SCIENTIFIC OPINION

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Safety and efficacy of furfuryl and furan derivatives belonging to chemical group 14 when used as flavourings for all animal species and categories

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 18 compounds belonging to chemical group 14 (furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms). They are currently authorised as flavours in food. This opinion concerns 13 compounds from this group. The FEEDAP Panel concludes that all compounds except 5-methylfurfural are safe at the proposed maximum use level for all animal species: furfural and furfuryl alcohol at 5 mg/kg complete feed; methyl 2-furoate and furfuryl acetate at 0.5 mg/kg complete feed; bis-(2-methyl-3-furyl) disulfide, furanmethanethiol, S-furfuryl acetothioate, difurfuryl disulfide, methyl furfuryl sulfide, 2-methylfuran-3-thiol, methyl furfuryl disulfide and methyl 2-methyl-3-furyl disulfide at 0.05 mg/kg complete feed. 5-Methylfurfural is safe at the proposed use level of 0.5 mg/kg complete feed for cattle, salmonids and non-food producing animals and at the use level of 0.3 mg/kg complete feed for pigs and poultry. No safety concern would arise for the consumer from the use of these compounds up to the highest safe level in feeds. Hazards for skin and eye contact and respiratory exposure are recognised for the majority of the compounds under application. Most are classified as irritating to the respiratory system. The concentrations considered safe for the target species are unlikely to have detrimental effects on the terrestrial and freshwater environments. Since all the compounds under assessment are used in food as flavourings, and their function in feed is essentially the same as that in food, no further demonstration of efficacy is necessary. In the absence of data on the stability in water for drinking, the FEEDAP Panel is unable to conclude on the safety or efficacy of the substances under this mode of delivery.

Keywords: sensory additives, feed flavourings, furfuryl derivatives, furan derivatives, safety, chemical group 14

Requestor: European Commission

Question number: EFSA-Q-2010-01218

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Table of contents

1. Introduction

1.1. Background and Terms of Reference

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

The European Commission received a request from Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)[2] for authorisation of 18 substances belonging to chemical group (CG) 14,[3] when used as a feed additive for all animal species (category: sensory additives; functional group: flavourings). CG 14 for flavouring substances is defined in Commission Regulation (EC) No 1565/2000[4] as "furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms".

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. The particulars and documents in support of the application were considered valid by EFSA as of 1 January 2010.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5.

EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment, and on the efficacy of the 5-methylfurfural, methyl 2-furoate, bis-(2-methyl-3-furyl) disulfide, furfural, furfuryl alcohol, furanmethanethiol, S-furfuryl acetothioate, difurfuryl disulfide, methyl furfuryl sulfide, 2-methylfuran-3-thiol, methyl furfuryl disulfide, methyl 2-methyl-3-furyl disulfide and furfuryl acetate, when used under the proposed conditions of use (see Section 3.1.3).

1.2. Additional information

The present application concerns 18 compounds, all of which except 4-(2-furyl)but-3-en-2-one [The EU Flavour Information System (FLAVIS) Number 13.044], 2-acetylfuran [13.054], 2-pentylfuran [13.059] and difurfuryl ether [13.061] have been assessed by the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA; WHO, 2001, 2002, 2009) and were considered safe for use in food. A group acceptable daily intake (ADI) was set for methyl 2-furoate [13.002], furfural [13.018], furfuryl alcohol [13.019] and furfuryl acetate [13.128].

Subsequently the EFSA Panel on Food Additive, Flavourings, Processing Aids and Materials in Contact with Food (CEF) considered the same compounds for use as food flavourings (EFSA, 2009; EFSA CEF Panel 2010a,b, 2011a,b,c, 2015) reaching the same overall conclusions except for difurfuryl sulfide [13.056]. For this compound and for 4-(2-furyl)but-3-en-2-one [13.044], 2-acetylfuran [13.054], 2-pentylfuran [13.059] and difurfuryl ether [13.061], the EFSA CEF Panel has been unable to reach a conclusion on their safety and additional toxicological data have been requested. The EFSA Panel on

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

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

[3] During the course of the assessment, this application was split and the present opinion covers 13 of the 18 substances under application (see Section 1.2).

[4] 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.

Additives and Products or Substances used in Animal Feed (FEEDAP) will also not proceed with an assessment of these five compounds until this issue has been resolved.

Consequently, the current opinion concerns only 13 of the compounds, namely 5-methylfurfural [13.001], methyl 2-furoate [13.002], bis-(2-methyl-3-furyl) disulfide [13.016], furfural [13.018], furfuryl alcohol [13.019], furanmethanethiol [13.026], S-furfuryl acetothioate [13.033], difurfuryl disulfide [13.050], methyl furfuryl sulfide [13.053], 2-methylfuran-3-thiol [13.055], methyl furfuryl disulfide [13.064], methyl 2-methyl-3-furyl disulfide [13.079] and furfuryl acetate [13.128], for which application was made.

The 13 compounds are currently listed in the European Union database of flavouring substances[5] and in the European Union Register of Feed Additives, respectively, and thus authorised for use in food and feed in the European Union. They have not been previously assessed by EFSA as feed additives.

Regulation (EC) No 429/2008[6] allows substances already approved for use in human food to be assessed with a more limited procedure than for other feed additives. However, the use of this procedure is always subject to the condition that food safety assessment is relevant to the use in feed.

2. Data and Methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[7] in support of the authorisation request for the use of the aliphatic and aromatic hydrocarbons as a feed additive. The technical dossier was prepared following the provisions of Article 7 of Regulation (EC) No 1831/2003, Regulation (EC) No 429/2008 and the applicable EFSA guidance documents.

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 aliphatic and aromatic hydrocarbons in animal feed. The Executive Summary of the EURL report can be found in Annex A.[8]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of the aliphatic and aromatic hydrocarbons is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance documents: Guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), Technical Guidance for assessing the safety of feed additives for the environment (EFSA, 2008), 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).

[5] 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.

[6] 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.

[7] FEED dossier reference: FAD-2010-0118.

[8] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/default/files/FinRep-FAD-2010-0118.pdf

3. Assessment

3.1. Characterisation

3.1.1. Characterisation of the flavouring additives

The molecular structures of the 13 additives under assessment are summarized in Figure 1, their physico-chemical characteristics in Table 1.

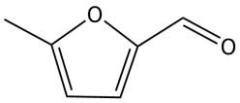
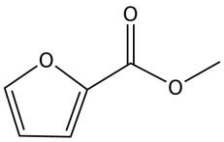
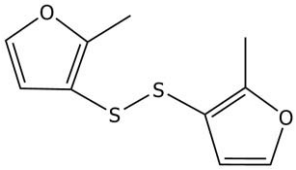
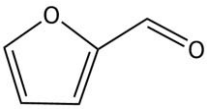
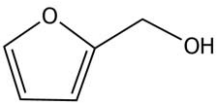
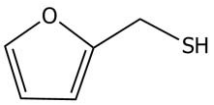
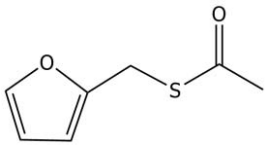
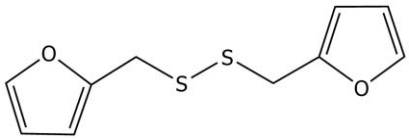
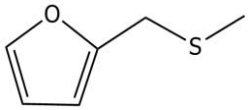
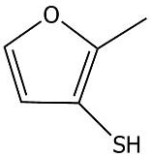
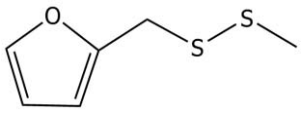
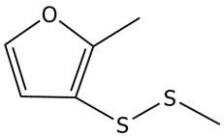
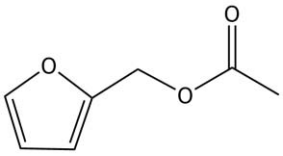
5-Methylfurfural [13.001] 	Methyl 2-furoate [13.002] 	bis-(2-Methyl-3-furyl) disulfide [13.016] 
Furfural [13.018] 	Furfuryl alcohol [13.019] 	Furanmethanethiol [13.026] 
S-Furfuryl acetothioate [13.033] 	Difurfuryl disulfide [13.050] 	Methyl furfuryl sulfide [13.053] 
2-Methylfuran-3-thiol [13.055] 	Methyl furfuryl disulfide [13.064] 	Methyl 2-methyl-3-furyl disulfide [13.079] 
Furfuryl acetate [13.128] 		

Figure 1: Molecular structures and FLAVIS numbers of the 13 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)]
5-Methylfurfural	620-02-0	13.001	$C_6H_6O_2$	110.11	Liquid	0.67
Methyl 2-furoate	611-13-2	13.002	$C_6H_6O_3$	126.11	Liquid	1.00
bis-(2-Methyl-3-furyl) disulfide	28588-75-2	13.016	$C_{10}H_{10}O_2S_2$	226.31	Liquid	4.14
Furfural	98-01-1	13.018	$C_5H_4O_2$	96.09	Liquid	0.41
Furfuryl alcohol	98-00-0	13.019	$C_5H_6O_2$	98.1	Liquid	0.28

Furanmethanethiol	98-02-2	13.026	C_5H_6OS	114.16	Liquid	1.96
S-Furfuryl acetothioate	13678-68-7	13.033	$C_7H_8O_2S$	156.2	Liquid	1.30
Difurfuryl disulfide	4437-20-1	13.050	$C_{10}H_{10}O_2S_2$	226.31	Liquid	4.03
Methyl furfuryl sulfide	1438-91-1	13.053	C_6H_8OS	128.19	Liquid	2.00
2-Methylfuran-3-thiol	28588-74-1	13.055	C_5H_6OS	114.16	Liquid	2.6
Methyl furfuryl disulfide	57500-00-2	13.064	$C_6H_8OS_2$	160.25	Liquid	2.95
Methyl 2-methyl-3-furyl disulfide	65505-17-1	13.079	$C_6H_8OS_2$	160.25	Liquid	3.01
Furfuryl acetate	623-17-6	13.128	$C_7H_8O_3$	140.01	Liquid	1.45

EU: European Union; CAS No: Chemical Abstract Service No.; Flavis number: EU Flavour Information System numbers.
(a): Logarithm of octanol–water partition coefficient.

All 13 substances are produced by chemical synthesis. Typically several routes of synthesis are available and described in the dossier.[9]

Data were provided on the batch to batch variation in five batches of each additive with the exception of methyl 2-methyl-3-furyl disulfide [13.079], for which only one batch was available because of the low use volume (< 1 kg/year).[10] For all compounds the content of the active substance exceeded the JECFA specifications (Table 2).

Table 2: Identity of the substances and data on purity

EU Register name	FLAVIS No.	JECFA specification minimum %[(a)]	Assay %	
			Average	Range
5-Methylfurfural	13.001	> 97	99.9	99.6–100
Methyl 2-furoate	13.002	> 98	99.8	98.9–100
bis-(2-Methyl-3-furyl) disulfide	13.016	> 98	98.8	97.9–99.7
Furfural	13.018	> 95	99.5	99.4–99.6
Furfuryl alcohol	13.019	> 97	99.1	98.7–99.7
Furanmethanethiol	13.026	> 97	99.6	99.0–99.9
S-Furfuryl acetothioate	13.033	> 95	99.7	98.7–100
Difurfuryl disulfide	13.050	> 96	97.7	96.9–98.5
Methyl furfuryl sulfide	13.053	> 97	99.2	98.4–99.7
2-Methylfuran-3-thiol	13.055	> 95	99.1	98.8–99.3
Methyl furfuryl disulfide	13.064	> 95	98.3	96.4–99.0
Methyl 2-methyl-3-furyl disulfide	13.079	> 97	99.9[(b)]	-
Furfuryl acetate	13.128	> 97	98.5	97.0–99.6

EU: European Union; Flavis number: EU Flavour Information System numbers; JECFA: The Joint FAO/WHO Expert Committee on Food Additives.
(a): FAO, 2006.
(b): 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 procedure applied by all consortium members. The parameters considered include residual solvents, heavy metals and other undesirable substances. However, no evidence of compliance was provided for these parameters.

3.1.2. Stability and homogeneity

A minimum shelf-life for 5-methyl furfural [13.001], furfural [13.018] and methyl 2-methyl-3-furyl disulfide [13.079] is stated to be 6 months. The shelf-life for the remaining 10 compounds under assessment is from 12 to 24 months when stored in closed containers under the recommended conditions. 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 premixtures and feed, use in water for drinking introduces other issues relating to product stability, such as degradation due to microbial activity. The FEEDAP Panel notes that 6 of 13 compounds in CG 14 have low water solubility (Log K_{ow} > 2), which makes it difficult to assess the safety in water for drinking. Considering this, and

[9] Technical dossier/Section II.
[10] Technical dossier/Section II/Annex 2.1 and Supplementary Information June 2011.

the absence of data on the short-term stability and homogeneity of the additives in water for drinking, the FEEDAP Panel is not in the position to conclude on the use of the additives in water for drinking.

3.1.3. Conditions of use

The applicant proposes the use of the 13 additives in feed or water for drinking for all animal species without withdrawal. In each case, the applicant proposes a normal use level and a high use level of five times the normal level in feed as shown in Table 3. No proposals are made for the dose to be used in water for drinking.

Table 3: Proposed conditions of use

EU Register name	FLAVIS No.	Feed concentration (mg/kg)	
		Normal	High
5-Methylfurfural	13.001	0.1	0.5
Methyl 2-furoate	13.002	0.1	0.5
bis-(2-Methyl-3-furyl) disulfide	13.016	0.01	0.05
Furfural	13.018	1	5
Furfuryl alcohol	13.019	1	5
Furanmethanethiol	13.026	0.01	0.05
S-Furfuryl acetothioate	13.033	0.01	0.05
Difurfuryl disulfide	13.050	0.01	0.05
Methyl furfuryl sulfide	13.053	0.01	0.05
2-Methylfuran-3-thiol	13.055	0.01	0.05
Methyl furfuryl disulfide	13.064	0.01	0.05
Methyl 2-methyl-3-furyl disulfide	13.079	0.01	0.05
Furfuryl acetate	13.128	0.1	0.5

EU: European Union; Flavis number: EU Flavour Information System numbers.

3.2. Safety

The assessment of safety is based on the highest use level proposed by the applicant (see Table 3).

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

The metabolism of furfuryl derivatives has been described in rodents and humans (WHO, 2001; EFSA CEF Panel, 2010b). Furfuryl esters are hydrolysed to furfuryl alcohol and the corresponding carboxylic acid. Furfuryl alcohol is subsequently oxidised to furfural and 2-furoic acid. Furoate esters are hydrolysed to 2-furoic acid and the corresponding alcohol. Furoic acid is excreted with urine as glycine conjugate after conversion to either furoyl-CoA or 2-furanacryloyl-CoA. 5-Methylfurfural is expected to follow similar metabolic pathways, i.e. oxidation and conjugation with glycine and alkyl oxidation.

Little is known about the specific metabolic pathways involved in metabolism of CG 14 compounds in livestock. Studies performed in hens (Jaffé and Cohn, cited by Pan and Fouts 1978), rabbits and dogs (Clayton and Clayton, 1981–1982, cited in the Hazardous Substances Data Bank, 2010[11]) after oral administration of furfural were identified by the applicant. In excreta of hens, furan-α-carboxylic acid and the ornithine conjugate were identified; in dogs and rabbits, furoic acid, furoyl glycine and furfuracryluric acid were excreted. Thus, as for rat, mouse and human, for dogs and rabbits glycine plays an important role in the conjugation of furoic acid (metabolite of furfuryl alcohol/furfural) for urinary excretion. In birds, ornithine is the most common conjugating amino acid of carboxylic compounds and the scarce available studies show that furfural is eliminated as ornithine conjugate. In goats fed with a diet containing 0.65% furfural, almost all of the compound disappeared in the ruminal fluid after 60 min; furfuryl alcohol incubated in goat liver homogenate was converted to furfural and subsequently to furoic acid (Kyuma et al., 1991, in Japanese, with abstract in English).

No metabolic studies in other target species could be found for the CG 14 compounds.

[11] Technical Dossier/Section III/Annex_III_12. Clayton GD and Clayton FE (Eds.), 1981-1982. Patty's Industrial Hygiene and Toxicology. Volume 2A, 2B, 2C. Toxicology. 3rd Ed. New York, John Wiley and Sons, pp. 2664–2665.Cited in: Hazardous Substances Data Bank, 2010. Furfural and furfuryl alcohol. Published by National Library of Medicine. HSDB Database.

Studies performed in several animal species (pigs, rabbits, pigeons, dogs and cats), showed that they preferentially conjugate carboxylic acids with glycine (Bridges et al., 1970), whereas in the chicken ornithine substitutes for glycine. In goats and cattle, carboxylic acids are also mainly eliminated as glycine conjugates as demonstrated with orally administered salicylic acid (Short et al., 1990). In aquatic species, carboxylic acids are preferentially eliminated after conjugation with taurine, but glycine can also be used (James, 1987). Thus, the furoic acid formed by oxidation of furfuryl alcohol and similar compounds are expected to be conjugated and predominantly excreted in urine.

A tissue distribution study was performed in rats by Nomeir et al. (1992) with orally administered radiolabelled furfuryl alcohol and furfural, at doses up to 27.5 and 12.5 mg/kg bw, respectively. The maximum percentage of radioactivity recovered in tissues 72 h after administration of the compounds was 0.5% and 0.6% of the administered doses of furfuryl alcohol and furfural, respectively, being liver and kidney the organs with the highest concentrations of radioactivity (83–88% of the dose was excreted in urine in the same period). These data indicate that the furfuryl derivatives are extensively excreted and no appreciable deposition is expected in farm animals at the low dose levels proposed to be included in feed.

For the thiol compounds, it is assumed that the fate in the target species is similar to that occurring in experimental animals, that is, S-oxidation, S-methylation and fission of the disulfide bond proceeding to oxidation at the SH group of the resulting hydrolysed compounds (EFSA CEF Panel, 2010c).

Free thiols can directly react with endogenous sulfur-containing substances, e.g. glutathione and proteins, to form mixed disulfides, or alternatively with glucuronic acid to give thio-beta-D-glucuronide conjugates. Simple sulfides may undergo sulfur oxidation, leading to sulfoxides which are further converted into sulfones. S-Thioesters are rapidly hydrolysed by lipases and esterases forming the corresponding carboxylic acids and thiols (EFSA CEF Panel, 2010c).

The enzymes involved in the biotransformation pathways of CG 14 compounds have been detected in many species, including mammals, birds and fish, and are assumed to be present in all the target species. The enzymes include esterases, cytochrome P450 monooxygenase families (Nebbia et al., 2003; Ioannides 2006), glycine-, glucuronide- methyl- and glutathione transferases (Watkins and Klaassen, 1986; Gusson et al., 2006). Thus, it is expected that the target species are able to metabolise these compounds and no appreciable residues are expected to remain in the food products for consumers.

3.2.2. Toxicological studies

Toxicological data (subchronic, repeated-dose studies, with multiple doses tested) could be found for furfural [13.018] and furanmethanethiol [13.026].

For furfural [13.018], a no observed adverse effect level (NOAEL) was derived from a study in rats (males/females, 10 animals/group) in which microencapsulated furfural was administered with diet at nominal doses of 0, 30, 60, 90 and 180 mg/kg bw per day for 3 months. The measured doses were reported to be ~ 10% lower. In males, a decrease in red blood cell count was observed at 180 mg/kg bw per day, and increases in mean corpuscular volume and mean corpuscular haemoglobin from 90 mg/kg bw per day. At the highest dose tested (180 mg/kg bw per day) decreased alkaline phosphatase was observed in females, decreased alanine aminotransferase in males, increased gamma-glutamyl transferase in females, increased plasma levels of albumin in both sexes and decreased plasma levels of potassium in females. Increased liver weight was observed in males at 180 mg/kg bw per day. Gross examination at autopsy revealed no treatment-related changes. Microscopic examination showed hepatocellular alterations in males receiving 90 mg/kg bw per day, with increasing incidences and severity at 180 mg/kg bw. A NOAEL of 54 mg/kg bw per day was determined for furfural (Jonker, 1999).

A NOAEL for furanmethanethiol [13.026] was derived from a 90-day study in rats given daily doses of 0, 1, 3 or 30 mg furanmethanethiol/kg bw by oral gavage (15 males/15 females per group). No effects were observed on clinical parameters (haemoglobin, packed cell volume, red blood cells, reticulocytes, neutrophils, eosinophils, lymphocytes and monocytes), renal function (urine: glucose, ketones, protein, blood, specific gravity, volume) and histological examination. At the highest dose tested, a decrease in the body weight was associated with a reduced feed intake. The lower body

weight was associated with differences in organ weight, i.e. reduced absolute organ weight and increased relative values. Increased haemoglobin and packed cell volume were observed at the highest dose tested. Thus a NOAEL of 3 mg/kg bw per day was identified (Phillips et al., 1977).

A repeated-dose toxicity study (90 days, only one dose tested) in rats was available for two compounds, namely bis-(2-methyl-3-furyl) disulfide [13.016] (Morgareidge and Oser 1970, unpublished) and 2-methylfuran-3-thiol [13.055] (Oser 1970, unpublished). Both studies considered a number of endpoints (survival, behaviour, body weight, feed intake; haematology, clinical chemistry and urine analysis;[12] gross pathology and histopathology), were properly reported and showed no effects at the dose tested. For these reasons, the FEEDAP Panel concluded that a NOAEL could be derived from these studies, i.e. 0.29 mg/kg bw per day for bis-(2-methyl-3-furyl) disulfide [13.016] and 5 mg/kg bw per day for 2-methylfuran-3-thiol [13.055]. However, it should be noted that only one dose was tested leaving a great deal of uncertainty regarding the precision of this value.

3.2.3. 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. Human exposure in the European Union (EU) to the individual compounds ranges from 0.27 to 440 µg/person per day (EFSA, 2009, EFSA CEF Panel, 2010b). This corresponds to 0.013 to 20.4 µg/kg$^{0.75}$ per day. These exposure levels are considered safe for humans. Table 4 summarises the result of the comparison with human exposure for representative target animals. The body weight of target animals is taken from the default values shown in Table 5.

Table 4: Comparison of exposure of humans and target animals (calculated from the proposed maximum feed concentrations, see Table 3) to the flavourings under application

Flavouring	Use level in feed (mg/kg)	Human exposure (µg/kg bw^{075}per day) [(a)]	Target animal exposure µg/kgbw^{075}per day		
			Salmon	Piglet	Dairy cow
5-Methylfurfural	0.5	6.49	11.8	52.6	77.7
Methyl 2-furoate	0.5	0.39	11.8	52.6	77.7
bis-(2-Methyl-3-furyl) disulfide	0.05	0.013	1.18	5.26	7.77
Furfural	5	20.4	118	526	777
Furfuryl alcohol	5	8.35	118	526	777
Furanmethanethiol	0.05	1.34	1.18	5.26	7.77
S-Furfuryl acetothioate	0.05	0.020	1.18	5.26	7.77
Difurfuryl disulfide	0.05	0.15	1.18	5.26	7.77
Methyl furfuryl sulfide	0.05	0.045	1.18	5.26	7.77
2-Methylfuran-3-thiol	0.05	0.024	1.18	5.26	7.77
Methyl furfuryl disulfide	0.05	0.039	1.18	5.26	7.77
Methyl 2-methyl-3-furyl disulfide	0.05	0.034	1.18	5.26	7.77
Furfuryl acetate	0.5	0.74	11.8	52.6	77.7

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

Table 4 shows that for all 13 compounds except furanmethanethiol [13.026] the intake by the target animals greatly exceeds that of humans, 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 for 12 of the 13 compounds under assessment. As an alternative, the maximum feed concentration that can be considered safe for the target animals can be derived from the lowest NOAEL if suitable data are available. Although human exposure to furanmethanethiol is higher than that calculated for salmonids, the FEEDAP Panel opts to use toxicological data in preference to extension from human exposure to determine safe levels for target species.

[12] Haematology: total and differential leukocyte counts, erythrocytes, haemoglobin, haematocrit; clinical chemistry: serum urea nitrogen, blood glucose, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and serum alkaline phosphatase; urine analysis: pH, specific gravity, qualitative test for albumin, glucose, occult blood and microscopic examination of the centrifuged urinary sediment.

Toxicological data were available for furfural [13.018] from which a NOAEL value could be derived (see Section 3.2.2). This NOAEL is also applied to furfuryl alcohol [13.019], furfuryl acetate [13.0128] and methyl 2-furoate [13.002] because they share common metabolic pathways with furfural and are interconverted by hydrolysis and oxidation/reduction reactions. Applying an uncertainty factor (UF) of 100 to the NOAELs, the maximum safe intake for the target species was derived for the compounds following the EFSA guidance for sensory additives (EFSA FEEDAP Panel, 2012a), and thus the maximum safe feed concentration was calculated. The results for furfural and related compounds are summarised in Table 5.

Table 5: Maximum safe concentration in feed for different target animals for furfural [13.018], furfuryl alcohol [13.019], furfuryl acetate [13.0128] and methyl 2-furoate [13.002]

Target animal	Default values		Maximum safe intake/feed concentration	
	Body Weight (kg)	Feed intake (g/day)[a]	Intake (mg/day)	Concentrations (mg/kg feed)[b]
Salmonids	2	40	1.1	27
Veal calves (milk replacer)	100	2,000	54	27
Cattle for fattening	400	8,000	216	24
Pigs for fattening	100	3,000	54	18
Sows	200	6,000	108	18
Dairy Cows	650	20,000	351	15
Turkeys for fattening	12	400	6.5	16
Piglets	20	1,000	11	11
Chickens for fattening	2	120	1.1	9
Laying hens	2	120	1.1	9
Dogs	15	250	8.1	29
Cats	3	60	1.6	24

(a): Complete feed with 88% DM, except milk replacer for veal calves (94.5% DM), and for cattle for fattening, dairy cows, dogs and cats for which the values are DM intake.
(b): Complete feed containing 88% DM, milk replacer 94.5% DM.

Toxicological data were also available furanmethanethiol [13.026] and for bis-(2-methyl-3-furyl) disulfide [13.016] and 2-methylfuran-3-thiol [13.055] derived from the single-dose studies. The NOAEL of furanmethanethiol [13.026] (3 mg/kg bw per day) was used also to derive a safe level in feed for thioester S-furfuryl acetothioate [13.033]. Again an UF of 100 was used. The results are summarised in Table 6.

Table 6: Maximum safe concentration in feed for different target animals for furanmethanethiol and S-furfuryl acetothioate (**A**), bis-(2-methyl-3-furyl) disulfide (**B**), and 2-methylfuran-3-thiol (**C**)

Target animal	Maximum safe intake (mg/day)[a]			Maximum feed concentration (mg/kg complete feed)[b]		
	A	B	C	A	B	C
Salmonids	0.06	0.01	0.10	1.5	0.15	2.5
Veal calves (milk replacer)	3.0	0.29	5.0	1.5	0.15	2.5
Cattle for fattening	12	1.16	20	1.3	0.13	2.2
Pigs for fattening	3.0	0.29	5.0	1.0	0.10	1.7
Sows	6.0	0.58	10.0	1.0	0.10	1.7
Dairy Cows	19.5	1.89	32.5	0.9	0.08	1.4
Turkeys for fattening	0.36	0.03	0.60	0.9	0.09	1.5
Piglets	0.6	0.06	1.00	0.6	0.06	1.0
Chickens for fattening	0.06	0.01	0.10	0.5	0.05	0.8
Laying hens	0.06	0.01	0.10	0.5	0.05	0.8
Dogs	0.45	0.04	0.75	1.6	0.15	2.6
Cats	0.09	0.01	0.15	1.3	0.13	2.2

(a): Complete feed with 88% DM, except milk replacer for veal calves (94.5% DM), and for cattle for fattening, dairy cows, dogs and cats for which the values are DM intake.
(b): Complete feed containing 88% DM, milk replacer 94.5% DM.

For the 5 remaining compounds, toxicity studies performed with the additive under assessment were not available. Therefore, the threshold of toxicological concern (TTC) approach, currently applied to estimate the acceptable exposure level for humans, was followed to derive the maximum safe feed concentration (EFSA Guidance on sensory additives; EFSA FEEDAP Panel, 2012a).

For the Cramer Class II compounds 5-methylfurfural [13.001], difurfuryl disulfide [13.050], methyl furfuryl sulfide [13.053] and methyl furfuryl disulfide [13.064], 0.5 mg/kg complete feed are safe for cattle, salmonids and non-food producing animals and 0.3 mg/kg complete feed for pigs and poultry.

For the remaining Cramer Class III compound methyl 2-methyl-3-furyl disulfide [13.079], the calculated safe use level is 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.

Conclusions on safety for the target species

The FEEDAP Panel concludes that:

- furfural [13.018] and furfuryl alcohol [13.019] are safe at the proposed maximum use level of 5 mg/kg complete feed for all animal species;
- methyl 2-furoate [13.002] and furfuryl acetate [13.128] are safe at the proposed maximum use level of 0.5 mg/kg complete feed for all animal species;
- 5-methylfurfural [13.001] is safe at the proposed use level of 0.5 mg/kg complete feed for cattle, salmonids and non-food producing animals and at the use level of 0.3 mg/kg complete feed for pigs and poultry;
- bis-(2-methyl-3-furyl) disulfide [13.016], furanmethanethiol [13.026], S-furfuryl acetothioate [13.033], difurfuryl disulfide [13.050], methyl furfuryl sulfide [13.053], 2-methylfuran-3-thiol [13.055], methyl furfuryl disulfide [13.064] and methyl 2-methyl-3-furyl disulfide [13.079] are safe at the proposed maximum use level of 0.05 mg/kg complete feed.

3.2.4. Safety for the consumer

The safety for the consumer of the compounds under assessment in CG 14 used as food flavours has already been assessed by JECFA (WHO, 2001, 2002) and EFSA (EFSA CEF Panel 2010b, 2011b). All compounds are currently authorised as food flavourings without limitations.[13] A group ADI of 0.5 mg/kg bw per day has been set for methyl 2-furoate [13.002], furfural [13.018], furfuryl alcohol [13.019] and furfuryl acetate [13.128].

Given the low use levels of CG 14 compounds to be applied in feed, and the expected metabolism and excretion in target animals (see Section 3.3.1), 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[14] 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 of the concentration in the environment are exempt from further assessment. Examination of the published literature shows that this applies to 5-methylfurfural [13.001], furfural [13.018] and furfuryl alcohol [13.019] [data taken from the Netherlands Organisation for Applied Scientific Research (TNO) database Volatile Compounds in Food ver. 14.1; Burdock, 2013]. Furfural [13.018] is expected to be

[13] 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.

[14] Technical dossier/Section II/Annex II.3.

toxic, however, its relatively high presence in nature (> 5 mg/kg in the food plants examined) excludes it from a further assessment of its toxicity for the environment.[15]

The applicant did not demonstrate that the other compounds (methyl 2-furoate [13.002], bis-(2-methyl-3-furyl) disulfide [13.016], furanmethanethiol [13.026], S-furfuryl acetothioate [13.033], difurfuryl disulfide [13.050], methyl furfuryl sulfide [13.053], 2-methylfuran-3-thiol [13.055], methyl furfuryl disulfide [13.064], methyl 2-methyl-3-furyl disulfide [13.079] and furfuryl acetate [13.128]) occur in the environment at levels above the maximum application rate. These substances are therefore assessed 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 (2008) with a fixed concentration in feed, there is a fixed order of PEC_{soil} from each species, with the lamb being the most critical.

Table 7: PEC values for lambs of specific flavourings of CG 14 under assessment

EU Register name	CAS No.	Dose mg/kg	PEC soil (µg/kg)	PEC pore water (µg/L)
Methyl 2-furoate	611-13-2	0.5	11	13.89
bis-(2-Methyl-3-furyl) disulfide	28588-75-2	0.05	1	0.004
Furanmethanethiol	98-02-2	0.05	1	0.24
S-Furfuryl acetothioate	13678-68-7	0.05	1	1.61
Difurfuryl disulfide	4437-20-1	0.05	1	0.004
Methyl furfuryl sulfide	1438-91-1	0.05	1	0.13
2-Methylfuran-3-thiol	28588-74-1	0.05	1	0.28
Methyl furfuryl disulfide	57500-00-2	0.05	1	0.07
Methyl 2-methyl-3-furyl disulfide	65505-17-1	0.05	1	0.08
Furfuryl acetate	623-17-6	0.5	11	8.69

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

Table 7 show the PEC_{soil} for lambs. The values for methyl-2-furoate [13.002] and furfuryl acetate [13.0128] are slightly above the threshold of 10 µg/kg (EFSA, 2008). The PEC for pore water, however, is dependent on the sorption, which is different for each compound. For these calculations, the substance-dependent constants organic carbon sorption constant (K_{oc}), molecular weight, vapour pressure and solubility are needed. These were estimated from the Simplified Molecular Input Line Entry Specification (SMILES) notation of the chemical structure using EPIWEB 4.1 (Table 8).[16] This program was also used to derive the SMILES notation from the CAS numbers. The K_{oc} value derived from the first-order molecular connectivity index was used, as recommended by the EPIWEB program.

Table 8: Physico-chemical properties predicted by EPIWEB 4.1

EU Register name	CAS No.	Predicted by EPIWEB 4.1				
		DT_{50}[(a)] (days)	Molecular weight (g/mol)	Vapour pressure (Pa)	Solubility (mg/L)	K_{oc}[(b)] (L/kg)
Methyl 2-furoate	611-13-2	7	126.11	121	13300	37
bis-(2-Methyl-3-furyl) disulfide	28588-75-2	25	226.31	0.02	9.27	13470
Furanmethanethiol	98-02-2	9	114.16	386	2216	245
S-Furfuryl acetothioate	13678-68-7	12	156.20	8.65	5510	31
Difurfuryl disulfide	4437-20-1	17	226.31	0.10	11.56	16690
Methyl furfuryl sulfide	1438-91-1	10	128.19	183	1843	446
2-Methylfuran-3-thiol	28588-74-1	11	114.16	3280	759.5	210
Methyl furfuryl disulfide	57500-00-2	12	160.25	10.68	206.2	813
Methyl 2-methyl-3-furyl disulfide	65505-17-1	14	160.25	10.68	184.6	730
Furfuryl acetate	623-17-6	8	140.14	135	4825	63

EU: European Union; CAS No: Chemical Abstracts Service; DT50: predicted environmental concentration.
(a): DT_{50}, half-life of the additive (by BioWin3).
(b): K_{oc}, organic carbon sorption constant.

[15] Technical dossier/ Supplementary information June 2011.
[16] Available online: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm

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

Six substances in Table 7 have $PEC_{pore\ water}$ > 0.1 µg/L, two of them have also a PEC_{soil} > 10 µg/kg. Therefore, these six substances are subjected to phase II risk assessment.

In the absence of experimental data, the phase II risk assessment was performed using ECOSAR v. 1.11, which estimates the half-maximal effective concentration (EC_{50}) for earthworms, fish, algae and *Daphnia* from the SMILES notation of the substance.

Table 9: The Predicted Environmental Concentration for surface water for lambs compared with the EC50 values in mg/L predicted by ECOSAR 1.11

EU Register name	LC_{50}[(a)] Earthworm (mg/kg)	LC_{50} Fish (mg/L)	LC_{50} Daphnia (mg/L)	EC_{50}[(b)] algae (mg/L)	PEC surface water (µg/L)
Methyl 2-furoate	3585	69	161	81	4.6
Furanmethanethiol	-	101	57	42	0.1
S-Furfuryl acetothioate	-	53	120	57	0.5
Methyl furfuryl sulfide	-	104	60	45	0.04
2-Methylfuran-3-thiol	-	1.6	0.3	0.2	0.1
Furfuryl acetate	2747	39	86	40	2.9

EU: European Union; EC50: half-maximal effective concentration; LC50: lethal concentration 50; PEC: predicted environmental concentration.
(a): LC_{50}, the concentration of a test substance which results in a 50% mortality of the test species.
(b): EC_{50}, the concentration of a test substance which results in 50% of the test animals being adversely affected (i.e. both mortality and sublethal effects).

The LC_{50} and EC_{50} values for acute toxicity (Table 9) divided by a UF of 1000 were much higher than the PEC values for soil and surface water for all compounds, indicating that there is no risk to the environment at the doses mentioned in Table 7.

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 safe dose of 0.047 mg/kg feed was calculated according to the EFSA guidance (EFSA, 2008). This dose would give a sediment concentration of 10 µg/kg, which is the threshold level of no concern.

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 freshwater environments. For the marine environment, the safe use level is estimated to be 0.05 mg/kg feed.

3.3. Efficacy

Because all 13 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.

4. Conclusions

The FEEDAP Panel concludes that all compounds except 5-methylfurfural [13.001] are safe at the maximum proposed use level for all animal species: furfural [13.018] and furfuryl alcohol [13.019] at 5 mg/kg complete feed; methyl 2-furoate [13.002] and furfuryl acetate [13.128] at 0.5 mg/kg complete feed; bis-(2-methyl-3-furyl) disulfide [13.016], furanmethanethiol [13.026], S-furfuryl acetothioate [13.033], difurfuryl disulfide [13.050], methyl furfuryl sulfide [13.053], 2-methylfuran-3-

thiol [13.055], methyl furfuryl disulfide [13.064] and methyl 2-methyl-3-furyl disulfide [13.079] at 0.05 mg/kg complete feed. 5-Methylfurfural [13.001] is safe at the proposed use level of 0.5 mg/kg complete feed for cattle, salmonids and non-food producing animals and at the use level of 0.3 mg/kg complete feed for pigs and poultry.

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

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

The concentrations considered safe for the target species are unlikely to have detrimental effects on the terrestrial and freshwater environments.

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

In the absence of data on the stability in water for drinking, the FEEDAP Panel is unable to conclude on the safety or efficacy of the substances under this mode of delivery.

Documentation provided to EFSA

1. Chemically defined flavourings from Flavouring Group 14 – furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms (CDG 14). August 2010. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).

2. Chemically defined flavourings from Flavouring Group 14 – furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms (CDG 14). Supplementary information. June 2011. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).

3. Chemically defined flavourings from Flavouring Group 14 – furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms (CDG 14). Supplementary information. May 2012. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).

4. Chemically defined flavourings from Flavouring Group 14 – furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms (CDG 14). Supplementary information. July 2012. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).

5. Evaluation report of the European Union Reference Laboratory for Feed Additives on the Methods(s) of Analysis for Chemically defined flavourings from Flavouring Group 14.

6. Comments from Member States.

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Abbreviations

ADI	acceptable daily intake
bw	body weight
CAS	Chemical Abstracts Service
CD	Commission Decision
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CG	chemical group
CDG	chemically defined group
DM	dry matter
DT_{50}	degradation half-time
EC	European Commission
EC_{50}	half-maximal effective concentration
ECOSAR	component program of EPI suite™
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
NOAEL	no observed adverse effect level
PEC	predicted environmental concentration
PEC_{swaq}	predicted environmental concentration of the additive (parent compound) in surface water
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 - Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis for Aliphatic and aromatic hydrocarbons

The *Chemically Defined Flavourings - Group 14* (*Furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms*), in this application comprises Eighteen 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 99%.

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 *CDG14* 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 *CDG14* 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 *CDG14* 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 *CDG14* 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*.

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

(*) Full list provided in EURL evaluation report, available from the EURL website.