

# Modification of the terms of authorisation regarding the maximum inclusion level of a feed additive consisting of 4-hydroxy-2,5-dimethylfuran-3(2H)-one for cats and dogs (V. MANE FILS)

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## Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the proposed modification of the terms of the authorisation regarding the maximum inclusion level of a feed additive consisting of 4-hydroxy-2,5-dimethylfuran-3(2H)-one for cats and dogs. 4-Hydroxy-2,5-dimethylfuran-3(2H)-one is currently authorised for use as a sensory additive (functional group: flavouring compounds) for cats and dogs at a recommended maximum content of 5 mg/kg complete feed. The applicant is requesting a modification of the authorisation to increase the recommended maximum content of the additive up to 25 mg/kg complete feed for cats and dogs. Based on the toxicological data available, the FEEDAP Panel concludes that 4-hydroxy-2,5-dimethylfuran-3(2H)-one is safe for dogs at 25 mg/kg feed and for cats at 18 mg/kg feed. The additive is irritant to skin, eyes and to the respiratory tract and is a skin sensitiser. No further demonstration of efficacy is necessary.

## KEYWORDS

4-hydroxy-2,5-dimethylfuran-3(2H)-one, cats, dogs, flavourings, safety, sensory additives

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## 1 | INTRODUCTION

### 1.1 | Background and Terms of Reference

Regulation (EC) No 1831/2003<sup>1</sup> establishes the rules governing the community authorisation of additives for use in animal nutrition. In particular, Article 13(3) of that regulation lays down that if the holder of an authorisation proposes changing the terms of the authorisation by submitting an application to the commission, accompanied by the relevant data supporting the request for the change, the authority shall transmit its opinion on the proposal to the commission and the Member States.

The European Commission received a request from V. MANE FILS<sup>2</sup> for the modification of the terms of the authorisation of the additive consisting of 4-hydroxy-2,5-dimethylfuran-3(2H)-one when used as a feed additive for cats and dogs (category: sensory additives; functional group: flavouring compounds).

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 13(3) (modification of the authorisation of a feed additive). The dossier was received on 20 October 2023 and the general information and supporting documentation are available at <https://open.efsa.europa.eu/questions/EFSA-Q-2023-00688>. The particulars and documents in support of the application were considered valid by EFSA as of 5 December 2023.

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 4-hydroxy-2,5-dimethylfuran-3(2H)-one, when used under the proposed conditions of use (see **Section 3.1.2**).

### 1.2 | Additional information

EFSA issued an opinion on the safety and efficacy of furanones and tetrahydrofurfuryl derivatives: 4-hydroxy-2,5-dimethylfuran-3(2H)-one, 4,5-dihydro-2-methylfuran-3(2H)-one, 4-acetoxy-2,5-dimethylfuran-3(2H)-one and linalool oxide (chemical group 13) when used as flavourings for all animal species (EFSA FEEDAP Panel, 2012).

The additive is currently authorised as a sensory additive (flavouring compounds) for use for cats and dogs (2b13010) at the recommended maximum content of 5 mg/kg of complete feed (with a moisture content of 12%).<sup>3</sup>

## 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<sup>4</sup> in support of the authorisation request for the use of 4-hydroxy-2,5-dimethylfuran-3(2H)-one as a feed additive.

The confidential version of the technical dossier was subject to a target consultation of the interested Member States from 06 December 2023 to 6 March 2024; the comments received were considered for the assessment.

In accordance with Article 38 of the Regulation (EC) No 178/2002<sup>5</sup> and taking into account the protection of confidential information and of personal data in accordance with Articles 39 to 39e of the same regulation, and of the Decision of EFSA's Executive Director laying down practical arrangements concerning transparency and confidentiality,<sup>6</sup> a non-confidential version of the dossier has been published on Open.EFSA.

According to Article 32c(2) of Regulation (EC) No 178/2002 and to the Decision of EFSA's Executive Director laying down the practical arrangements on pre-submission phase and public consultations, EFSA carried out a public consultation on the non-confidential version of the technical dossier from 30 January to 20 February 2024 for which no comments were received.

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, other scientific reports and experts' (elicitation) knowledge, to deliver the present output.

<sup>1</sup>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.

<sup>2</sup>V. MANE FILS, 620 route de Grasse Le Bar Sur Loup – France.

<sup>3</sup>Commission Implementing Regulation (EU) 2022/1452 of 1 September 2022, OJ L 228, 02.09.2022, p. 17.

<sup>4</sup>Dossier reference: FEED-2023-18246.

<sup>5</sup>Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–48.

<sup>6</sup>Decision <https://www.efsa.europa.eu/en/corporate-pubs/transparency-regulation-practical-arrangements>

## 2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of 4-hydroxy-2,5-dimethylfuran-3(2H)-one is in line with the principles laid down in Regulation (EC) No 429/2008<sup>7</sup> and the relevant guidance documents: Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), Guidance on the assessment of the safety of feed additives for the users (EFSA FEEDAP Panel, 2023).

## 3 | ASSESSMENT

4-Hydroxy-2,5-dimethylfuran-3(2H)-one is currently authorised for use as a sensory feed additive (functional group: flavouring compounds) for cats and dogs at a recommended maximum content of 5 mg/kg complete feed.

The applicant is requesting a modification of the 'other provisions' of the authorisation to increase the recommended maximum content of the active substance up to 25 mg/kg complete feed for cats and dogs.

### 3.1 | Characterisation

#### 3.1.1 | Characterisation of the additive

4-Hydroxy-2,5-dimethylfuran-3(2H)-one (racemate) (synonym: furaneol; strawberry furanone) is identified with the single Chemical Abstracts Service (CAS) number 3658-77-3, the EU Flavour Information System (FLAVIS) number 13.010. It has the molecular formula  $C_6H_8O_3$  and molecular weight 128.1 g/mol and belongs to the Chemical Group (CG) 13 for flavouring substances defined in Commission Regulation (EC) No 1565/2009 as 'furanones and tetrahydrofurfuryl derivatives. 4-Hydroxy-2,5-dimethylfuran-3(2H)-one is freely soluble<sup>8</sup> in water 315 g/L at 25°C.<sup>9</sup>

The additive was characterised in a previous assessment (EFSA FEEDAP Panel, 2012).

It is produced by chemical synthesis (e.g. by the addition of acetylene to acetaldehyde followed by ozonolysis to give hexane-2,5-diol-3,4-dione which is then cyclised in the presence of a mineral acid). It is authorised for use in feed for cats and dogs with a purity of 98%.

The applicant provided analyses on five batches<sup>10</sup> of the additive demonstrating that the purity of 4-hydroxy-2,5-dimethylfuran-3(2H)-one is in compliance with the authorised specifications (all the five batches show values of 100% of purity).

#### 3.1.2 | Conditions of use

The additive is currently authorised to be used in feed for cats and dogs.

Under other provisions, it is stated:

1. The additive shall be incorporated into the feed in the form of a premixture.
2. In the directions for use of the additive and premixtures, the storage conditions and stability to heat treatment shall be indicated.
3. On the label of the additive, the following shall be indicated: 'Recommended maximum content of the active substance per kg of complete feedingstuff with a moisture content of 12%: — cats and dogs: 5 mg.'
4. The functional group, the identification number, the name and the added amount of the active substance shall be indicated on the label of the premixture where the use level on the label of the premixture would result in exceeding the level referred to in point 3.
5. For users of the additive and premixtures, feed business operators shall establish operational procedures and organisational measures to address potential risks by inhalation, dermal contact or eyes contact. Where those risks cannot be eliminated or reduced to a minimum by such procedures and measures, the additive and premixtures shall be used with personal protective equipment, including skin, eye and breathing protection.

The applicant is requesting to increase the maximum recommended content from 5 to 25 mg/kg complete feed for cats and dogs.

<sup>7</sup>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.

<sup>8</sup>For solubility terms, see Table 2 of the Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles (EFSA Scientific Committee, 2021).

<sup>9</sup>Chen Y, Sidisky LM; J Chromatogr A 1218(38): 6817–6822 (2011).

<sup>10</sup>Annex\_II\_2\_13\_010\_CoA\_CONF.pdf.

## 3.2 | Safety

The additive is intended to be used only in feed for dogs and cats, and therefore, there is no need to perform an assessment of the safety for the consumers and the environment.

### 3.2.1 | Safety for the target species

In the previous assessment (EFSA FEEDAP Panel, 2012), the FEEDAP Panel concluded that 4-hydroxy-2,5-dimethylfuran-3(2H)-one was safe at the concentration proposed by the applicant of 5 mg/kg complete feed for all target species.

The maximum safe concentration of 4-hydroxy-2,5-dimethylfuran-3(2H)-one in feed was derived from the lowest no observed adverse effect level (NOAEL) of 200 mg/kg body weight (bw) per day identified in a 2-year carcinogenicity study in rats exposed to the additive under assessment. The NOAEL was identified based on reduced body weight gain and reduced survival in males at 400 mg/kg bw per day (Kelly & Bolte, 2003).<sup>11</sup>

The assessment of genotoxicity potential of 4-hydroxy-2,5-dimethylfuran-3(2H)-one was performed in a previous EFSA opinion in which it was concluded that there was no concern for genotoxicity (EFSA CEF Panel, 2011).

No tolerance studies in dogs or cats nor (geno)toxicological studies have been provided by the applicant. The NOAEL of 200 mg/kg bw per day which was identified and applied in the previous evaluation (EFSA FEEDAP Panel, 2012) is still considered valid for the current assessment. Applying an uncertainty factor (UF) of 100 to the NOAEL, the safe daily dose for the target species was derived following the EFSA FEEDAP Guidance on the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), and thus, the maximum safe feed concentration of the additive was calculated. Owing to the unusually low capacity for glucuronidation in cats (Court & Greenblatt, 1997; Lautz et al., 2021), the safe concentration in complete feed for this species was calculated applying an additional UF of 5 to the UF of 100 mentioned above.

The calculated maximum safe concentrations of the additive in complete feed (88% dry matter, DM) are 100 and 18 mg/kg for dogs and cats, respectively.

#### 3.2.1.1 | Conclusions on safety for the target species

The FEEDAP Panel concludes that 4-hydroxy-2,5-dimethylfuran-3(2H)-one acid is safe for dogs at the maximum recommended level of 25 mg/kg complete feed and for cats at 18 mg/kg complete feed.

### 3.2.2 | Safety for the users

In the previous assessment (EFSA FEEDAP Panel, 2012), and in absence of data, the FEEDAP Panel concluded that it was prudent to treat 4-hydroxy-2,5-dimethylfuran-3(2H)-one as irritant to skin, eyes and the respiratory tract and as skin sensitiser.

In the current application, no additional data was provided other than the safety data sheet<sup>12</sup> which is aligned with the concerns identified by the Panel in the previous assessment. Therefore, the Panel confirms its previous conclusions.

## 3.3 | Efficacy

In the previous assessment (EFSA FEEDAP Panel, 2012), the FEEDAP Panel concluded that since 4-hydroxy-2,5-dimethylfuran-3(2H)-one is used in food as a flavouring, and its function in feed is essentially the same as that in food, no further demonstration of efficacy is necessary. The FEEDAP Panel considers that the increase in the maximum recommended level would not affect the previous conclusion on efficacy.

## 4 | CONCLUSIONS

The FEEDAP Panel concludes that 4-hydroxy-2,5-dimethylfuran-3(2H)-one is safe for dogs at the maximum recommended level of 25 mg/kg complete feed and for cats at 18 mg/kg complete feed.

The additive is irritant to skin, eyes and to the respiratory tract and is a skin sensitiser.

Since 4-hydroxy-2,5-dimethylfuran-3(2H)-one is used in food as a flavouring and its function in feed is essentially the same as that in food, no further demonstration of efficacy is necessary.

### ABBREVIATIONS

BW	body weight
CAS	Chemical Abstracts Service
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids

<sup>11</sup>The description of the study is available in the JECFA WHO FOOD ADDITIVES SERIES: 54.

<sup>12</sup>Annex\_II\_8\_13\_010\_SDS\_CONF.pdf.

CG	chemical group
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
FLAVIS	The EU Flavour Information System
NOAEL	no observed adverse effect level

## CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact [interestmanagement@efsa.europa.eu](mailto:interestmanagement@efsa.europa.eu).

## REQUESTOR

European Commission

## QUESTION NUMBER

EFSA-Q-2023-00688

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