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Safety and efficacy of the feed additives 2-acetylfuran [13.054] and 2-pentylfuran [13.059] belonging to chemical group 14 for animal species (FEFANA asbl)

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Mojca Durjava, Maryline Kouba, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa, Ruud Woutersen, Paul Brantom, Andrew Chesson, Johannes Westendorf, Paola Manini and Birgit Dusemund

Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of 2-acetylfuran [13.054] and 2-pentylfuran [13.059] belonging to chemical group 14 (furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms), when used as sensory additives (flavourings) in feed for all animal species. 2-Acetylfuran [13.054] was tested in tolerance studies in chickens for fattening, weaned piglets and cattle for fattening. No adverse effects were observed in the tolerance studies at 10-fold the intended use level. The FEEDAP Panel concluded that 2-acetylfuran [13.054] is safe for these species at the proposed use level of 0.5 mg/kg and conclusions were extrapolated to all animal species. For 2-pentylfuran [13.059], the Panel concluded that it is safe at the proposed maximum use level in feed of 0.5 mg/kg. No safety concern would arise for the consumer from the use of 2-acetylfuran [13.054] and 2-pentylfuran [13.059] up to the proposed maximum use level in feed as flavourings. The additives should be considered as irritant to skin and eyes and the respiratory tract, and as dermal and respiratory sensitisers. The use of 2-acetylfuran [13.054] and 2-pentylfuran [13.059] as flavours in animal feed was not expected to pose a risk for the environment. Since 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 was considered necessary.

Keywords: sensory additives, feed flavourings, furan derivatives, 2-acetylfuran, 2-pentylfuran, safety, efficacy

Requestor: European Commission

Question number: EFSA-Q-2015-00819

Correspondence: feedap@efsa.europa.eu

Panel members: Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Mojca Durjava, Maryline Kouba, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa and Ruud Woutersen.

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1. Introduction

1.1. Background and Terms of Reference

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

The European Commission received a request from Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)[2] for authorisation of 18 substances (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) belonging to chemical group (CG) 14, when used as feed additives for all animal species (category: sensory additives; functional group: flavourings). CG 14 for flavouring substances is defined in Commission Regulation (EC) No 1565/2000 as 'furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms.' During the course of the assessment, this application was split, and the present opinion covers only five out of the 18 substances under application (see Section 1.2). Moreover, the application for 4-(2-furyl)but-3-en-2-one [13.044], difurfuryl sulfide [13.056] and difurfuryl ether [13.061] was withdrawn.[4]

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the applications to the European Food Safety Authority (EFSA) as applications under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 10(2) (re-evaluation of an authorised feed additive). During the course of the assessment, the applicant withdrew the application for the use of chemically defined flavourings in water for drinking.[5] EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of this 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 feed additive consisting of 2-acetylfuran (EU Flavour Information System (FLAVIS) number) [13.054] and 2-pentylfuran [13.059], when used under the proposed conditions of use (see Section 3.1.3).

1.2. Additional information

The initial application on CG 14 concerned 18 compounds, intended to be used as feed flavourings for all animal species. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) has already delivered an opinion on 13 of the 18 compounds included in CG 14 (EFSA FEEDAP Panel, 2016).

The remaining compounds 4-(2-furyl)but-3-en-2-one [13.044], 2-acetylfuran [13.054], difurfuryl sulfide [13.056], 2-pentylfuran [13.059] and difurfuryl ether [13.061] were excluded from the previous opinion because at that time the assessment for use in food as flavouring was not complete. The EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (EFSA CEF Panel) had requested additional toxicity data for difurfuryl sulfide [13.056] (EFSA CEF Panel, 2010) and additional

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

[2] On 13/03/2013, EFSA was informed by the applicant that 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, 1,050 Brussels, Belgium.

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

[4] The applicant informed EFSA (29 June 2020) on the intention to withdraw the application for 4-(2-furyl)but-3-en-2-one [13.044], difurfuryl sulfide [13.056] and difurfuryl ether [13.061]. On 01 July 2021 the EC informed EFSA on the withdrawal of the three compounds.

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

genotoxicity data to complete the assessment of 2-acetylfuran [13.054], 2-pentylfuran [13.059], difurfuryl ether [13.061] (EFSA CEF Panel, 2011) and 4-(2-furyl)but-3-en-2-one [13.044] (EFSA CEF Panel, 2012). For 4-(2-furyl)but-3-en-2-one [13.044], difurfuryl sulfide [13.056] and difurfuryl ether [13.061] the requested data were not submitted, and the substances have been deleted from the Union list. Since the applicant withdrew the application for 4-(2-furyl)but-3-en-2-one [13.044], difurfuryl sulfide [13.056] and difurfuryl ether [13.061], these compounds are also excluded from the present assessment.

The EFSA Panel on Food Additives and Flavourings (EFSA FAF Panel) has delivered an opinion in 2021 and concluded that the genotoxicity concerns for 2-acetylfuran [13.054] and 2-pentylfuran [13.059] could be ruled out and there was no safety concern at the estimated level of intake as flavouring substances (EFSA FAF Panel, 2021).

The compounds under assessment, 2-acetylfuran [13.054] and 2-pentylfuran [13.059] are currently listed in the European Union database of flavouring substances and in the European Union Register of Feed Additives,[7] respectively, and thus authorised for use in food and feed in the European Union.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[8] in support of the authorisation request for the use of the compounds under assessment as feed additives.

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

EFSA has verified the EURL report as it relates to the methods used for the control of flavourings from CG 14 – Furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms – in animal feed.[9]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of active substance (trade name of the product) is in line with the principles laid down in Regulation (EC) No 429/2008[10] and the relevant guidance documents: Guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012b), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019) and Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018).

3. Assessment

The additives under assessment, 2-acetylfuran [13.054] and 2-pentylfuran [13.059], belong to CG 14 'furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms'. They are intended to be used as a sensory additive (functional group: flavouring compounds) in feed for all animal species.

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

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

[8] FEED dossier reference: FAD-2010-0413.

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

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

3.1. Characterisation

3.1.1. Characterisation of the flavouring substances

The chemical structure of the flavouring additives under application are shown in Figure 1 and their physico-chemical characteristics in Table 1.

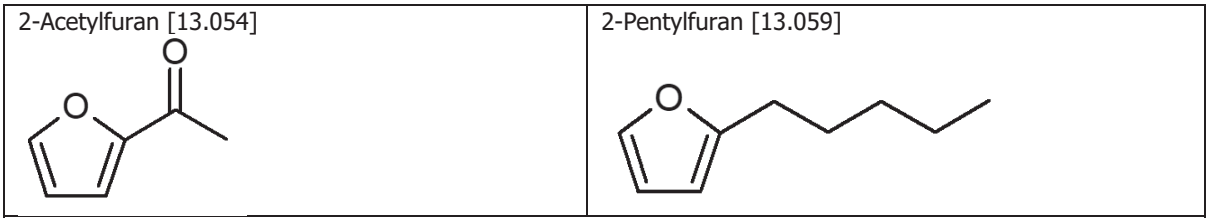

Figure 1: Chemical structures, EU register names and [FLAVIS numbers] of the flavouring compounds under assessment

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)]
2-Acetylfuran	1192-62-7	13.054	$C_6H_6O_2$	110.11	Liquid	0.52
2-Pentylfuran	3777-69-3	13.059	$C_9H_{14}O$	138.21	Liquid	3.87

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

The compounds under assessment are produced by chemical synthesis and the typical routes of synthesis are described in the technical dossier for each compound.[11]

Data were provided on the batch-to-batch variation in five batches of 2-acetylfuran [13.054] and six batches of 2-pentylfuran [13.059].[12] The content of the active substance for each compound (Table 2) exceeded in all batches the minimum content reported in the specifications set by the Joint FAO/WHO Expert Committee on Food Add (JECFA) (FAO, 2006).

Table 2: Identity of the substances and data on batch-to-batch variation

EU Register name	FLAVIS No	JECFA specification minimum % [(1)]	Assay %	
			Average	Range
2-Acetylfuran	13.054	97	99.6	99.3–100
2-Pentylfuran	13.059	99	99.5	99.2–99.9

(1): FAO, 2006.

The applicant states that 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, mercury, cadmium, lead and arsenic and other undesirable substances. However, no evidence of compliance was provided for these parameters.

3.1.2. Shelf life

The minimum shelf life of 2-acetylfuran [13.054] and 2-pentylfuran [13.059] is claimed to be 24 months, when stored in closed containers under recommended conditions.[13] However, no data supporting this statement were provided.

[11] Technical dossier FAD-2010-0417.
[12] Technical dossier FAD-2010-0417/Section II/Annex 2.1 and Supplementary information May 2011.
[13] Technical dossier FAD-2010-0417/Supplementary information June 2011.

3.1.3. Conditions of use

2-Acetylfuran [13.054] and 2-pentylfuran [13.059] are intended for use in feed for all animal species without withdrawal period.

For each of the compounds under assessment, the applicant proposes a normal use level of 0.1 mg/kg complete feed and a maximum use level of 0.5 mg/kg complete feed.

3.2. Safety

The assessment of safety of the compounds is based on the maximum use level proposed by the applicant (0.5 mg/kg complete feed).

The compounds under assessment have been recently evaluated by EFSA as food flavourings (EFSA FAF Panel, 2021), and no safety concerns were identified.

3.2.1. Safety for the target species

3.2.1.1. Safety of 2-acetylfuran for the target species

2-Acetylfuran was excluded from the initial assessment (EFSA FEEDAP Panel, 2016) because there was uncertainty about its genotoxicity (EFSA CEF Panel, 2011). Subsequently, the concern for the genotoxicity of 2-acetylfuran has been ruled out (EFSA FAF Panel, 2021).

To support the safety for the target animals the applicant provided three tolerance studies in chickens for fattening, weaned piglets and cattle for fattening performed with a mixture of flavourings named 'Milky-Vanilla'. The mixture included 2-acetylfuran [13.054] and other 15 flavouring compounds, which were tested each at the maximum recommended dose (MRD, 1×) and two overdoses, 3× MRD and 10× MRD per kg complete feed. For 2-acetylfuran the doses tested were 0.5 mg/kg (1× MRD), 1.5 mg/kg (3× MRD) and 5.0 mg/kg (10× MRD). The test item, the feed preparation and the results of the tolerance studies were fully described in a previous opinion (EFSA FEEDAP Panel, 2023, see also the Appendix).

In those three studies, no adverse effects were seen at an intended overdose of 10 times the maximum recommended dose for the compounds tested, including 2-acetylfuran [13.054]. Therefore, the additive is safe for those species at the maximum recommended level (0.5 mg/kg complete feed). The margin of safety was similar between the studied species, consequently the Panel considers that the conclusions can be extrapolated to all animal species. This would be in line with the principles of the FEEDAP Guidance on sensory additives (EFSA FEEDAP Panel, 2012a).

In its assessment of 2-acetylfuran [13.054] as a food flavour, the EFSA FAF Panel identified a no observed adverse effect level (NOAEL) of 22.6 mg/kg body weight (bw) per day (the highest dose tested) from a 90-day study in rat (EFSA FAF Panel, 2021). Applying an uncertainty factor (UF) of 100 to this NOAEL, the FEEDAP Panel calculated maximum safe concentrations in complete feed for all target species (EFSA FEEDAP Panel, 2017), which ranged from 2 mg/kg in cats[14] to 11.9 mg/kg in dogs and 44.2 mg/kg in ornamental fish. The maximum safe levels obtained support the conclusion from the tolerance studies.

3.2.1.2. Safety of 2-pentylfuran for the target species

The concern for the genotoxicity of 2-pentylfuran previously identified (EFSA CEF Panel, 2011) has been ruled out (EFSA FAF Panel, 2021).

For 2-pentylfuran [13.059], not tested in the tolerance trial, the applicant proposed to extrapolate the conclusions for 2-acetylfuran [13.054] tested in the tolerance studies and belonging to the same chemical group.

Read-across has been widely applied in the risk assessment of food and feed flavourings. Based on considerations related to structural and metabolic similarities, flavourings are grouped into chemical groups as defined in Annex I of Regulation (EC) No 1565/2000[3] and structural groups named Flavouring Group Evaluation (FGE). According to the guidance on the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), 'The conclusions obtained for an individual flavouring may be extended to other flavourings belonging to the same structural group (e.g. an FGE)'.

[14] Since glucuronidation of the secondary alcohol arising from the reduction of the keto group in 2-acetylfuran [13.054] is an important metabolic pathway facilitating the excretion of the parent compound, the calculation of safe concentrations in cat feed needs an additional UF of 5.

The use of read-across within a chemical group is applied on a case-by-case basis, considering the structural features, the physico-chemical properties and the expected reactivity of the compounds under assessment, as discussed in the paragraphs below.

The FEEDAP Panel considers that the proposal for read-across is not justified by structural and metabolic similarity. The keto group in 2-acetylfuran [13.054] can be reduced to a secondary alcohol followed by conjugation with glucuronic acid, which makes it suitable for excretion via urine. 2-Pentylfuran [13.059] has an aliphatic side chain, which is relatively inert. Although oxidation of the alpha-position is possible, it requires more energy than the reduction of the keto group. This favours alternative metabolic pathways, such as ring opening, which will produce more reactive metabolites with higher toxicity (EFSA FAF Panel, 2021).

In line with the FEEDAP Panel guidance on the safety for the target species (EFSA FEEDAP Panel, 2017), the safety for target animals can be derived from toxicological studies with oral administration in laboratory animals. In the assessment of 2-pentylfuran [13.059] as a food flavour, the EFSA FAF Panel derived a benchmark dose (BMD) lower confidence limit for a benchmark response of 10% ($BMDL_{10}$) of 8.51 mg/kg bw per day from a 90-day gavage study in rats, based on the most reliable BMDL for clinical chemistry data, plasma total bilirubin as indicator of red blood cell damage. Applying an UF of 100 to the $BMDL_{10}$, the safe daily dose of 2-pentylfuyran [13.059] for the target species was derived following the EFSA Guidance on the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017), and thus the maximum safe feed concentration of 2-pentylfuran [13.059] was calculated (Table 3). Since glucuronidation of the secondary alcohol arising from the reduction of the keto group in 2-pentylfuran is an important metabolic pathway facilitating the excretion of the parent compound, the calculation of safe concentrations in cat feed needs an additional UF of 5 due to the low capacity for glucuronidation in cats (Court and Greenblatt, 1997; Lautz et al., 2021).

The results allow to conclude that 2-pentylfuran [13.059] is safe at the maximum proposed use level of 0.5 mg/kg complete feed for all animal species (Table 3).

Table 3: Maximum safe concentration in feed of 2-pentylfuran [13.059] for target animal species and categories calculated from the $BMDL_{10}$ of 8.51 mg/kg bw per day

Animal category	Body weight (kg)	Feed intake (g DM/day)	Daily feed intake (g DM/kg bw)	Maximum safe concentration (mg/kg feed)(1)
Chicken for fattening	2	158	79	0.9
Laying hen	2	106	53	1.4
Turkey for fattening	3	176	59	1.3
Piglet	20	880	44	1.7
Pig for fattening	60	2,200	37	2.0
Sow lactating	175	5,280	30	2.7
Veal calf (milk replacer)	100	1,890	19	4.3
Cattle for fattening	400	8,000	20	3.7
Dairy cow	650	20,000	31	2.4
Sheep/goat	60	1,200	20	3.7
Horse	400	8,000	20	3.7
Rabbit	2	100	50	1.5
Salmon	0.12	2.1	18	4.3
Dog	15	250	17	4.5
Cat(2)	3	60	20	0.7
Ornamental fish	0.012	0.54	5	16.6

DM: dry matter.
(1): Complete feed containing 88% DM, milk replacer 94.5% DM.
(2): The uncertainty factor for cats is increased by an additional factor of 5 because of the reduced capacity of glucuronidation.

3.2.1.3. Conclusions on safety for the target species

Based on the tolerance studies in chickens for fattening, piglets and cattle for fattening in which no adverse effects were seen at intended 10-fold overdose, the FEEDAP Panel considers that 2-acetylfuran [13.054] is safe for these species at the maximum proposed use level of 0.5 mg/kg

complete feed. As the margin of safety is similar in all species, the conclusions are extrapolated to all animal species.

The FEEDAP Panel concludes that 2-pentylfuran [13.059] is safe at the maximum proposed use level of 0.5 mg/kg complete feed for all animal species.

3.2.2. Safety for the consumer

The safety for the consumer of 2-acetylfuran [13.054] and 2-pentylfuran [13.059] used as food flavours has been recently assessed by EFSA (EFSA FAF Panel, 2021) and no safety concerns were identified. The compounds are currently authorised in the EU as food flavourings without limitations.[6]

Although deposition and residue studies of the compound in farm animals are not available, the FEEDAP Panel considers that the use of 2-acetylfuran [13.054] and 2-pentylfuran [13.059] in animal feed would not increase the human exposure to these compounds. This is based on the low use levels to be applied in feed and the expected metabolism and excretion in target animals.

Consequently, no safety concern would arise for the consumer from the use of 2-acetylfuran [13.054] and 2-pentylfuran [13.059] as feed flavourings up to the maximum proposed use level in feed.

3.2.3. Safety for the user

No specific data on the safety for the user were provided.

In the safety data sheets,[15] hazard for skin contact and respiratory exposure are recognised for 2-acetylfuran [13.054] and for eye contact for 2-pentylfuran [13.059].

The compounds should be considered as irritant to skin and eyes and the respiratory tract, and as dermal and respiratory sensitisers.

3.2.4. Safety for the environment

The addition 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 2-acetylfuran [13.054] and 2-pentylfuran [13.059] occur in the environment at levels well above the application rate of 0.5 mg/kg complete feed.[16]

Therefore, no environmental risk is foreseen from the use of 2-acetylfuran [12.003] and 2-pentylfuran [13.059] up to the highest safe levels in feed.

3.3. Efficacy

Since 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.

4. Conclusions

2-Acetylfuran [13.054] and 2-pentylfuran [13.059] are safe at the maximum proposed use level of 0.5 mg/kg complete feed for all animal species.

No safety concerns would arise for the consumer from the use of 2-acetylfuran [13.054] and 2-pentylfuran [13.059] up to the proposed maximum use level in feed as flavourings.

The compounds should be considered as irritant to skin and eyes and the respiratory tract, and as dermal and respiratory sensitisers.

No environmental risk is foreseen for the compounds up to the highest safe levels in feed.

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

[15] Technical dossier FAD-2010-0417/Section II/Annex_II_3. Hazard for skin contact and respiratory exposure are recognised for 2-acetylfuran [13.054] and for eye contact for 2-pentylfuran [13.059].

[16] Technical dossier FAD-2010-0417/Supplementary information June 2011. Data taken from the Netherlands Organisation for Applied Scientific Research (TNO) database Volatile Compounds in Food ver. 14.1; Burdock, 2003.

5. Documentation provided to EFSA/Chronology

Date	Event
14/09/2010	Dossier received by EFSA. Chemically defined flavourings from Chemical Group 14 - Furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms for all animal species and categories. CDG 14. Submitted by FEFANA Asbl/Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)
18/10/2010	Reception mandate from the European Commission
01/12/2010	Application validated by EFSA – Start of the scientific assessment
09/12/2010	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterisation, safety for target species, safety for the consumer, safety for the user and efficacy*
28/02/2011	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives
	Comments received from Member States
14/06/2011	Reception of supplementary information from the applicant - Scientific assessment remained suspended
19/07/2011	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 (addendum) – Scientific assessment suspended. *Issues: safety for the consumer*
03/05/2012	Reception of supplementary information from the applicant - Scientific assessment remained suspended
22/06/2012	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 (addendum) – Scientific assessment suspended. *Issues: safety for the consumer*
16/07/2012	Reception of supplementary information from the applicant - Scientific assessment remained suspended
10/12/2015	The applicant was informed that the application was split into two separate questions with two different EFSA-Q-numbers. The initial EFSA-Q-2010-01218 was assigned to the 10 compounds for which EFSA has completed the evaluation as food flavours, whereas the new EFSA-Q-2015-00819 was assigned to the 25 compounds, for which the assessment was pending
10/03/2016	Partial withdrawal from EC: use in water (Art. (4))
01/12/2021	Reception of supplementary information from the applicant - Scientific assessment re-started
01/02/2023	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

References

Court MH and Greenblatt DJ, 1997. Molecular basis for deficient acetaminophen glucuronidation in cats. An Interspecies Comparison of Enzyme Kinetics in Liver Microsomes. Biochemical Pharmacology, 53, 1041–1047. https://doi.org/10.1016/s0006-2952(97)00072-5

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2010. Scientific Opinion on Flavouring Group Evaluation 65 (FGE.65): Consideration of sulfur-substituted furan derivatives used as flavouring agents evaluated by JECFA (59th meeting) structurally related to a subgroup of substances within the group of "Furfuryl and furan derivatives with and without additional side-chain substituents and heteroatoms from chemical group 14" evaluated by EFSA in FGE.13Rev1 (2009). EFSA Journal 2010;8(7)1406, 54 pp. https://doi.org/10.2903/j.efsa.2010.1406

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2011. Scientific Opinion on Flavouring Group Evaluation 67, Revision 1 (FGE.67Rev.1): consideration of 40 furan substituted aliphatic hydrocarbons, alcohols, aldehydes, ketones, carboxylic acids and related esters, sulfides, disulfides and ethers evaluated by JECFA at the 65th meeting (JECFA, 2006b) and re-evaluated at the 69th meeting (JECFA, 2009c). EFSA Journal 2011;9(10):2315, 77 pp. https://doi.org/10.2903/j.efsa.2011.2315

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2012. Scientific Opinion on Flavouring Group Evaluation 222: consideration of genotoxicity data on representatives for alpha, beta-unsaturated furyl derivatives with the alpha, beta-unsaturation in the side chain from subgroup 4.6 of FGE.19 by EFSA. EFSA Journal 2012;10(5):2748, 18 pp. https://doi.org/10.2903/j.efsa.2012.2748

EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes M, Aquilina G, Castle L, Engel K-H, Fowler P, Frutos Fernandez MJ, Fürst P, Gundert-Remy U, Gürtler R, Husøy T, Manco M, Moldeus P, Passamonti S, Shah R, Waalkens-Berendsen I, Wölfle D, Wright M, Benigni R, Bolognesi C, Chipman K, Cordelli E, Degen G, Marzin D, Svendsen C, Carfì M, Vianello G and Mennes W, 2021. Scientific Opinion on Flavouring Group Evaluation 67, Revision 3 (FGE.67Rev3): consideration of 23 furan-substituted compounds evaluated by JECFA at the 55th, 65th, 69th and 86th meetings. EFSA Journal 2021;19(2):6362, 83 pp. https://doi.org/10.2903/j.efsa.2021.6362

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012a. Guidance for the preparation of dossiers for sensory additives. EFSA Journal 2012;10(1):2534, 26 pp. j.efsa.2012.2534.

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012b. Guidance on studies concerning the safety of use of the additive for users/workers. EFSA Journal 2012;10(1):2539, 5 pp. https://doi.org/10.2903/j.efsa.2012.2539

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2016. Scientific opinion on the safety and efficacy of furfuryl and furan derivatives belonging to chemical group 14 when used as flavourings for all animal species and categories. EFSA Journal 2016;14(2):4389, 19 pp. https://doi.org/10.2903/j.efsa.2016.4389

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Galobart J, Innocenti ML and Martino L, 2017. Guidance on the assessment of the safety of feed additives for the target species. EFSA Journal 2017;15(10):5021, 19 pp. https://doi.org/10.2903/j.efsa.2017.5021

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Galobart J, Innocenti ML and Martino L, 2018. Guidance on the assessment of the efficacy of feed additives. EFSA Journal 2018;16(5):5274, 25 pp. https://doi.org/10.2903/j.efsa.2018.5274

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis V, Bastos M, Christensen H, Dusemund B, Kouba M, Kos Durjava M, López-Alonso M, López Puente S, Marcon F, Mayo B, Pechová A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen R, Brock T, de Knecht J, Kolar B, van Beelen P, Padovani L, Tarres-Call J, Vettori MV and Azimonti G, 2019. Guidance on the assessment of the safety of feed additives for the environment. EFSA Journal 2019;17(4):5648, 78 pp. https://doi.org/10.2903/j.efsa.2019.5648

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis V, Azimonti G, Bastos M, Christensen H, Dusemund B, Kouba M, Fašmon Durjava M, López-Alonso M, López Puente S, Marcon F, Mayo B, Pechová A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen R, Brantom P, Chesson A, Dierick N, Martelli G, Westyendorf J, Anguita M, Ortuño Casanova J and Manini P, 2023. Safety of 27 flavouring compounds providing a Milky-Vanilla flavour and belonging to different chemical groups for use as feed additives in all animal species (FEFANA asbl). EFSA Journal 2023;21(1):7713, 25 pp. https://doi.org/10.2903/j.efsa.2023.7713

FAO, 2006. FAO JECFA Monographs 1: Combined Compendium of Food Additive Specifications—Joint FAO/WHO Expert Committee on Food Additives—All specifications monographs from the 1st to the 65th meeting (1956–2005). Volume 4. Analytical methods, test procedures and laboratory solutions used by and referenced in the food additive specifications. Food and Agricultural Organization of the United Nations, Rome. Available online: http://www.fao.org/docrep/009/a0691e/a0691e00.htm

Lautz LS, Jeddi MZ, Girolami F, Nebbia C and Dorne JLCM, 2021. Metabolism and pharmacokinetics of pharmaceuticals in cats (*Felix sylvestris* catus) and implications for the risk assessment of feed additives and contaminants. Toxicology Letters, 338, 114–127. https://doi.org/10.1016/j.toxlet.2020.11.014

Abbreviations

ADFI	average daily feed intake
ADG	average daily gain
ANOVA	analysis of variance
BMD	benchmark dose
$BMDL_{10}$	BMD lower confidence limit for a benchmark response of 10%
BW	body weight
CAS	Chemical Abstracts Service
CDG	chemically defined group
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids

CG	chemical group
DM	dry matter
EEIG	European Economic Interest Grouping
EURL	European Union Reference Laboratory
FAF	EFSA Panel on Food Additives and Flavourings
FAO	Food Agricultural 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
FL-no	FLAVIS number
HACCP	hazard analysis and critical control points
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
Log K_{ow}	logarithm of octanol–water partition coefficient
MRD	maximum recommended dose
NOAEL	no observed adverse effect level
UF	uncertainty factor
WHO	World Health Organization

Appendix A – Tolerance trials with a mixture of flavourings including 2-acetylfuran

A.1. Test item and feed preparation

The mixture tested in tolerance studies is named 'Milky-Vanilla' and included 16 flavouring compounds belonging to several chemical groups. The individual components of the mixture, their FLAVIS numbers, the maximum recommended dose (MRD, 1×) proposed by the applicant and the two overdoses tested, 3× MRD or 10× MRD per kg complete feed, are described in Table A.1.

Table A.1: Individual components of the mixture and intended dosages tested in tolerance trials

CG	EU register name	FLAVIS No	1× MRD	3× MRD	10× MRD
			mg/kg complete feed		
01	Butyric acid	08.005	125	375	1,250
01	Ethyl isovalerate	09.447	25	75	250
03	2-Methyl-2-pentenoic acid	08.055	5	15	50
05	6-Methylhept-5-en-2-one	07.015	4.5	13.5	45
05	Nonan-2-one	07.020	10	30	100
05	5-Methylhept-2-en-4-one	07.139	5	15	50
09	Dodecano-1,5-lactone	10.008	25	75	250
14	5-Methylfurfural	13.001	5	15	50
14	2-Acetylfuran	13.054	0.5	1.5	5
21	4-Phenylbut-3-en-2-one	07.024	5	15	50
23	4-Methoxybenzaldehyde (anisaldehyde)	05.015	25	75	250
23	Piperonal	05.016	5	15	50
23	Vanillin	05.018	125	375	1,250
23	Benzyl benzoate	09.727	5	15	50
23	Benzyl salicylate	09.752	25	75	250
26	Diphenyl ether	04.035	5	15	50

EU: European Union; FLAVIS No: EU Flavour Information System numbers; MRD: maximum recommended dose.

More details on the feed preparation are given in a previous opinion (EFSA FEEDAP Panel, 2023).

A.2. Tolerance study in chickens for fattening

A total of 800 one-day-old male chickens for fattening (Ross 308) were distributed to 32 pens in groups of 25 animals and allocated to 4 dietary treatments (8 replicates per treatment), blocking applied depending on the situation of the pen in the room. Two basal diets (starter up to day 14, and grower from day 15 to 36) based on maize and soya bean meal were either not supplemented (control) or supplemented with the mixture to provide 1× MRD, 3× MRD or 10× MRD per kg feed (confirmed by analysis). The test mixture was added daily to the basal diet. Feed from the previous day was removed from the feeder in each pen and weighed. Animals were under study for 36 days, diets were offered in mash form and presented coccidiostats for the whole duration of the study.

Mortality and health status were checked daily, and dead animals were necropsied. Animals were weighed on days 1, 14 and 35 (pen basis), feed intake was registered per pen and feed to gain ratio was calculated. Blood samples were taken from 2 birds per pen (one on day 35 and the other one on day 36) for haematology and blood biochemistry[18] (the birds were randomly selected at the beginning of the study). At 36 days of age, two chickens from each pen from control and 10× MRD treatment groups were sacrificed and used for necropsy and gross pathology evaluations. The basic study design was a randomised complete block design of 4 dietary treatments allocated in 8 blocks, with pen location as block criteria. An analysis of variance (ANOVA) was done with the data (pen basis,

[17] Total count for erythrocytes, packed cell volume, haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, total and differential counts for leukocytes, platelet counts.

[18] Sodium, potassium, chloride, calcium, phosphate, magnesium, total protein, albumin, globulin, glucose, uric acid, cholesterol, creatinine, bilirubin, acute phase protein, amylase, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and creatine kinase.

individual for the blood parameters) and considering the treatment and the block as the main effects. Group means were compared with Tukey test. The significance level was set at 0.05.

The birds were in general good health throughout the study (mortality range: 1.1–2.7%, not statistically different between treatments). The feed intake and final body weight of the animals were lower (16% and 19% respectively) than the ones expected for the genotype of birds used but this could be due partly to the use of mash feed and the low body weight at the first day of age.

Birds receiving the mixture at 10× MRD showed significantly lower ($P < 0.05$) body weight at 35 d, average daily gain (ADG) and average daily feed intake (ADFI) (BW 1,748 g; ADG 48.8 g and ADFI 78.5 g) when compared to both control animals (BW 1,851 g; ADG 51.8 g and ADFI 82.4 g) and 3× MRD (BW 1,848 g; ADG 51.7 g and ADFI 82.0 g). No significant differences were observed between chickens receiving 1× MRD and 10× MRD. No differences were observed in the feed to gain ratio among the four groups. These results indicate that animals receiving the highest dosage of the product ingested less food, likely due to excessive flavour.

Dietary treatment had no significant effect on the haematological profile of chickens for fattening at the end of the study, except for mean corpuscular haemoglobin (MCH) values which were slightly lower, although significant ($P < 0.05$), in chickens receiving the mixture at 10× MRD relative to the control diet (50.8 vs. 52.5 pg). No significant effects of dietary treatment on any of the serum biochemical parameters were observed, except for a significantly higher creatinine in chickens of group receiving 3× MRD (0.211 mg/dL) when compared with both the control diet (0.186 mg/dL) and group 10× MRD (0.189 mg/dL) This effect was not treatment-related and considered to be of marginal biological significance.

Concerning gross pathology, liver weight, expressed as a percentage of body weight, was higher in chickens receiving 10× MRD of the test product compared with animals on the control diet (2.67% vs. 2.39%). No other differences were observed in the remaining organs.

The FEEDAP Panel concludes that the components of the mixture are safe under the proposed conditions of use with a margin of safety of 10.

A.3. Tolerance study in weaned piglets

A total of 144 Piétrain × (Landrace × Large White) weaned piglets of 33 days of age, half females and half males, with an initial body weight of 8.3 kg, were distributed according to body weight and sex to 36 pens each containing four animals (two males and two females), representing 9 replicates per treatment. Two basal diets (pre-starter, up to day 14 of trial and starter, from 15 to 42 day of trial), mainly based on maize and soya bean meal, were either not supplemented (control) or supplemented with the mixture to provide: 1× MRD, 3× MRD or 10× MRD per kg feed (confirmed by analysis). Feed was offered on *ad libitum* basis in mash form for 42 days.

Mortality and health status were checked daily. Piglets were individually weighed on days 1, 14 and 42 of trial. Feed intake was registered per pen and average daily gain, average daily feed intake and feed to gain ratio were calculated. At the end of the experiment (day 42 of trial), blood samples were taken from 2 piglets per pen (one male and one female randomly selected at the beginning of the trial) for haematology[17] and blood biochemistry.[19] At 42 days of age, one piglet from each pen from the control group and the group receiving the mixture at 10× MRD was sacrificed and used for gross pathology evaluations. The experimental unit was the pen for production traits and the individual animal for blood parameters. All data were analysed by using a generalised linear model. The treatment and the block were the main effects for production traits; the treatment, the block and the sex were the main effects for blood parameters. Tukey's test was used as post-hoc analysis. The significance level was set at $P < 0.05$.

The health status of the piglets was good throughout the study. Two animals died in the 1-fold group (due to enteritis and pneumonia). No differences were observed among groups for body weight (mean value for final BW 35.3 kg) and daily feed intake (mean value 1,067 g) while feed to gain ratio was significantly lower in each of the treatment groups (1.63, 1.64 and 1.63 for 1×, 3× and 10× MRD) compared to the control group (1.72).

As concerns blood analyses, no significant differences were observed for haematology and biochemical analyses of plasma. With respect to blood serum, glucose concentration was significantly

[19] Sodium, potassium, chloride, calcium, phosphate, magnesium, total protein, albumin, globulin, glucose, uric acid, cholesterol, creatinine, bilirubin, acute phase protein, amylase, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), creatine kinase, prothrombin time and fibrinogen.

higher in pigs receiving 1× MRD (119 mg/dL) when compared to animals receiving 10× MRD (113 mg/dL); creatinine concentration was significantly higher in the 10× MRD (1.11 mg/dL) than in the 3× MRD treatment group (1.02 mg/dL); total protein and albumin concentrations were significantly higher in the 1× MRD (54.3 g/L and 32.3 g/L respectively) than in the 3× MRD treatment group (52.1 g/L and 30.0 g/L, respectively) and phosphorous concentration was significantly higher in pigs receiving 1× MRD (10.0 mg/dL) compared to control animals (9.4 mg/dL). These effects were not dose-related and considered of low biological relevance.

At necropsy, no significant macroscopic lesions were observed.

The FEEDAP Panel concludes that the components of the mixture are safe under the proposed conditions of use with a margin of safety of 10.

A.4. Tolerance study in cattle for fattening

A total of 24 bulls (Holstein, 345 kg body weight) were used for the study. The bulls were housed in individual pens (2.90 × 1.97 m; 3 m^2 net space; natural lighting) and the four dietary treatments were allocated considering the body weight of the animals (6 replicates per treatment) in a random complete block design. Before the start of the experimental phase, the bulls received a common mash concentrate for 14–28 days to collect basal data (blood samples, body weight and feed intake). From the start of the study, the animals were fed the test concentrate and straw. The test concentrate was based on maize grain meal, barley grain meal, maize gluten feed and wheat middlings and was either not supplemented (control) or supplemented with the mixture to provide 1× MRD, 3× MRD or 10× MRD per kg concentrate feed (confirmed by analysis). Feed was prepared daily, and the animals had free access to the mash concentrate and to straw in two separate feeders. Feed from the previous day was removed from the feeder in each pen and weighed. Water was offered *ad libitum* in each pen. Although the duration of the study was planned to be 42 days, finally it was extended to 49 days. Mortality and health status were checked every day. Animals were weighed on days 1, 7, 21, 42 and 49, while feed intake was registered daily for concentrate and straw; feed to gain ratio was calculated. Blood samples were taken on days 1, 7 and 49 from all animals for haematology[17] and blood biochemistry.[20] An ANOVA was carried out with the pen as the experimental unit. The significance level was set at 0.05.

The general health of the animals was good throughout the study and no animals died. For the overall period, there were no statistically significant differences in final body weight (control group 427 kg), average daily weight gain (control group 1.68 kg/day), feed intake (concentrate and straw 9.8 kg) or feed to gain ratio (control group 5.90) among treatments. Regarding the blood haematology and biochemistry data, no differences were observed between treatments.

The study showed no negative effects when the additive was added up to 10-fold of the MRD in the concentrate. Considering the intake of straw, the levels tested would correspond to 0.87, 2.58 and 8.55× the MDR. As the intake of concentrate was about 85% of the total dry matter (DM) intake of the animals, the real exposure to the additive was lower than the one intended in the conditions of use.

Consequently, the FEEDAP Panel concludes that the components of the mixture are safe under the proposed conditions of use with a margin of safety of at least at 8.5.

[20] Alkaline phosphatase, amylase, gamma-glutamyl transferase, alanin aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, calcium, phosphate, magnesium, potassium, sodium, chloride, cholesterol, lactic acid, albumin, total protein, urea, creatinine, glucose, biliary salts.