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SCIENTIFIC OPINION

Scientific Opinion on the safety and efficacy of furanones and tetrahydrofurfuryl derivatives: 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one and 3-hydroxy-4,5-dimethylfuran-2(5H)-one (chemical group 13) when used as flavourings for all animal species[1]

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)[2,3]

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ABSTRACT

5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one and 3-hydroxy-4,5-dimethylfuran-2(5H)-one belong to chemical group 13 (furanones and tetrahydrofurfuryl derivatives) and are authorised for use as flavours in food. These additives are safe at concentrations of 0.05 mg/kg feed for poultry and pigs and 0.08 mg/kg feed for cattle, salmonids and non food-producing animals. The concentration of the additives should be appropriately reduced if used in water for drinking. If used simultaneously in feed and water for drinking, the total intake should not exceed the maximum dose resulting from the use of the flavourings in feed alone. At the levels safe for target animal species these products are safe for the consumers of animal products. The FEEDAP Panel considers it prudent to treat the compounds under assessment as irritant to skin, eyes and the respiratory tract and as skin sensitisers. The proposed concentration of 0.08 mg flavouring compound/kg feed is unlikely to have detrimental effects on the environment except when used in feed for fish in sea cages, in which case the safe concentration would be 0.047 mg/kg. Since both compounds 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.

KEY WORDS

sensory additives, furanones and tetrahydrofurfuryl derivatives, chemical group 13

[1] On request from the European Commission, Question No EFSA-Q-2012-00632, adopted on 5 March 2014.

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SUMMARY

Following a request from the European Commission, the 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 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one and 3-hydroxy-4,5-dimethylfuran-2(5H)-one (furanones and tetrahydrofurfuryl derivatives belonging to chemical group 13) when used as flavours for all animal species. These two additives are currently listed in the European Union database of flavouring substances and are authorised for use as flavours in food.

These additives are safe at concentrations of 0.05 mg/kg feed for poultry and pigs and 0.08 mg/kg feed for cattle, salmonids and non-food-producing animals. The concentrations of the additives should be appropriately reduced if used in water for drinking. If used simultaneously in feed and water for drinking, the total intake should not exceed the maximum dose resulting from the use of the flavourings in feed alone.

At the levels safe for target animal species these products are safe for the consumers of animal products.

The FEEDAP Panel considers it prudent to treat the compounds under assessment as irritant to skin, eyes and the respiratory tract and as skin sensitisers.

The proposed concentration of 0.08 mg flavouring compound/kg feed is unlikely to have detrimental effects on the environment except when used in feed for fish in sea cages, in which case the safe concentration would be 0.047 mg/kg.

Since both compounds 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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BACKGROUND

Regulation (EC) No 1831/2003[4] 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, at the latest one year before the expiry date of the authorisation given pursuant to Directive 70/524/EEC for additives with a limited authorisation period, and within a maximum of seven years after the entry into force of this Regulation for additives authorised without a time limit or pursuant to Directive 82/471/EEC.

The European Commission received a request from the Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)[5] for authorisation of the six substances listed in Table 1, to be used as feed additives for all animal species (category: sensory additives; functional group: flavourings) under the conditions mentioned in Table 1.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicant the technical dossier in support of this application.[6] According to Article 8 of that Regulation, 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. The particulars and documents in support of the application were considered valid by EFSA as of 12 November 2010.

The six substances belonging to CG 13 have been previously assessed by JECFA (WHO, 1999a,b) and EFSA (2008b; 2009a, b; EFSA CEF Panel 2011, 2013) as food flavourings.

This application has been divided during the course of the assessment. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) delivered an opinion (EFSA FEEDAP Panel, 2012) on four substances, i.e. 4-hydroxy-2,5-dimethylfuran-3(2H)-one [the EU Flavour Information System (FLAVIS) number: 13.010], 4,5-dihydro-2-methylfuran-3(2H)-one [13.042], 4-acetoxy-2,5-dimethylfuran-3(2H)-one [13.099] and linalool oxide [13.140], which were considered safe for use in food by the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) (EFSA 2008a; EFSA CEF Panel, 2011). The other two compounds belonging to CG 13, 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030] were excluded from the assessment based on an outstanding issue with regards to possible genotoxicity (EFSA, 2009b). The EFSA CEF Panel has subsequently delivered an opinion in which these two substances were considered not to give rise to concern with respect to genotoxicity and could accordingly be evaluated using the Procedure (EFSA, CEF Panel 2013). According to Regulation (EC) No 1565/2000,[7] 'Substances classified by JECFA as to present no safety concern at the current levels of intake with the exception of substances which have been accepted on the sole basis that their estimated intake is lower than the threshold of concern of 1.5 μg per person per day, as laid down in the reports of the 46th, 49th, 51st and 53rd JECFA meetings need not to be re-evaluated.'

[4] 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.

[5] 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.

[6] EFSA Dossier reference: FAD-2010-0408.

[7] 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.

The two substances evaluated by JECFA at the 49th meeting were not further evaluated by EFSA and were considered safe for use as food flavours.

Consequently this opinion deals exclusively with 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030].

Both additives are listed as food and feed flavourings in the Union list of Flavouring substances[8] and in the European Union Register of Feed Additives, respectively. They have not been previously assessed by EFSA as feed additives.

TERMS OF REFERENCE

According to Article 8 of Regulation (EC) No 1831/2003, EFSA shall 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 the efficacy of the compounds 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one and 3-hydroxy-4,5-dimethylfuran-2(5H)-one, when used under the conditions described in Table 1.

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

Table 1: Description and conditions of use of the additive as proposed by the applicant

Additive	Chemical defined flavourings from Chemical Group 13: 3-Hydroxy-4,5-dimethylfuran-2(5H)-one 4,5-Dihydro-2-methylfuran-3(2H)-one 4-Acetoxy-2,5-dimethylfuran-3(2H)-one 4-Hydroxy-2,5-dimethylfuran-3(2H)-one 5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one Linalool oxide
Registration number/EC No/No (if appropriate)	-
Category(ies) of additive	2. Sensory additives
Functional group(s) of additive	b) flavouring compounds

Description			
Composition, description	Chemical formula	Purity criteria	Method of analysis
3-Hydroxy-4,5-dimethylfuran-2(5H)-one (CAS No 28664–35–9)	$C_6H_8O_3$	97.5 %	Gas Chromatography – Mass Spectrometry (GC-MS)
4,5-Dihydro-2-methylfuran-3(2H)-one (CAS No 3188–00–9)	$C_5H_8O_2$	97 %	Gas Chromatography – Mass Spectrometry (GC-MS)
4-Acetoxy-2,5-dimethylfuran-3(2H)-one (CAS No 4166–20–5)	$C_8H_{10}O_4$	85 % (SC: 4-Hydroxy-2,5-dimethyl-3(2H)-furanone)	Gas Chromatography – Mass Spectrometry (GC-MS)
4-Hydroxy-2,5-dimethylfuran-3(2H)-one (CAS No 3658–77–3)	$C_6H_8O_3$	98 %	Gas Chromatography – Mass Spectrometry (GC-MS)
5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one (CAS No 698–10–2)	$C_7H_{10}O_3$	95 %	Gas Chromatography – Mass Spectrometry (GC-MS)
Linalool oxide (CAS No 1365–19–1)[9]	$C_{10}H_{18}O_2$	95 %	Gas Chromatography – Mass Spectrometry (GC-MS)

Trade name	-
Name of the holder of authorisation	-

Conditions of use				
Species or category of animal	Maximum Age	Minimum content	Maximum content	Withdrawal period
		mg/kg of complete feedingstuffs		
All species and categories	-	-	-	-

Other provisions and additional requirements for the labelling	
Specific conditions or restrictions for use	-

[9] The CAS number listed here is for the *cis* and *trans* forms. The CAS number listed for 13.140 in the JECFA TRS 928 (WHO, 2005) is 1365-19-1, whereas the CAS number listed in the JECFA compendium is 5989-33-3, which is for the trans form.

Specific conditions or restrictions for handling	All feedingstuffs and water for drinking, as part of a premixture only
Post-market monitoring	-
Specific conditions for use in complementary feedingstuffs	-

Maximum Residue Limit (MRL)			
Marker residue	Species or category of animal	Target tissue(s) or food products	Maximum content in tissues
-	-	-	-

ASSESSMENT

1. Introduction

Chemical Group (CG) 13 for flavouring substances is defined in Commission Regulation (EC) No 1565/2000[10] as 'furanones and tetrahydrofurfuryl derivatives'. The present application concerns six compounds which can be assigned to this CG.

The six substances belonging to CG 13 have been previously assessed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (WHO, 1999a, b) and EFSA (2008b, 2009a, b; EFSA CEF Panel, 2011, 2013) as food flavourings.

This application has been divided during the course of the assessment. The EFSA FEEDAP Panel delivered an opinion (EFSA FEEDAP Panel, 2012) on four substances, i.e. 4-hydroxy-2,5-dimethylfuran-3(2H)-one [13.010], 4,5-dihydro-2-methylfuran-3(2H)-one [13.042], 4-acetoxy-2,5-dimethylfuran-3(2H)-one [13.099] and linalool oxide [13.140], which were considered safe for use in food by the EFSA CEF Panel (EFSA 2008a; EFSA CEF Panel, 2011). The other two compounds belonging to CG 13, 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030], were excluded from the assessment based on an outstanding issue with regard to possible genotoxicity (EFSA, 2009b). The EFSA CEF Panel has subsequently delivered an opinion in which the genotoxicity concern for these two substances has been ruled out (EFSA CEF Panel, 2013).

Consequently, this opinion deals exclusively with 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030]. The compounds included in this assessment are not widely distributed in nature.

5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one (also known as ethyl sotolone or maple furanone) [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030] (also known as sotolone) have been assessed by the JECFA (1999) and considered safe for use as food flavourings without limit. No acceptable daily intake (ADI) values were specified. The CEF Panel considered the same compounds for use as food flavourings (EFSA, 2009b; EFSA CEF Panel, 2013). Since these two substances were considered not to give rise to concern with respect to genotoxicity, they can be evaluated using the Procedure. According to Regulation (EC) No 1565/2000,[11] '*Substances classified by the JECFA as to present no safety concern at the current levels of intake with the exception of substances which have been accepted on the sole basis that their estimated intake is lower than the threshold of concern of 1.5 µg per person per day, as laid down in the reports of the 46th, 49th, 51st and 53rd JECFA meetings need not to be re-evaluated*.' The two substances evaluated by the JECFA at the 49th meeting were not further evaluated by EFSA and were considered safe for use as food flavours.

The compounds under application are currently listed in the European Union (EU) list of flavouring substances and thus authorised for use in food in the EU.[12]

A consortium of companies supplying flavours to the feed industry has requested authorisation for the use of 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one and 3-hydroxy-4,5-dimethylfuran-2(5H)-one as additives to feed and water for drinking (category: sensory additives; functional group: flavouring compounds) for use in all animal species.

[10] 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.
[11] OJ L 180, 19.7.2000, p. 8.
[12] OJ L 267, 2.10.2012, p. 1.

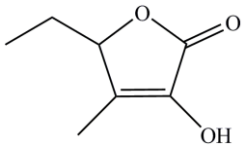
Regulation (EC) No 429/2008[13] allows substances already approved for use in human food to be assessed with a more limited procedure than for other feed additives. However, the use of this procedure is always subject to the condition that food safety assessment is relevant to the use in feed.

2. Characterisation

2.1. Characterisation of the flavouring additives

The molecular structures of the two additives under assessment are shown in Figure 1 and their physico-chemical characteristics summarised in Table 2.

5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023]



3-Hydroxy-4,5-dimethylfuran-2(5H)-one [10.030]

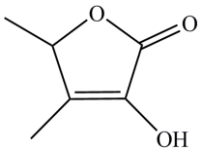


Figure 1: Molecular structures and FLAVIS numbers of 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one flavourings and 3-hydroxy-4,5-dimethylfuran-2(5H)-one from CG 13

Table 2: Chemically defined flavourings from CG 13 under assessment

Name	CAS No	FLAVIS No	Molecular formula	Molecular weight	Physical status	Log K_{ow}
5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one	698-10-2	10.023	$C_7H_{10}O_3$	142.15	Liquid	0.05
3-Hydroxy-4,5-dimethylfuran-2(5H)-one	28664-35-9	10.030	$C_6H_8O_3$	128.13	Liquid	–0.44

The two substances are produced by chemical synthesis. Typically, several routes of synthesis are available and described in the dossier.[14]

Data were provided on the batch-to-batch variation of five batches of each additive.[15] The content of the active substance exceeded the JECFA specifications (WHO, 2006) for both compounds (Table 3).

Table 3: Specification of the substances and data on purity

Name	JECFA specification (%)	Assay (%)	
		Average	Range
5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one	95.0	99.8	99.1–100.0
3-Hydroxy-4,5-dimethylfuran-2(5H)-one	97.5	98.2	97.9–98.6

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.

[13] 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.
[14] Technical dossiers/Section II.
[15] Technical dossiers/Section II/Annex 2.1 and Supplementary Information June 2011.

2.2. Stability

A shelf life of at least 18 and 24 months is claimed for 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030], respectively, when stored in closed containers under recommended conditions (in a cool and dry place). This assessment is made on the basis of compliance with the original specification after storage.

Although no data are required for the stability of volatile additives in premixes and feed, use in water for drinking introduces other issues relating to product stability, such as degradation due to microbial activity. As no data on the short-term stability of the additive in water for drinking were provided, the FEEDAP Panel is not in the position to comment on this route of administration.

2.3. Conditions of use

The applicant proposes the use of the two additives in feed or water for drinking for all animal species without withdrawal time. In each case, the applicant proposes a normal use level of 1 mg/kg complete feed and a high use level of 5 mg/kg. No specific proposals are made for doses to be used in water for drinking.

2.4. Evaluation of the analytical methods by the European Union Reference Laboratory (EURL)

EFSA has verified the EURL report as it relates to the methods used for the control of furanones and tetrahydrofurfuryl derivatives in animal feed. The Executive Summary of the EURL report can be found in Appendix A.

3. Safety

The assessment of safety is based on the highest use level proposed by the applicant (5 mg/kg complete feed for the two additives).

The two compounds under assessment have already been assessed by the JECFA (WHO, 1999a, b), which considered them safe as food flavourings. The JECFA based this conclusion on the No Observed Adverse Effect Levels (NOAELs) from the study by Posternak et al. (1969) for 3-hydroxy-4-methylfuran-2(5H)-one [10.023] and from the study by Munday and Kirby (1973; unpublished) for 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030]. These studies are described in the WHO FAS 40 (WHO, 1999b; chapters 2.1.2.3 and 2.1.2.4). The Committee did not have specific metabolism studies for these two substances and concluded that "*the use of these substances as flavouring agents would not present safety concerns at the estimated current levels of intake*" (WHO, 1999a).[16]

However, in 2009 the CEF Panel considered that the metabolism of these two compounds by hydrolysis and oxidation gives rise to α,β-unsaturated ketones, with a structural alert for genotoxicity (EFSA, 2009b).

In a subsequent opinion the CEF Panel assessed the results of a bacterial reverse mutation assay (Ames test) (Bowen, 2011) and an *in vitro* micronucleus assay with human peripheral blood lymphocytes (Lloyd, 2011) on 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023]. The results of the Ames test showed no statistically significant increases in revertant numbers following 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one treatments in any of the test strains (TA98, TA100, TA1535, TA1537 and TA102), either in the absence or presence of S9-mix. The results of the micronucleus assay showed the absence of induction of micronucleated binucleate (MNBN) cells as a result of treatment with 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one at concentrations either reaching 10 mM or inducing 50–60 % toxicity. The CEF Panel concluded that 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-

[16] TRS 884, p. 52.

one [10.023] does not induce micronuclei in cultured human peripheral blood lymphocytes following treatment in the absence or in the presence of S9-mix (EFSA CEF Panel, 2013).

On the basis of these new genotoxicity data the CEF Panel ruled out the genotoxicity concern for [10.023] and the structurally related substance, 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030] and confirmed the conclusion of JECFA (WHO, 1999a) that they are safe for use as food flavourings at the current level of use.

3.1. Safety for the target species

The first approach to the safety assessment for target species takes account of the applied use levels in animal feed relative to the maximum reported exposure of humans on the basis of the metabolic body weight as described in the guidance for sensory additives (EFSA FEEDAP Panel, 2012). In the EU,, human exposure to 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one and 3-hydroxy-4,5-dimethylfuran-2(5H)-one is, respectively, 11 and 1.8 µg/person per day, corresponding to 0.51 to 0.08 µg/kg$^{0.75}$ per day (EFSA, 2009b). Compared with human exposure, the calculated intake by target species (salmonids 118 µg/kg$^{0.75}$, piglets 526 µg/kg$^{0.75}$ and dairy cows 777 µg/kg$^{0.75}$ per day) from the proposed maximum feed concentration of 5 mg/kg complete feed would greatly exceed that of humans (230- to 9 700-fold) resulting from use in food. As a consequence, 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 that can be considered safe for the target animal may be derived from an appropriate NOAEL (EFSA FEEDAP Panel, 2012).

The applicant did not provide new studies on these substances. The two studies on which the JECFA based its conclusion could not be used to assess the safety for target animals because sufficient details of the studies were not available for assessment; they included a mixture of flavourings (Munday and Kirkby, 1973, as cited by JECFA (WHO, 1999b)), or used a single low dose only (males 1.3 mg/kg body weight (bw) and females 1.5 mg/kg bw per day; Posternak et al., 1969). No other suitable toxicological studies could be identified from which to derive a NOAEL for 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030]. Therefore, the threshold of toxicological concern (TTC) was used to derive safe feed concentrations for these Cramer Class III compounds. This provides values of 0.08 mg/kg complete feed for cattle, salmonids and non food-producing animals and 0.05 mg/kg complete feed for pigs and poultry (EFSA FEEDAP Panel, 2012).

3.1.1. Conclusions on the safety for target species

The calculated safe use levels for 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030] are 0.08 mg/kg complete feed for cattle, salmonids and non food-producing animals and 0.05 mg/kg complete feed for pigs and poultry.

The concentration of the additives should be appropriately reduced if used in water for drinking. If used simultaneously in feed and water for drinking, the total intake should not exceed the maximum dose resulting from the use of the flavourings in feed alone.

3.2. Safety for the consumer

The two substances under assessment, 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030], are considered safe for use as food flavours at the current estimated levels of intake (EFSA CEF Panel, 2013).

The FEEDAP Panel considers that, in addition to its use as a flavouring additive in food, 3-hydroxy-4,5-dimethylfuran-2(5H)-one, (sotolone) [10.030] is present in food and beverages, including roasted coffee, fenugreek seeds, lovage as well as in aged alcoholic beverages, such as sherry, Madeira, port wine and sake (Holscher and Steinhart, 1994; Blank et al., 1997; Wagenstaller and Buettner, 2013a).

5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one (maple furanone or abhexone) occurs in coffee (Holscher and Steinhart, 1994; Wagenstaller and Buettner, 2013a), soy sauce, Swiss cheese and melon.

No information was submitted by the applicant on the metabolism and possible residues of these two specific compounds. However, the glucuronides of 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030] were detected in the urine of healthy humans (Wagenstaller and Buettner, 2013b), the latter at concentrations of 10–100 µg/L (Wagenstaller and Buettner, 2013a, 2014). The FEEDAP Panel considers this finding as an indication of the terminal metabolism of these compounds through glucuronidation. Phase II metabolism is shared among mammals, birds and fish and the conjugates of the additives are expected to be rapidly excreted.

In addition, because of their low lipophilicity, the FEEDAP Panel considers that both compounds would be expected to have a low bioaccumulation potential.

3.2.1. Conclusions on the safety for the consumer

The FEEDAP Panel considers it unlikely that exposure of consumers arising from consumption of animal products would be greater than direct exposure from these food flavourings, when these compounds are used up to the highest safe level in feed. Therefore, the use of these compounds in animal nutrition is considered safe for consumers when used up to the highest safe level in feed (0.08 mg/kg for cattle and salmonids and 0.05 mg/kg complete feed for pigs and poultry).

3.3. Safety for the user

No experimental data on the safety for the user were provided for 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one and 3-hydroxy-4,5-dimethylfuran-2(5H)-one. The FEEDAP Panel considers it prudent to treat the compounds under assessment as irritant to skin, eyes and the respiratory tract and as skin sensitisers.

3.4. Safety for the environment

According to the EFSA guidance for assessing the safety of feed additives for the environment (EFSA, 2008b), a stepwise approach can be used to assess the 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. However, 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030] are not known to occur in the environment at levels above the application rate of 0.08 mg/kg feed. The two substances are, therefore, assessed subsequently in a predicted environmental concentration (PEC) calculation for soil (PEC_{soil}) arising from the application rate. When the calculations are performed according to the EFSA guidance (2008b) with a fixed concentration in feed, there is a fixed order of PEC_{soil} from each species. In the initial calculation of the PEC_{soil}, only soil- and animal-dependent constants, but no substance-dependent constants, are used. An initial phase I calculation of EFSA (2008b) guidance assumes that all substances are excreted completely in manure. The differences in feed intake and nitrogen excretion in various animal categories yield a fixed PEC_{soil} sequence at a given dose of the additive. This sequence, from highest to lowest PEC_{soil}, is lambs for fattening, pigs for fattening, sheep and goats, veal calves, dairy cows, cattle for fattening, sows (with piglets), broilers, laying hens and turkeys. The use of fish feed in sea cages can result in a PEC for sediment above 10 µg/kg when the fish feed concentration is above 0.047 mg/kg, regardless of the properties of the additive, when calculated according to the guidance (EFSA, 2008b). The PEC_{soil} for lambs gives the highest PEC_{soil} values. The PEC_{soil} value of 1.71 µg/kg of 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030] for lambs is well below the threshold of 10 µg/kg (EFSA, 2008b). The PEC for porewater, however, is dependent on the sorption, which is different for each compound. For these calculations, the substance-dependent constants K_{oc} (organic carbon sorption constant), MW (molecular weight), VP (vapour pressure) and SOL (solubility) are needed.

These were estimated from the SMILES (Simplified Molecular Input Line Entry Specification) notation of the chemical structure using EPIWEB 4.1 (Table 4).[17] This program was also used to derive the SMILES notation from the Chemical Abstracts Service (CAS) numbers, which were provided by the applicant. The K_{oc} value derived from the first-order molecular connectivity index was used, as recommended by the EPIWEB program. The half-life 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): half-life = 10y where $y = (-r \times 1.07 + 4.12)$. The y is the general regression used to derive estimates of aerobic environmental biodegradation half-lives from BioWin3 model output. Since the half-life of both compounds was five days, the plateau values were almost identical to the initial values when calculated according to EFSA (2008b) guidance. This indicates that the biodegradation is expected to be rapid enough to avoid accumulation in soil.

Table 4: Physico-chemical properties predicted by EPIWEB 4.1 of 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one and 3-hydroxy-4,5-dimethylfuran-2(5H)-one

EU Register name	Predicted by EPIWEB 4.1					
	FLAVIS No	DT_{50} [(a)] (days)	Molecular weight (g/mol)	Vapour pressure (Pa)	Solubility (mg/L)	K_{oc} [(b)] (L/kg)
5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one	10.023	5	142.16	0.0079	74390	10
3-Hydroxy-4,5-dimethylfuran-2(5H)-one	10.030	5	128.13	0.025	222800	1.4

(a): DT_{50}, half-life of the additive in manure.
(b): K_{oc}, organic carbon sorption constant.

Table 5: EC_{50} values in mg/L predicted by ECOSAR 1.11 of 5-ethyl-3-hydroxy-4-methylfuran-2(5H)-one and 3-hydroxy-4,5-dimethylfuran-2(5H)-one

Name	FLAVIS No	Fish (mg/L)	*Daphnia* (mg/L)	EC_{50} [(a)] algae (mg/L)	PEC surface water (µg/L)
5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one	10.023	262	607	389	2
3-Hydroxy-4,5-dimethylfuran-2(5H)-one	10.030	457	1233	772	4

(a): EC_{50}, the concentration of a test substance which results in 50 % of the test animals being adversely affected (i.e. both mortality and sub-lethal effects).

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}) for fish, algae and *Daphnia* from the SMILES notation of the substance. The EC_{50} values divided by a safety factor of 1 000 were much higher than the PEC values for surface water from Table 5, indicating that, according to the guidance (EFSA, 2008b), there is no risk to the environment, except when these substances are used in feed for fish in sea cages, in which case the feed additive concentration should be less than 0.047 mg/kg feed. The use of these additives in fish feed in aquaculture does not give a predicted environmental concentration above the trigger value of 0.1 µg/L when calculated according to the guidance (EFSA, 2008b).

3.4.1. Conclusions on the safety for the environment

The concentrations considered safe for the target species (0.05 mg flavouring compound/kg feed for poultry and pigs and 0.08 mg flavouring compound/kg feed for cattle, salmonids and non food-

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

producing animals) are unlikely to have detrimental effects on the environment. The only exception is when these substances are used in feed for fish in sea cages, in which case the safe concentration would be 0.047 mg/kg feed.

4. Efficacy

Since both compounds 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.

CONCLUSIONS

5-Ethyl-3-hydroxy-4-methylfuran-2(5H)-one [10.023] and 3-hydroxy-4,5-dimethylfuran-2(5H)-one [10.030] are safe at concentrations of 0.05 mg/kg feed for poultry and pigs and 0.08 mg/kg feed for cattle, salmonids and non-food-producing animals. The concentration of the additives should be appropriately reduced if used in water for drinking. If used simultaneously in feed and water for drinking, the total intake should not exceed the maximum dose resulting from the use of the flavourings in feed alone.

At the maximum levels considered safe for target animal species, these products are also safe for the consumers of animal products.

The FEEDAP Panel considers it prudent to treat the compounds under assessment as irritant to skin, eyes and the respiratory tract and as skin sensitisers.

The proposed concentration of 0.08 mg flavouring compound/kg feed is unlikely to have detrimental effects on the environment except when used in feed for fish in sea cages, in which case the safe concentration would be 0.047 mg/kg.

Since both compounds 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 Group 13 Furanones and tetrahydro-furfuryl derivatives. November 2010. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).

2. Chemically Defined Group 13 Furanones and tetrahydro-furfuryl derivatives. Supplementary information. July 2011. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).

3. Chemically Defined Group 13 Furanones and tetrahydro-furfuryl derivatives. Supplementary information. January 2012. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).

4. Chemically Defined Group 13 Furanones and tetrahydro-furfuryl derivatives. Supplementary information. July 2012. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).

5. Chemically Defined Group 13 Furanones and tetrahydro-furfuryl derivatives. Supplementary information. November 2013. 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 13 Furanones and tetrahydro-furfuryl derivatives.

7. Comments from Member States received through the ScienceNet.

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APPENDIX

Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis for Group 13 Furanones and tetrahydro-furfuryl derivatives[18]

The *Chemically Defined Flavourings – Group 13* (*Furanones and tetrahydro-furfuryl derivatives*), in this application comprises six 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 95 % to 98 % and 85 % for 4-acetoxy-2,5-dimethylfuran-3(2H)-one.

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 *CDG13* 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 *CDG13* 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 CDG13 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 CDG13 in the mixture of flavouring compounds.

[18] Full list provided in the EURL evaluation report, available on the EURL website: http://irmm.jrc.ec.europa.eu/SiteCollectionDocuments/FinRep-FAD-2010-0119.pdf

ABBREVIATIONS

ADI	acceptable daily intake
BioWin	component program of Episuite™
bw	body weight
CAS	Chemical Abstracts Service
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CD	Commission Decision
CG	chemical group
CDG	chemically defined group
EC	European Commission
EC_{50}	half-maximal effective concentration
ECOSAR	component program of Episuite™
EFSA	European Food Safety Authority
EPI suite	Estimation Programs Interface (EPI) Suite™
EU	European Union
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 (EU Association of Specialty Feed Ingredients and their Mixtures)
FGE	Food Group Evaluation
FLAVIS	The EU Flavour Information System
GC–MS	gas chromatography–mass spectrometry
HACCP	Hazard Analysis and Critical Control Point
JECFA	Joint FAO/WHO Expert Committee on Food Additives
K_{oc}	organic carbon sorption constant
K_{ow}	octanol–water partition coefficient
Log K_{ow}	logarithm of octanol–water partition coefficient
MRL	maximum residue limit
MNBN	micronucleated binucleate
MW	molecular weight
NOAEL	No Observed Adverse Effect Level
PEC	predicted environmental concentration
SMILES	simplified molecular input line entry specification
SOL	solubility
TTC	threshold of toxicological concern
VP	vapour pressure
WHO	World Health Organization