cis)-enyl formate, hex-3-enyl butyrate, hex-3-enyl hexanoate, hex-3-enyl isovalerate, and hex-3(cis)-enyl isobutyrate), when used as a feed additive for all animal species (category: sensory additives; functional group: flavourings). CG 4 for flavouring substances is defined in Commission Regulation (EC) No 1565/2000³ as 'non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters with esters containing unsaturated alcohols and acetals containing unsaturated alcohols or aldehydes. No aromatic or heteroaromatic moiety as a component of an ester or acetal.' During the assessment, the applicant expressed the intention to withdraw the application for hex-4(cis)-en-1-ol (EU Flavour Information System (FLAVIS) number) [02.160].⁴ This compound is excluded from the present assessment.

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 25 August 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 citronellol [02.011], hex-3(cis)-en-1-ol [02.056], (Z)-non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094], (-)-3,7-dimethyl-6-octen-1-ol [02.229], citronellal [05.021], undec-10-enal [05.035], non-6(cis)-enal [05.059], 2,6-dimethylhept-5-enal [05.074], hex-3(cis)-enal [05.075], (Z)-hept-4-enal [05.085], (Z)-1-ethoxy-1-(3-hexenyloxy)ethane [06.081], citronellic acid [08.036], citronellyl acetate [09.012], citronellyl butyrate [09.049], citronellyl formate [09.078], citronellyl propionate [09.129], hex-3(cis)-enyl acetate [09.197], hex-3(cis)-enyl formate [09.240], hex-3-enyl butyrate [09.270], hex-3-enyl hexanoate [09.271], hex-3-enyl isovalerate [09.505] and hex-3(cis)-enyl isobutyrate [09.536], when used under the proposed conditions of use (see Section 3.1.3).

1.2. Additional information

Twenty-two of the 23 compounds have been previously assessed by Joint FAO/WHO Expert Committee on Food Additives (JECFA) (WHO, 1999a,b, 2000, 2002a, 2004a,b) and found to be of

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 Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG), Avenue Louise 130A, B-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 (4 July 2012) on the intention to withdraw the application for hex-4(cis)-en-1-ol [FLAVIS Number 02.216].

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.

no safety concern when used at the estimated intake level. The compound not assessed by JECFA was (-)-3,7-dimethyl-6-octen-1-ol [02.229]. In 1979, JECFA set a group acceptable daily intake (ADI) of 0.5 mg/kg body weight (bw) per day for citral, geranyl acetate, citronellol, linalool and linalyl acetate expressed as citral (WHO, 1980) based on a no-observed-effect level (NOEL) of 51 mg/kg bw per day from a single-dose study in rat (Oser, 1958). In 2004, the ADI was retained (WHO, 2004a).

Subsequently, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) concluded that all 23 compounds do not give rise to safety concern when used as flavours in food (EFSA, 2008a, 2009; EFSA CEF Panel, 2010a,b; EFSA CEF Panel, 2010c, 2011, 2013a,b).

All 23 compounds are currently listed in the Regulation (EU) No 872/2012⁶ and in the European Union Register of Feed Additives, and thus authorised for use in food and feed in the European Union (EU), respectively. They have not been previously assessed by EFSA as feed additives.

Regulation (EC) No 429/2008⁷ 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 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 dossier⁸ in support of the authorisation request for the use of the compounds belonging to CG 4 as feed additives. 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.

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 the 'non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols, aldehydes, acids, acetals and esters with esters containing unsaturated alcohols and acetals containing unsaturated alcohols or aldehydes. No aromatic or heteroaromatic moiety as a component of an ester or acetal' 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 23 compounds belonging to CG 4, 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, 2008b), 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).

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-2010-0041.

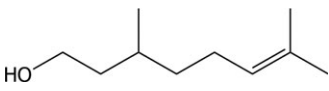
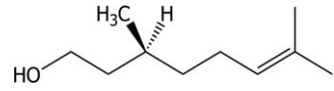
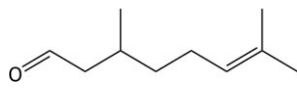
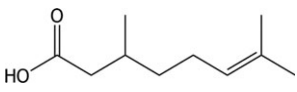
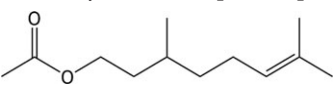

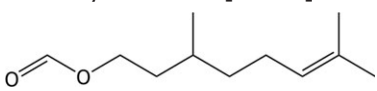
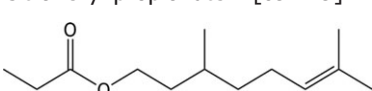
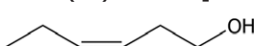
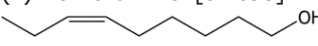
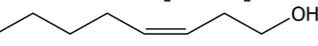
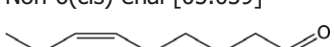

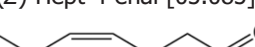
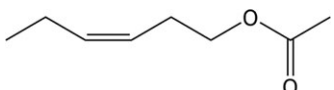
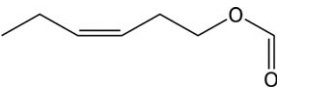
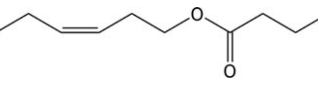
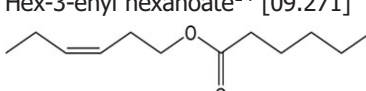
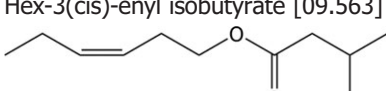
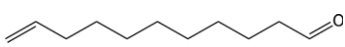
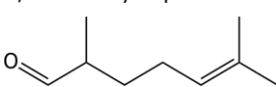
⁹ The full report is available on the EURL website: <https://ec.europa.eu/jrc/sites/default/files/FinRep-FAD-2010-0041.pdf>

3. Assessment

3.1. Characterisation

3.1.1. Characterisation of the flavouring substances

The molecular structures of the 23 flavouring additives under assessment are shown in Figure 1 and their physicochemical characteristics in Table 1.

Citronellol ¹⁰ [02.011] 	(-)-3,7-Dimethyl-6-octen-1-ol [02.229] 	Citronella ¹⁰ [05.021] 
Citronellic acid ¹⁰ [08.036] 	Citronellyl acetate ¹¹ [09.012] 	Citronellyl butyrate ¹¹ [09.049] 
Citronellyl formate ¹¹ [09.078] 		Citronellyl propionate ¹¹ [09.129] 
Hex-3(cis)-en-1-ol [02.056] 	(Z)-Non-6-en-1-ol [02.093] 	Oct-3-en-1-ol ¹² [02.094] 
Non-6(cis)-enal [05.059] 	Hex-3(cis)-enal [05.075] 	(Z)-Hept-4-enal [05.085] 
Hex-3(cis)-enyl acetate [09.197] 	Hex-3(cis)-enyl formate [09.240] 	Hex-3-enyl butyrate ¹³ [09.270] 
Hex-3-enyl hexanoate ¹⁴ [09.271] 	Hex-3(cis)-enyl isobutyrate [09.563] 	
Undec-10-enal [05.035] 	2,6-Dimethylhept-5-enal ¹⁵ [05.074] 	

¹⁰ Racemate.

¹¹ R- or S-enantiomer not specified by CAS No in Register (EFSA CEF Panel, 2013b; FGE.06Rev 4).

¹² JECFA evaluated cis-3-octen-1-ol. CAS No in Register refers to the (Z)-isomer. Register name to be changed to Oct-3Z-en-1-ol (EFSA CEF Panel 2010b, 2013b; FGE.05Rev2 and FGE.06Rev4).

¹³ JECFA evaluated cis-3-hexenyl butyrate. CAS No in Register refers to the (Z)-isomer (EFSA, 2008a; FGE02.rev1). Register name to be changed to hex-3(cis)-enyl butyrate.

¹⁴ JECFA evaluated cis-3-hexenyl hexanoate. CAS No in Register refers to the (Z)-isomer (EFSA, 2008a; FGE02.rev1). Register name to be changed to hex-3(cis)-enyl hexanoate.

¹⁵ JECFA evaluated 2,6-dimethyl-5-heptenal. (R)- or (S)-enantiomer not specified by CAS in Register (EFSA CEF Panel, 2013b).

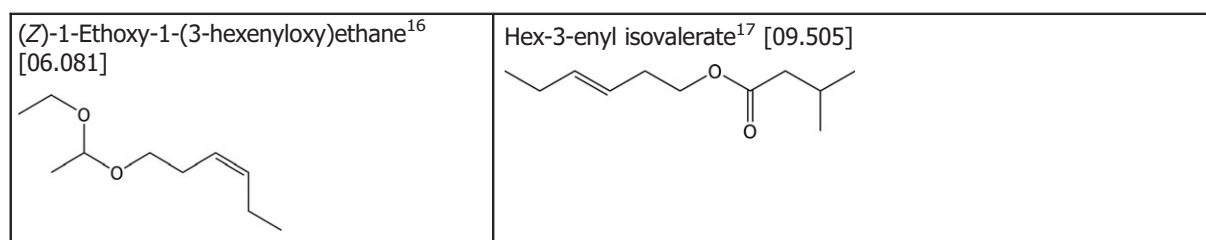


Figure 1: Molecular structures and [FLAVIS numbers] of the 23 flavouring compounds under assessment

Table 1: Chemical Abstracts Service (CAS) and FLAVIS numbers and some characteristics of the chemically defined flavourings under assessment

EU register name	CAS no.	FLAVIS no.	Molecular formula	Molecular weight	Physical state	Log K_{ow} ^(a)
Citronellol	106-22-9	02.011	C ₁₀ H ₂₀ O	156.27	Liquid	3.91
Hex-3(<i>cis</i>)-en-1-ol	928-96-1	02.056	C ₆ H ₁₂ O	100.16	Liquid	1.61
(Z)-Non-6-en-1-ol	35854-86-5	02.093	C ₉ H ₁₈ O	142.24	Liquid	3.01
Oct-3-en-1-ol	20125-84-2	02.094	C ₈ H ₁₆ O	128.21	Liquid	2.68
(-)-3,7-Dimethyl-6-octen-1-ol	7540-51-4	02.229	C ₁₀ H ₂₀ O	156.27	Liquid	3.56 ^(b)
Citronellal	106-23-0	05.021	C ₁₀ H ₁₈ O	154.25	Liquid	3.53
Undec-10-enal	112-45-8	05.035	C ₁₁ H ₂₀ O	168.28	Liquid	4.12
Non-6(<i>cis</i>)-enal	2277-19-2	05.059	C ₉ H ₁₆ O	140.23	Liquid	3.11
2,6-Dimethylhept-5-enal	106-72-9	05.074	C ₉ H ₁₆ O	140.23	Liquid	3.00
Hex-3(<i>cis</i>)-enal	6789-80-6	05.075	C ₆ H ₁₀ O	98.14	Liquid	1.58
(Z)-Hept-4-enal	6728-31-0	05.085	C ₇ H ₁₂ O	112.17	Liquid	2.17
(Z)-1-Ethoxy-1-(3-hexenyloxy)ethane	28069-74-1	06.081	C ₁₀ H ₂₀ O ₂	172.27	Liquid	3.01
Citronellic acid	502-47-6	08.036	C ₁₀ H ₁₈ O ₂	170.25	Liquid	3.35
Citronellyl acetate	150-84-5	09.012	C ₁₁ H ₂₂ O ₂	198.31	Liquid	4.22
Citronellyl butyrate	141-16-2	09.049	C ₁₄ H ₂₆ O ₂	226.36	Liquid	5.34
Citronellyl formate	105-85-1	09.078	C ₁₁ H ₂₀ O ₂	184.28	Liquid	3.87
Citronellyl propionate	141-14-0	09.129	C ₁₃ H ₂₄ O ₂	212.33	Liquid	4.81
Hex-3(<i>cis</i>)-enyl acetate	3681-71-8	09.197	C ₈ H ₁₄ O ₂	142.2	Liquid	2.42
Hex-3(<i>cis</i>)-enyl formate	33467-73-1	09.240	C ₇ H ₁₂ O ₂	128.17	Liquid	2.10
Hex-3-enyl butyrate	16491-36-4	09.270	C ₁₀ H ₁₈ O ₂	170.25	Liquid	3.48
Hex-3-enyl hexanoate	31501-11-8	09.271	C ₁₂ H ₂₂ O ₂	198.31	Liquid	4.54
Hex-3-enyl isovalerate	10032-11-8	09.505	C ₁₁ H ₂₀ O ₂	184.28	Liquid	3.83
Hex-3(<i>cis</i>)-enyl isobutyrate	41519-23-7	09.563	C ₁₀ H ₁₈ O ₂	170.25	Liquid	3.29

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

(a): Logarithm of octanol–water partition coefficient.

(b): Generated from EPI-Suite 4.01.

All of the compounds under consideration are produced by chemical synthesis or, in the case of (-)-3,7-dimethyl-6-octen-1-ol [02.229], derived by fractional distillation of essential oils (e.g. ex *Citronella* or *Geranium* species) and saponification of extracts. Typical routes of synthesis are described for each compound.¹⁸

Data was provided on the batch-to-batch variation in five batches of each additive except hex-3-enyl hexanoate [09.271] for which only one batch was provided due to the low use volume (< 1 kg/year).¹⁹ The content of the active substance exceeded the JECFA specifications for all compounds (Table 2),

¹⁶ Register name to be changed to 1-ethoxy-1-(3Z-hexenyloxy)ethane. Racemate of 1-ethoxy-1-(3Z-hexenyloxy)ethane (EFSA CEF Panel, 2011; FGE.96).

¹⁷ (Z)- or (E)-isomer not specified by CAS No in Register (EFSA CEF Panel, 2010c; FGE.01Rev2).

¹⁸ Technical dossier/Section II.

¹⁹ Technical dossier/Section II/Annex 2.1 and Supplementary information May 2011.

except hex-3(*cis*)-enyl formate [09.240] (for which one batch was below JECFA specifications) and hex-3(*cis*)-enal [05.075]. Data for this compound was provided only for a formulated product which for four batches contains approximately 30% triacetin and for a fifth batch in which the triacetin content was stated to be 50%. Triacetin (glycerol triacetate) is a recognised food additive (E1518) and is used as a solvent/carrier for flavourings.²⁰ Both JECFA (WHO, 1975) and the SCF (European Commission, 1995) assessed triacetin without specifying an ADI.

Table 2: Identity of the substances and data on purity

EU register name	FLAVIS no.	JECFA minimum specification % ^(a)	Assay %	
			Average	Range
Citronellol	02.011	90 ^(b)	97.2	95.0–98.9
Hex-3(<i>cis</i>)-en-1-ol	02.056	98 ^(c)	98.7	98.5–99.1
(<i>Z</i>)-Non-6-en-1-ol	02.093	95	96.7	95.7–97.4
Oct-3-en-1-ol ^(d)	02.094	96 ^(e)	97.0	96.7–97.3
(-)-3,7-Dimethyl-6-octen-1-ol ^(f)	02.229	– ^(g)	76.4 ^(h)	75.0–79.1
Citronellal	05.021	85 ⁽ⁱ⁾	97.3	89.8–99.4
Undec-10-enal	05.035	90	97.9 ^(j)	94.6–98.7
Non-6(<i>cis</i>)-enal	05.059	90 ^(k)	97.9	96.4–99.8
2,6-Dimethylhept-5-enal	05.074	85 ^(l)	88.3	86.2–90.8
Hex-3(<i>cis</i>)-enal	05.075	97	69.1 ^(m)	61.4–66.1
Hept-4-enal	05.085	98 ⁽ⁿ⁾	98.9	98.0–99.4
(<i>Z</i>)-Hept-4-enal		93	95.2 ^(o)	94.0–95.9 ^(o)
(<i>Z</i>)-1-Ethoxy-1-(3-hexenyloxy)ethane	06.081	97	99.1	98.2–99.5
Citronellic acid	08.036	90 ^(p)	99.3	98.6–100
Citronellyl acetate	09.012	92 ^(q)	98.4	96.0–99.2
Citronellyl butyrate	09.049	90 ^(q)	99.3	99.3–99.6
Citronellyl formate	09.078	90 ^(q)	95.8	91.0–98.2
Citronellyl propionate	09.129	90 ^(q)	98.0	95.8–99.7
Hex-3(<i>cis</i>)-enyl acetate	09.197	98 ^(r)	99.7	99.0–100
Hex-3(<i>cis</i>)-enyl formate	09.240	95	96.7	94.7–99.0
Hex-3-enyl butyrate	09.270	95	99.7	99.2–100
Hex-3-enyl hexanoate	09.271	96	99.2 ^(s)	99.2
Hex-3-enyl isovalerate	09.505	95	99.9	99.7–100
Hex-3(<i>cis</i>)-enyl isobutyrate	09.563	98	99.6	99.2–100

EU: European Union; FLAVIS number: EU Flavour Information System numbers; JECFA: The Joint FAO/WHO Expert Committee on Food Additives.

(a): FAO (2006).

(b): Racemate. Min. Assay value 90%. Other constituents: diunsaturated and saturated C10 alcohols, citronellyl acetate, citronellal (EFSA CEF Panel, 2013a).

(c): At least 98% as sum of (*Z*)- and (*E*)-isomers; min. 92% of (*Z*)-isomer (Technical dossier Supplementary information May 2011).

(d): JECFA evaluated *cis*-3-octen-1-ol (CAS No as in Register). CAS No in Register refers to the (*Z*)-isomer. Register name to be changed to Oct-3*Z*-en-1-ol (EFSA CEF Panel, 2010b, 2013b).

(e): At least 96% of C₈H₁₆O, as (*Z*)-isomer (Technical dossier Supplementary information May 2011).

(f): The product name specifies citronellol (ex *Geranium*).

(g): Not evaluated by JECFA. According to EFSA: at least 90% *cis*-isomer; secondary components 2–6% diunsaturated and saturated C10 alcohols, 2–4% citronellyl acetate and 2–3% citronellal (EFSA CEF Panel, 2013b).

(h): At least 75%. Average of four batches, a fifth batch has a purity of 98.6%, min. 75%. Other identified components: geraniol (8%).

(i): Racemate. Min. assay value 85% (as C₁₀H₁₈O). Racemate. Secondary components: 1,8-cineole, 2-isopropylidene-5-methylcyclohexanol, linalool and citronellyl acetate (EFSA CEF Panel, 2013a).

(j): At least 90% (min. 97% total decenals).

²⁰ Commission Regulation (EU) No 1130/2011 of the European Parliament and of the Council of 11 November 2011 amending Annex III to Regulation (EC) No 1338/2008 of the European Parliament and of the Council on food additives establishing a Union list of food additives approved for use in food additives, food enzymes, food flavourings and nutrients. OJ L 295, 12.11.2011, p. 178.

- (k): At least 90%; secondary component 6–9% *trans*-6-nonenal.
- (l): *R*- or *S*-enantiomer not specified by CAS No in the Register (EFSA CEF Panel, 2013b). At least 85%; secondary components: 9–10% 6-methyl-5-hepten-2-one; 1–2% 2,6-dimethyl-6-heptenal.
- (m): Product used by the customers is diluted in triacetin (up to 50%). Average of four batches, a fifth batch has a purity of 92.5% and is diluted in 50% triacetin.
- (n): At least 98% as sum of (*Z*)- and (*E*)- isomers; min. 93% of (*Z*)-isomer; secondary component: 2–5% (*E*)- isomer.
- (o): (*Z*)-isomer (Technical dossier Supplementary information May 2011).
- (p): Racemate. Min. assay value 90%. Other main constituents: citronellal; citronellyl acetate, nerol and geraniol (EFSA CEF Panel, 2013a).
- (q): *R*- or *S*-enantiomer not specified by CAS No in Register (EFSA CEF Panel, 2013b; FGE.06REV 4).
- (r): At least 98% as sum of (*Z*)- and (*E*)- isomers; min. 92% of (*Z*)-isomer (Technical dossier Supplementary information May 2011).
- (s): One batch, use of the product is 1 kg/year or less.

Potential contaminants are considered as part of the product specification and are monitored as part of the Hazard Analysis and Critical Control Point system 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 minimum shelf life of the compounds under assessment ranges from 6 to 24 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 23 compounds in feed for all animal species without a withdrawal time. 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 highest use level proposed by the applicant (5 mg/kg).

3.2.1. Absorption, distribution, metabolism and excretion and residues

In general, compounds belonging to CG 4 are rapidly absorbed, distributed, metabolised and excreted (WHO, 1999b; EFSA, 2010b, 2013b).

The metabolic reactions involved in the biotransformation of straight-chain and branched-chain unsaturated primary aliphatic alcohols, aldehydes, carboxylic acids and esters (WHO, 1999b; EFSA (EFSA CEF Panel, 2010b, 2013b) are: (i) hydrolysis of esters (Heymann, 1980); (ii) oxidation of linear and branched-chain alcohols and aldehydes to acids, by high capacity NAD⁺/NADP-dependent enzymes (Voet and Voet, 1990; Feron et al., 1991; Parkinson, 1996); (iii) reduction of aldehydes to alcohols by NAD(P)H-dependent reductases; (iv) conjugation with glucuronic acid of alcohols (a minor pathway for primary alcohols) and polar metabolites resulting from a combination of omega-, omega-1- and beta-oxidation (Diliberto et al., 1990); (v) metabolism of the resulting linear- or branched-chain unsaturated carboxylic acids to carbon dioxide in the tricarboxylic acid cyclic and fatty acid pathway (Voet and Voet, 1990), by β -oxidation (linear- and short-chain branched carboxylic acids) or ω -oxidation (medium- and long-chain carboxylic acids, presence of ethyl or propyl side chains); (vi) isomerisation reactions by enoyl-CoA isomerase (shift of the double bond from δ^3 - to δ^2 -enoyl CoA, when unsaturation begins at an odd-numbered carbon) and 3-hydroxyacyl-CoA epimerase (*cis* to *trans* isomerisation of δ^2 -enoyl-CoA); (vii) saturation of unsaturated short-chain acids, to yield a substrate that may participate in the fatty acid pathway (Stryer, 1988; EFSA, 2010b, 2013b).

Unsaturated carboxylic acids are metabolised by well-recognised pathways leading to the production of acetyl-CoA and propionyl-CoA, which enter general metabolism (Stryer, 1988).

Aliphatic acetals, such as (*Z*)-1-ethoxy-1-(3-hexenyloxy)ethane [06.081], undergo hydrolysis in the acidic environment of gastric fluid. The resulting alcohols and aldehydes are absorbed and metabolised as outlined above (WHO, 2002b). Acetals absorbed before acid hydrolysis will be oxidised by liver cytochromes to the corresponding acids (Vicchio and Callery, 1989).

Metabolism studies in laboratory animals are available for citronellol [02.012], citronellal [05.021] and citronellic acid [09.012].

(or (*Z*)-hept-4-enal) and hex-3(*cis*)-enal that can be present in milk as a result of degradation of linolenic acid (Bendall, 2001; Bendall and Olney, 2001) and in the fat of pasture-fed lambs (Sivadier et al., 2008). Similarly, the introduction of hex-3-en-1-ol into the rumen of a dairy cow (5 g) also resulted in its appearance in milk in µg/L levels (Honkanen et al., 1964). In a controlled study, citronellol was found in Ragusano cheese (4 months ripening) from fresh pasture cow milk, being absent in cheese made from the milk of cows fed total mixed ration (Carpino et al., 2004). Citronellol was identified in 11 out of 14 plant species grazed by the animals in the pasture system.

3.2.2. Toxicological studies

Subchronic, repeated-dose studies, with multiple doses tested could be found only for hex-3(*cis*)-en-1-ol [02.056] and 2,6-dimethylhept-5-enal [05.074], tested individually, and for citronellyl acetate [09.012] when tested as an admixture with geranyl acetate. An additional study was identified in which citronellol [02.011] was tested as an admixture with linalool at a single dose level.

In a 98-day study in rats (males/females, 15 animals/sex and group), three doses of hex-3(*cis*)-en-1-ol [02.056] (0, 310, 1,250 and 5,000 mg/kg corresponding to 0, 30, 127 and 410 mg/kg bw per day in males, and to 0, 42, 168 and 721 mg/kg bw per day in females) were administered via water for drinking. The study investigated haematological and urinary parameters, gross pathology and histopathology. From this study, a no observed adverse effect level (NOAEL) of 127 mg/kg bw per day was derived for hex-3(*cis*)-en-1-ol based on effects observed at the highest dose tested: a transitory anaemia in females (reduced haemoglobin observed after 6 weeks but not after 14 weeks), an increase in the relative weights of kidneys and adrenals in males and an increase in the concentration of urine also in males. However, there were no histological signs of renal damage and no indications of abnormal kidney functions, and nephrotoxic effects were not observed at lower dosages neither in males nor in females (Gaunt et al., 1969).

Because of similarity in structure and metabolism, the NOAEL derived for hex-3(*cis*)-en-1-ol [02.056] is extrapolated to (*Z*)-non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094], non-6(*cis*)-enal [05.059], hex-3(*cis*)-enal [05.075], (*Z*)-hept-4-enal [05.085], hex-3(*cis*)-enyl acetate [09.197], hex-3(*cis*)-enyl formate [09.240], hex-3-enyl butyrate [09.270], hex-3-enyl hexanoate [09.271] and hex-3(*cis*)-enyl isobutyrate [09.563]. Hex-3-enyl isovalerate [09.505] is not included because the exact stereoisomeric form is not known.

In a subchronic study in rats (males/females, 15 animals/sex and group), 2,6-dimethylhept-5-enal [05.074] was administered with diet at doses of 0, 9, 37 and 150 mg/kg bw per day (measured values) for 3 months. The study examined body weight, feed and water intake, haematology (at week 6 and 13), gross pathology and histopathological changes. At the highest dose tested, serum glucose was increased in both sexes compared with controls and an increase in liver and kidney weights was observed in females. A NOAEL of 37 mg/kg bw per day was determined for 2,6-dimethylhept-5-enal (Gaunt et al., 1983).

The subchronic toxicity of citronellyl acetate [09.012] was tested in mice and rats as an admixture with geranyl acetate (NTP, 1987). The test material is described as geranyl acetate in admixture with a maximum 17% citronellyl acetate. It was administered by gavage at doses of 0, 125, 500 and 1,000 mg/kg bw per day in mice (males/females, 10 animals/sex and group) and of 0, 250, 500, 1,000, 2,000 and 4,000 mg/kg bw per day in rats (males/females, 10 animals/sex and group) for 13 weeks. The study examined mortality, body weight, gross pathology and histopathological changes. No adverse effects were seen, however, no data were available on haematological parameters and clinical chemistry. The same admixture with 71% geranyl acetate and 29% citronellyl acetate was not considered carcinogenic to mice and rats in a 2-year study. However, the reduced survival observed in high-dose male rats, high-dose male mice, and high- and low-dose female mice lowered the sensitivity of these studies for detecting neoplastic responses in these groups. The low survival in mice was associated with infections. In male rats, the marginal increases of squamous cell papillomas of the skin and tubular cell adenomas of the kidney may have been related to administration of the mixture (NTP, 1987). A NOAEL could not be derived from this study.

A mixture of citronellol [02.011] and linalool (1:1 by weight) was administered to rats (10 males/10 females) at dietary levels of 100 mg/kg bw per day for 12 weeks. No treatment-related effects were seen, except a depression in growth and food intake in males which was attributed to the reduced palatability of the test materials. The study considered urine analysis and haematology (on three rats per sex and group), gross pathology (on all animals, liver and kidney weights were

recorded). Histopathology was not performed, although tissues were preserved at necropsy. The NOEL for citronellol was 50 mg/kg bw per day, the only dose tested (Oser, 1958).

Although there was a later NTP study (1987), JECFA did not use these results because of serious concerns about infections and low survival to revise the ADI, which remains based on the Oser study. Consequently, the FEEDAP Panel retains a NOAEL of 50 mg/kg bw per day derived from the 90-day study with citronellol [02.011] in rat (Oser, 1958) as a group NOAEL for citronellol and related citronellyl derivatives.

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. Human exposure in the EU to the individual compounds ranges from 0.32 to 3,700 µg/person per day (EFSA, 2008a, 2009; EFSA CEF Panel, 2010a,b,c, 2011, 2013a,b). This corresponds to 0.01–172 µg/kg^{0.75} per day. These exposure levels are considered safe for humans. 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 (calculated from the proposed maximum feed concentrations of 5 mg/kg feed) to the flavourings under application

Flavouring	Use level in feed (mg/kg)	Human exposure (µg/kg bw ^{0.75} per day) ^(a)	Target animal exposure µg/kg bw ^{0.75} /day		
			Salmon	Piglet	Dairy cow
Citronellol	5	15	118	526	777
Hex-3(<i>cis</i>)-en-1-ol	5	172	118	526	777
(<i>Z</i>)-Non-6-en-1-ol	5	0.10	118	526	777
Oct-3-en-1-ol	5	0.22	118	526	777
(-)-3,7-Dimethyl-6-octen-1-ol	5	17.2	118	526	777
Citronellal	5	38	118	526	777
Undec-10-enal	5	0.01	118	526	777
Non-6(<i>cis</i>)-enal	5	0.08	118	526	777
2,6-Dimethylhept-5-enal	5	1.25	118	526	777
Hex-3(<i>cis</i>)-enal	5	0.19	118	526	777
(<i>Z</i>)-Hept-4-enal	5	0.07	118	526	777
(<i>Z</i>)-1-Ethoxy-1-(3-hexenyloxy)ethane	5	0.21	118	526	777
Citronellic acid	5	0.13	118	526	777
Citronellyl acetate	5	8.81	118	526	777
Citronellyl butyrate	5	1.25	118	526	777
Citronellyl formate	5	4.04	118	526	777
Citronellyl propionate	5	1.62	118	526	777
Hex-3(<i>cis</i>)-enyl acetate	5	25.51	118	526	777
Hex-3(<i>cis</i>)-enyl formate	5	1.72	118	526	777
Hex-3(<i>cis</i>)-enyl butyrate	5	6.03	118	526	777
Hex-3(<i>cis</i>)-enyl hexanoate	5	1.62	118	526	777
Hex-3-enyl isovalerate	5	0.37	118	526	777
Hex-3(<i>cis</i>)-enyl isobutyrate	5	0.56	118	526	777

bw: body weight.

(a): Metabolic body weight (kg bw^{0.75}) for a 60-kg person = 21.6.

Table 4 shows that for all compounds, except hex-3(*cis*)-en-1-ol, the intake by the target animals greatly exceeds that of humans, resulting from use in food. Consequently, safety for the target species at the feed concentration applied cannot be derived from the risk assessment for food use.

As an alternative, the maximum feed concentration which can be considered safe for the target animals can be derived from the lowest NOAEL if suitable data are available. Toxicological data derived from a subchronic, repeated-dose study were available for hex-3(*cis*)-en-1-ol [02.056],

2,6-dimethylhept-5-enal [05.074] and citronellol [02.011], from which a NOAEL value could be derived (see Section 3.2.2). The NOAEL of 127 mg/kg bw per day for hex-3(*cis*)-en-1-ol [02.056] is considered to apply also to (*Z*)-non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094], non-6(*cis*)-enal [05.059], hex-3(*cis*)-enal [05.075], (*Z*)-hept-4-enal [05.085], hex-3(*cis*)-enyl acetate [09.197], hex-3(*cis*)-enyl formate [09.240], hex-3-enyl butyrate [09.270], hex-3-enyl hexanoate [09.271] and hex-3(*cis*)-enyl isobutyrate [09.563]. Similarly, the NOAEL of 50 mg/kg bw per day for citronellol [02.011] can be applied to (-)-3,7-dimethyl-6-octen-1-ol [02.229], citronellal [05.021], citronellic acid [08.036], citronellyl acetate [09.012], citronellyl butyrate [09.049], citronellyl formate [09.078] and citronellyl propionate [09.129]. Applying an uncertainty factor (UF) of 100 to the respective NOAELs, the maximum safe intake for the target species was derived following the EFSA Guidance for sensory additives (EFSA FEEDAP Panel, 2012a), and thus the maximum safe feed concentration was calculated (Table 4). The UF for cats is increased by an additional factor of 5 because of the reduced capacity of glucuronidation (Court and Greenblatt, 1997).

Table 4: Maximum safe concentration in feed for different target animals for (A) hex-3(*cis*)-en-1-ol and related compounds, (B) 2,6-dimethylhept-5-enal, and (C) citronellol and related compounds

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	2.5	0.7	1.0	64	19	25
Veal calves (milk replacer)	100	2,000	127	37	50	64	19	25
Cattle for fattening	400	8,000	508	148	200	56	16	22
Dairy Cows	650	20,000	825	241	325	36	11	14
Piglets	20	1,000	25	7.4	10	25	7	10
Pigs for fattening	100	3,000	127	37	50	42	12	17
Sows	200	6,000	254	74	100	42	12	17
Chickens for fattening	2	120	2.5	0.7	1.0	21	6	8
Laying hens	2	120	2.5	0.7	1.0	21	6	8
Turkeys for fattening	12	400	15	4.4	6.0	38	11	15
Dogs	15	250	19	5.6	7.5	67	20	26
Cats ^(c)	3	60	0.8	0.2	0.3	11	3	4.4

(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 expressed as 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 of glucuronidation (Court and Greenblatt, 1997).

(A): hex-3(*cis*)-en-1-ol, (*Z*)-non-6-en-1-ol, oct-3-en-1-ol, non-6(*cis*)-enal, hex-3(*cis*)-enal, (*Z*)-hept-4-enal, hex-3(*cis*)-enyl acetate, hex-3(*cis*)-enyl formate, hex-3(*cis*)-enyl butyrate, hex-3(*cis*)-enyl hexanoate and hex-3(*cis*)-enyl isobutyrate.

(B): 2,6-dimethylhept-5-enal.

(C): citronellol, (-)-3,7-dimethyl-6-octen-1-ol, citronellal, citronellic acid, citronellyl acetate, citronellyl butyrate, citronellyl formate and citronellyl propionate.

As individual reliable NOAELs could not be identified for the remaining three compounds, 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, i.e. undec-10-enal [05.035], (*Z*)-1-ethoxy-1-(3-hexenyloxy)ethane [06.081] and hex-3-enyl isovalerate [09.505], the calculated safe use level 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.

3.2.3.1. Conclusions on safety for the target species

The FEEDAP Panel concludes that:

- hex-3(*cis*)-en-1-ol [02.056], (*Z*)-non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094], non-6(*cis*)-enal [05.059], hex-3(*cis*)-enal [05.075], (*Z*)-hept-4-enal [05.085], hex-3(*cis*)-enyl acetate [09.197], hex-3(*cis*)-enyl formate [09.240], hex-3-enyl butyrate [09.270], hex-3-enyl hexanoate [09.271]

- and hex-3(*cis*)-enyl isobutyrate [09.563] are safe at the proposed maximum use level of 5 mg/kg complete feed for all target species;
- citronellol [02.011], (-)-3,7-dimethyl-6-octen-1-ol [02.229], citronellal [05.021], 2,6-dimethylhept-5-enal [05.074], citronellic acid [08.036], citronellyl acetate [09.012], citronellyl butyrate [09.049], citronellyl formate [09.078] and citronellyl propionate [09.129] are safe at the proposed maximum use level of 5 mg/kg complete feed for all target species, except cats, for which the proposed normal use level of 1 mg/kg is considered safe;
 - undec-10-enal [05.035], (*Z*)-1-ethoxy-1-(3-hexenyloxy)ethane [06.081] and hex-3-enyl isovalerate [09.505] are safe at the proposed normal use levels of 1 mg/kg complete feed for all animal species.

3.2.4. Safety for the consumer

The safety for the consumer of the 23 compounds used as food flavours has been already assessed by JECFA (WHO, 2000, 2002a) and EFSA (EFSA, 2008a; EFSA 2013a,b). All compounds are currently authorised in the EU as food flavourings without limitations.⁶

Given the low use levels of CG 4 compounds to be applied in feed, and the expected extensive metabolism and excretion in target animals (see Section 3.2.1), the FEEDAP Panel considers that the possible residues in food derived from animals fed with these flavourings would not appreciably increase the human intake levels of these compounds.

3.2.5. Safety for the user

No specific data on the safety for the user were provided. In the material safety data sheets,²¹ 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.

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 13 substances, citronellol [02.011], hex-3(*cis*)-en-1-ol [02.056], (-)-3,7-dimethyl-6-octen-1-ol [02.229], citronellal [05.021], hex-3(*cis*)-enal [05.075], citronellic acid [08.036], citronellyl acetate [09.012], citronellyl butyrate [09.049], citronellyl formate [09.078], hex-3(*cis*)-enyl acetate [09.197], hex-3(*cis*)-enyl formate [09.240], hex-3-enyl butyrate [09.270] and hex-3-enyl hexanoate [09.271], which occur in the environment at levels above the application rate of 5 mg/kg feed (data taken from the Netherlands Organisation for Applied Scientific Research (TNO) database Volatile Compounds in Food ver. 14.1; Burdock, 2009).²²

The other 10 compounds, namely (*Z*)-non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094], undec-10-enal [05.035], non-6(*cis*)-enal [05.059], 2,6-dimethylhept-5-enal [05.074], (*Z*)-hept-4-enal [05.085], (*Z*)-1-ethoxy-1-(3-hexenyloxy)ethane [06.081], citronellyl propionate [09.129], hex-3-enyl isovalerate [09.505] and hex-3(*cis*)-enyl isobutyrate [09.563] do not occur in the environment at levels above the application rate of 1–5 mg/kg feed. However, the FEEDAP Panel considers that there is a high probability of complete hydrolysis in the target animal of the three esters, citronellyl propionate [09.129], hex-3-enyl isovalerate [09.505] and hex-3(*cis*)-enyl isobutyrate [09.563], resulting in citronellol and hex-3(*cis*)-en-1-ol, which are naturally occurring compounds. Similarly, considering the metabolism in the target animal (see Section 3.2.1), it is expected that undec-10-enal [05.035], non-6(*cis*)-enal [05.059], 2,6-dimethylhept-5-enal [05.074] and hept-4-enal [05.085] will be mineralised to CO₂. Therefore, these compounds are excluded from further assessment.

For the remaining three compounds, namely non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094] and (*Z*)-1-ethoxy-1-(3-hexenyloxy)ethane [06.081], the predicted environmental concentration for soil (PEC_{soil}) was calculated based on the use rate (Table 5) and compared with the trigger values for compartments set in the phase I of the relevant EFSA guidance (EFSA, 2008b).

²¹ Technical dossier/Section II/Annex II.3.

²² Technical dossier/Supplementary information June 2011.

Table 5: Predicted environmental concentration (PEC) values of non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094] and (Z)-1-ethoxy-1-(3-hexenyloxy)ethane [06.081]

EU register name	CAS no.	Dose mg/kg	PEC _{soil} (µg/kg)	PEC _{pore water} (µg/L)	PEC _{surface water} (µg/L)
Non-6-en-1-ol	35854-86-5	5	107	79	26
Oct-3-en-1-ol	20125-84-2	5	107	134	45
(Z)-1-Ethoxy-1-(3-hexenyloxy)ethane	28069-74-1	1.5	32	22	7

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

The PEC_{soil} values are above the threshold of 10 µg/kg (EFSA, 2008b). The PEC for pore water (PEC_{pore water}), however, is dependent on the sorption, which is different for each compound. For these calculations, the substance-dependent constants, such as 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 (Table 6) using EPIWEB 4.1.²³ 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.

The half-life (DT₅₀) 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 by 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.

Table 6: Physicochemical properties predicted by EPIWEB 4.1 for non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094] and (Z)-1-ethoxy-1-(3-hexenyloxy)ethane [06.081]

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)
Non-6-en-1-ol	35854-86-5	3	142.24	2	619.3	69
Oct-3-en-1-ol	20125-84-2	3	128.22	7	1,855	38
(Z)-1-Ethoxy-1-(3-hexenyloxy)ethane	28069-74-1	6	172.27	65	180	77

EU: European Union; CAS No: Chemical Abstract Service number.

(a): DT₅₀, half-life of the additive (EPIWB 4.1.BioWin3).

(b): K_{oc} , organic carbon sorption constant (EPIWB 4.1.KocWin2.0).

The three substances in Table 5 have PEC_{pore water} above 0.1 µg/L, and a PEC_{soil} above 10 µg/kg. Therefore, these three substances 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 (EC₅₀) for earthworms, fish, green algae and daphnids from the SMILES notation of the substance. The predicted no effect concentration (PNEC) for terrestrial environment (PNEC_{soil}) was determined by dividing the LC₅₀ 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 an UF of 1,000.

For the three 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 (Table 7). The PEC/PNEC for surface water was < 1 for 1-ethoxy-1-(3-hexenyloxy)ethane [06.081], indicating that there is no risk to the fresh water environment at the dose considered safe for target species. For non-6-en-1-ol [02.093] and oct-3-en-1-ol [02.094], the maximum proposed use level would result in PEC_{sw}/PNEC ratio > 1. For both compounds, the proposed normal use level of 1 mg/kg feed would not cause a risk for the fresh water environment.

²³ Available online: <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm>

Table 7: Phase II environmental risk assessment of soil and aquatic compartments for non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094] and (Z)-1-ethoxy-1-(3-hexenyloxy)ethane [06.081] when 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	LC ₅₀ ^(a) earthworm (mg/kg)			PNEC _{soil} (µg/kg)	PEC _{soil} (µg/kg)	PEC/PNEC
Soil						
Non-6-en-1-ol	191			191	107	0.56
Oct-3-en-1-ol	194			194	107	0.55
(Z)-1-Ethoxy-1-(3-hexenyloxy)ethane	238			238	32	0.13
Aquatic	LC ₅₀ Fish (mg/L)	LC ₅₀ Daphnids (mg/L)	EC ₅₀ ^(b) Algae (mg/L)	PNEC _{aquatic} (µg/L)	PEC _{sw} ^(c) (µg/L)	PEC/PNEC
Non-6-en-1-ol	12	8	9	8	27	3.38
Oct-3-en-1-ol	31	19	17	17	45	2.65
(Z)-1-Ethoxy-1-(3-hexenyloxy)ethane	20	12	13	12	7	0.6

EU: European Union; EC₅₀: half-maximal effective concentration; LC₅₀: lethal concentration 50; PNEC: predicted no effect concentration; PEC: predicted environmental concentration.

(a): LC₅₀: the concentration of a test substance which results in a 50% mortality of the test species.

(b): EC₅₀: the concentration of a test substance which results in 50% of the test animals being adversely affected (i.e. both mortality and sublethal effects).

(c): PEC_{sw}: predicted environmental concentration in surface water.

The use of all additives in fish feed in 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 0.05 mg/kg would ensure that the threshold for the predicted environmental concentration of the additive (parent compound) in sediment (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 environments, except for non-6-en-1-ol [02.093] and oct-3-en-1-ol [02.094], for which the proposed normal use level of 1 mg/kg feed would not cause an environmental risk. For the marine environment, the safe use level is estimated to be 0.05 mg/kg feed.

3.3. Efficacy

As the 23 compounds under assessment are also 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.

4. Conclusions

The FEEDAP Panel concludes that hex-3(*cis*)-en-1-ol [02.056], (Z)-non-6-en-1-ol [02.093], oct-3-en-1-ol [02.094], non-6(*cis*)-enal [05.059], hex-3(*cis*)-enal [05.075], (Z)-hept-4-enal [05.085], hex-3(*cis*)-enyl acetate [09.197], hex-3(*cis*)-enyl formate [09.240], hex-3-enyl butyrate [09.270], hex-3-enyl hexanoate [09.271] and hex-3(*cis*)-enyl isobutyrate [09.563] are safe at proposed maximum use level of 5 mg/kg feed for all target species; citronellol [02.011], (-)-3,7-dimethyl-6-octen-1-ol [02.229], citronellal [05.021], 2,6-dimethylhept-5-enal [05.074], citronellic acid [08.036], citronellyl acetate [09.012], citronellyl butyrate [09.049], citronellyl formate [09.078] and citronellyl propionate [09.129] are safe at proposed maximum use level of 5 mg/kg complete feed for all target species, except cats for which the proposed normal use level of 1 mg/kg is considered safe; undec-10-enal [05.035], (Z)-1-ethoxy-1-(3-hexenyloxy)ethane [06.081] and hex-3-enyl isovalerate [09.505] are safe at the proposed normal use levels of 1 mg/kg complete feed for all animal species.

No safety concern would arise for the consumer from the use of these compounds up to the highest safe levels in feed.

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 environments, except for non-6-en-1-ol [02.093] and oct-3-en-1-ol [02.094] for which the proposed normal use level of 1 mg/kg feed is considered safe.

As all of the compounds under assessment are also 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 Group 04 - Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters with esters containing unsaturated alcohols and acetals containing unsaturated alcohols or aldehydes. No aromatic or heteroaromatic moiety as a component of an ester or acetal (CDG 04). June 2010. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
- 2) Chemically Defined Group 04 - Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters with esters containing unsaturated alcohols and acetals containing unsaturated alcohols or aldehydes. No aromatic or heteroaromatic moiety as a component of an ester or acetal (CDG 04). Supplementary information. May 2011. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
- 3) Chemically Defined Group 04 - Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters with esters containing unsaturated alcohols and acetals containing unsaturated alcohols or aldehydes. No aromatic or heteroaromatic moiety as a component of an ester or acetal (CDG 04). Supplementary information. March 2012. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
- 4) Chemically Defined Group 04 - Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters with esters containing unsaturated alcohols and acetals containing unsaturated alcohols or aldehydes. No aromatic or heteroaromatic moiety as a component of an ester or acetal (CDG 04). Supplementary information. July 2012. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
- 5) Chemically Defined Group 04 - Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters with esters containing unsaturated alcohols and acetals containing unsaturated alcohols or aldehydes. No aromatic or heteroaromatic moiety as a component of an ester or acetal (CDG 04). Supplementary information. June 2016. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
- 6) Evaluation report of the European Union Reference Laboratory for Feed Additives on the Methods(s) of Analysis for Chemically Defined Group 04 (CDG04 Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters with esters containing unsaturated alcohols and acetals containing unsaturated alcohols or aldehydes. No aromatic or heteroaromatic moiety as a component of an ester or acetal).
- 7) Comments from Member States.

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Abbreviations

bw	body weight
CAS	Chemical Abstracts Service
CD	Commission Decision
CDG	chemically defined group
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CG	chemical group
DM	dry matter
DT ₅₀	degradation half-time
EC ₅₀	half-maximal effective concentration
ECOSAR	component program of EPI suite™
EEIG	European Economic Interest Grouping
EPI suite	Estimation Programs Interface (EPI) Suite™
EURL	European Union Reference Laboratory
FAO	Food and Agriculture Organization
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed

FFAC	Feed Flavourings authorisation Consortium of (FEFANA) the EU Association of Specialty Feed Ingredients and their Mixtures
FGE	Flavouring Group Evaluation
FLAVIS	the EU Flavour Information System
FL-No	FLAVIS number
GC–MS	gas chromatography–mass spectrometry
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
K_{oc}	organic carbon sorption constant
K_{ow}	octanol–water partition coefficient
LC_{50}	lethal concentration 50
$\log K_{ow}$	logarithm of octanol–water partition coefficient
NAD	nicotinamide adenine dinucleotide
NADP+	nicotinamide adenine dinucleotide phosphate
NOEL	no observed effect level
NOAEL	no observed adverse effect level
PEC	predicted environmental concentration
PEC_{sed}	predicted environmental concentration of the additive (parent compound) in sediment
$PEC_{pore\ water}$	predicted environmental concentration for pore water
PEC_{soil}	predicted environmental concentration for soil
PEC_{sw}	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
SMILES	Simplified Molecular Input Line Entry Specification
TNO	Netherlands Organisation for Applied Scientific Research
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 Chemically Defined Flavourings – Group 04

The *Chemically Defined Flavourings - Group 04 (CDG04 - Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols/aldehydes/acids, acetals and esters with esters containing unsaturated alcohols and acetals containing unsaturated alcohols or aldehydes)*, in this application comprises 24 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 85% to 98%.

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 *CDG04* in the *feed additive*, the Applicant submitted a qualitative multi-analyte gas-chromatography mass-spectrometry (GC-MS) method, using Retention Time Locking (RTL), which allows a close match of retention times on GC-MS. By making an adjustment to the inlet pressure, the retention times can be closely matched to those of a reference chromatogram. It is then possible to screen samples for the presence of target compounds using a mass spectral database of RTL spectra. The Applicant 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 EURL. The Applicant provided the typical chromatogram for the *CDG04* 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 twenty chemically defined flavourings belonging to twenty 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. Since the substances of *CDG04* 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 *CDG04* 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.

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*.