SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 29 September 2021

doi: 10.2903/j.efsa.2021.6904

# Safety of a feed additive consisting of a dried aqueous ethanol extract from the leaves of *Melissa officinalis* L. for all animal species (Nor-Feed SAS)

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## Abstract

The additive under assessment is a dried aqueous ethanol extract of *Melissa officinalis* L. leaves, intended to be used as a sensory additive (flavouring compound) in feed for all animal species. The aqueous ethanol extract is specified to contain ≥ 10% of hydroxycinnamic acid derivatives including ≥ 3% of rosmarinic acid. In a previous assessment, considering the contradictory data from the Ames tests and uncertainty about the qualitative and quantitative presence of flavonoids and other compounds in the extract from *M. officinalis* L. leaves, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) could not conclude on the safety of the additive at the proposed use levels of up to 100 mg/kg complete feed for the target species, the consumer and the user. The new data submitted identified luteolin 3′-glucuronide as the only flavonoid present in the additive, improved the characterisation of the hydroxycinnamates present and demonstrated that the additive is not genotoxic. The FEEDAP Panel concludes that the additive under assessment is safe up to the maximum proposed use level of 100 mg/kg complete feed for all animal species. The use in water for drinking is safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed. No safety concern would arise for the consumer from the use of the additive up to the highest safe level in animal nutrition. The exposure of users to dusts from the additive is not of concern. No data are provided on irritant properties for eyes or skin, thus no conclusion can be drawn on these aspects. Due to the nature of the additive, it may be assumed to be potentially both a skin and respiratory sensitiser.



**Keywords:** sensory additives, flavouring compounds, *Melissa officinalis* L., Melissa extract, hydroxycinnamic acids, rosmarinic acid, safety

**Requestor:** European Commission

**Question number:** EFSA-Q-2021-00175

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**Declarations of interest:** The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch.

**Acknowledgements:** The Panel wishes to thank the following for the support provided to this scientific output Montserrat Anguita and Jaume Galobart.

**Suggested citation:** EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis V, Azimonti G, Bastos ML, Christensen H, Fašmon Durjava M, Kouba 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, Westendorf J, Manini P, Pizzo F and Dusemund B, 2021. Scientific Opinion on the safety of a feed additive consisting of a dried aqueous ethanol extract from the leaves of *Melissa officinalis* L. for all animal species (Nor-Feed SAS). EFSA Journal 2021;19(10):6904, 10 pp. https://doi.org/10.2903/j.efsa.2021.6904

**ISSN:** 1831-4732



The EFSA Journal is a publication of the European Food Safety Authority, a European agency funded by the European Union.

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# 1. Introduction

## 1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition and, in particular, Article 9 defined the term of the authorisation by the Commission.

The Commission received an application from Nor-Feed SAS[2] for the authorisation and the re-evaluation of the product *Melissa officinalis* L. dry extract (Nor-Feed SAS) when used as a feed additive for all animal species (category: sensory additives; functional group: flavourings compounds, Table 1).

**Table 1:** Description of the substance

| **Category of additive** | **Sensory additives** |
|---|---|
| **Functional group of additive** | Flavourings |
| **Description** | *Melissa officinalis* L. dry extract |
| **Target animal category** | All animal species |
| **Applicant** | Nor-Feed SAS |
| **Type of request** | New opinion |

On 28 January 2020, the Panel on Additives and Products or Substances used in Animal Feed of the European Food Safety Authority ("Authority"), in its opinion on the safety and efficacy of the product could not conclude on the safety of the product for the following reasons:

> Toxicity and genotoxicity data of the identified components of the extract do not raise concerns. However, the analysis of the extract is incomplete. In the absence of adequate data on the composition and in view of the incomplete genotoxicity testing, the FEEDAP Panel is unable to conclude on the safety of the additive for the target species and the consumer.
>
> The data on the dusting potential indicate that there is a potential for user exposure by inhalation. In the absence of specific studies, the FEEDAP Panel could not conclude on the safety for the user.

The Commission gave the possibility to the applicant to submit complementary information and data in order to complete the assessment and to allow a revision of Authority's opinion. The new data have been received on 25 February 2021.

In view of the above, the Commission asks the Authority to deliver a new opinion on the safety of *Melissa officinalis* L. dry extract as a feed additive for all animal species based on the additional data submitted by the applicant.

## 1.2. Additional information

The subject of the assessment is a feed additive consisting of a dried aqueous ethanol extract of *Melissa officinalis* L. leaves, intended for use as a sensory additive (flavouring compound) for all animal species.

The FEEDAP Panel issued an opinion on the safety and efficacy of a dried aqueous ethanol extract of *Melissa officinalis* L. leaves when used as a sensory additive in feed and water for drinking for all animal species (EFSA FEEDAP Panel, 2020). Since there was uncertainty about the qualitative and quantitative presence of flavonoids and other compounds in the extract from *M. officinalis* L. leaves and considering the incomplete dataset on genotoxicity testing, the Panel could not conclude on the safety of the additive for the target species and the consumer. In the absence of specific studies, the FEEDAP Panel could not conclude on the safety of the additive for the user.

The additive under assessment, *M. officinalis* L. dry extract, is currently authorised as feed additive according to the entry in the European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003 (2b natural products – botanically defined).

[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] Nor-Feed SAS, 3 Rue Amedeo Avogadro, 49070 Beaucouzé, France.

# 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[3] in support to a previous application on the same product.[4]

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment regarding the methods used for the control of the *M. officinalis* dry extract in animal feed are valid and applicable for the current application.[5]

## 2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of *M. officinalis* dry extract is in line with the principles laid down in Regulation (EC) No 429/2008[6] and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012), 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) and Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017c).

# 3. Assessment

The additive under assessment, *Melissa officinalis* extract, is a dried aqueous ethanol extract of the dried leaves of *Melissa officinalis* L. (originating from France).[7] It is specified to contain ≥ 10% of hydroxycinnamic acid derivatives including ≥ 3% of rosmarinic acid.

The additive is intended to be used as a sensory additive (functional group: flavouring compounds) in feed for all animal species up to a maximum level of 100 mg/kg complete feed (corresponding to up to 6 mg rosmarinic acid/kg complete feed) or 100 mg/kg water for drinking.

In the previous opinion (EFSA FEEDAP Panel, 2020), owing to the uncertainty about the qualitative and quantitative presence of flavonoids and other compounds in the extract from *M. officinalis* L. leaves and considering the incomplete data set on genotoxicity testing, the Panel could not conclude on the safety of the additive for the target species and for the consumer. In the absence of specific studies, the FEEDAP Panel could not conclude on the safety of the additive for the user.

The applicant has now provided new data to address the issues previously identified regarding the characterisation of the additive, to allow an assessment of the genotoxicity of the additive and to evaluate the exposure of users to dust.

## 3.1. Characterisation

### 3.1.1. Characterisation of *Melissa officinalis* extract

The additive was previously shown to contain a dry matter content of about 96% and 4% of water (EFSA FEEDAP Panel, 2020). The identified constituents of the dry matter fraction were ash (13.2%) and total phenolic compounds (14% described in the dossier as 'total hydroxycinnamic derivatives'). Total phenolic compounds were analysed by the Arnow assay, a colourimetric assay, and calculated as rosmarinic acid equivalents (RAE). A rosmarinic acid content of 5.4% was separately determined by high-performance liquid chromatography (HPLC) with ultraviolet detection using an external standard. Some minor amounts of other hydroxycinnamic acids (ferulic acid, chlorogenic acid, caffeic acid, *p*-coumaric acid) were also identified in the chromatogram (one batch); however, the quantification was done by estimating the relative peak area without using a standard, leading only to semiquantitative results. Approximately 60% of the fraction determined by the colourimetric method

[3] FEED dossier reference: FAD-2021-0019.
[4] FEED dossier reference: FAD-2010-0251.
[5] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0251.pdf
[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] At the time of application, the applicant stated that they sourced the raw material (more than 50%) from the Anjou region, France (variety used: Melia 3, more than 50%).

was unidentified, and the literature search provided by the applicant on the composition of *M. officinalis* extracts from leaves suggested the presence of flavonoids (luteolin, quercetin, etc.) in the extract. The FEEDAP Panel concluded that the qualitative and quantitative presence of flavonoids in the fraction 'phenolic compounds' of the additive under assessment was unknown.

The applicant has further investigated the presence of flavonoids in the extract under assessment. The analysis was done by HPLC with diode array detection (DAD). The analysis showed that the only flavonoid determined in the additive was luteolin-3′-glucuronide in a concentration of 1.43 mg/kg additive and that hesperidin, naringenin, eriocitrin, apigenin, luteolin, rutin, quercetin and kaempferol were not present.[8]

The applicant provided literature data[9] about the quantification of hydroxycinnamic acids in *M. officinalis* extract by HPLC with DAD (Belščak-Cvitanović et al., 2017) and compared these to the results of the Arnow assay. The results show that the values determined by the Arnow assay were more than two times higher compared to the HPLC method. Similar results were obtained by investigations of Carocho et al. (2015) and Arceusz et al. (2015). These data also confirmed that rosmarinic acid is by far the most abundant phenolic compound in *M. officinalis* extracts, comprising about half of the total fraction of phenolic compounds. Other identified compounds reported in the literature were i.e. caffeic acid, caffeic acid oligomers, chlorogenic acid, ferulic acid, coumaric acids, syringic acid, lithospermic acid, salvianolic acid, caftaric acid and gallic acid. The FEEDAP Panel considers that the uncertainty about the qualitative and quantitative presence of flavonoids and other compounds in the extract have been addressed and that the additive is sufficiently characterised.

Based on the literature data, the total concentration of phenolic compounds in the additive is estimated by multiplication of the value of rosmarinic acid (5.4%) with a factor of two, resulting in a total phenolic content of 11% (110,000 mg/kg).

## 3.2. Safety

In the previous opinion (EFSA FEEDAP Panel, 2020), the FEEDAP Panel concluded that contradictory results were obtained in the genotoxicity testing in bacteria for induction of gene mutations. The FEEDAP Panel also noted that data submitted did not fulfil the requirements for *in vitro* genotoxicity testing in mammalian cells (EFSA Scientific Committee, 2011). Consequently, the FEEDAP Panel could not conclude on the genotoxicity of the additive under assessment and consequently on the safety of the additive for the target species and the consumer.

The data on the dusting potential indicate that there is a potential for user exposure by inhalation. In the absence of specific studies, the FEEDAP Panel could not conclude on the safety of the additive for the user.

### 3.2.1. Genotoxicity

The applicant submitted two *in vitro* genotoxicity studies.

#### 3.2.1.1. Bacterial reverse mutation test

In order to investigate the potential of the additive to induce gene mutations in bacteria, an Ames test was performed according to the Organisation for Economic Co-operation and Development (OECD) Testing Guideline (TG) 471, Good Laboratory Practice (GLP) compliant.[10] The test was performed using the *Salmonella* Typhimurium strains [redacted] in the presence and absence of metabolic activation (S9 mix). [redacted] A preliminary toxicity test showed that [redacted] caused inhibition of bacterial growth. Two independent mutagenicity tests were performed at concentrations between [redacted]. The number of revertant colonies did not exceed the background at any test concentration. Negative and positive controls were in the expected range.

The FEEDAP Panel concludes that the test item did not induce gene mutations in bacteria under the experimental conditions employed in this study.

[8] Technical dossier/Complementary information Melissa officinalis.
[9] Technical dossier/Complementary information 280521.
[redacted]

#### 3.2.1.2. *In vitro* mammalian cell micronucleus test

A GLP-compliant *in vitro* micronucleus test to investigate the induction of chromosomal damage by the additive was performed in [redacted], following the OECD TG 487.[11] The test item was dissolved in water. Appropriate positive and negative control chemicals were used, and the results obtained confirmed that the experimental system was sensitive and valid. The test consisted of a 3-h treatment period with and without metabolic activation (S9 mix) and a 24-h treatment period without metabolic activation. Cytotoxicity was observed [redacted]. Based on this finding, concentrations of [redacted]. No statistically significant or biologically relevant increases of micronuclei were observed in any of the tests performed.

The FEEDAP Panel concludes that the additive under assessment did not induce structural or numerical chromosome aberrations *in vitro* in mammalian cells under the experimental conditions employed in this study.

The negative results obtained by the bacterial mutagenicity test and micronucleus test in mammalian cells *in vitro* are sufficient to exclude the concern for a genotoxicity potential of the additive.

### 3.2.2. Safety for the target species

In the previous opinion, the Panel concluded that, although the identified components did not raise concern for target species, the analysis of the extract was incomplete. The FEEDAP Panel noted that there was a significant unknown fraction which probably contained flavonoids, and which prevented the Panel from reaching a final conclusion on the safety for target species (EFSA FEEDAP Panel, 2020).

The new data submitted establishes that the presence of flavonoids in the additive is limited to minor levels of luteolin-3′-glucuronide, which are not associated with concern in view of the wide distribution of luteolin glycosides in the plant kingdom. Therefore, it is assumed that the compounds determined by colourimetric detection effectively belong to the class of hydroxycinnamic acids.

In the absence of specific data on the compounds present in the additive (e.g. Arceusz et al., 2015; Carocho et al., 2015; Belščak-Cvitanović et al., 2017), the safety is assessed on the basis of structural and toxicological similarity with rosmarinic acid. Thus, the no observed adverse effect level (NOAEL) of 300 mg/kg body weight (bw) per day for rosmarinic acid derived from the 90-day study in rats (Lasrado et al. 2015, as described in EFSA FEEDAP Panel, 2020) is selected as a group NOAEL for the fraction of hydroxycinnamic acids.

Applying an uncertainty factor (UF) of 100 to the NOAEL for hydroxycinnamic acids, the safe daily dose for the target species was derived following the EFSA Guidance on the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), and thus the maximum safe feed concentration of hydroxycinnamic acids was calculated (Table 2). Since glucuronidation of the hydroxylated or oxygenated metabolites of rosmarinic acid and hydroxycinnamic acids is an important metabolic pathway facilitating the excretion of these compounds, the calculation of safe concentrations in cat feed needs an additional UF of 5. This factor is due to the unusually low capacity for glucuronidation in cats (Court and Greenblatt, 1997; Lautz et al., 2021).

**Table 2:** Maximum safe concentration in feed of hydroxycinnamic acids for the different target animal categories

| Animal category | Default values | | Maximum safe intake/concentration | |
|---|---|---|---|---|
| | Body weight (kg) | Feed intake (g DM/day) | Intake (mg/day) | Concentration in feed (mg/kg feed)(1) |
| Chicken for fattening | 2 | 158 | 6 | 33 |
| Laying hen | 2 | 106 | 6 | 50 |
| Turkey for fattening | 3 | 176 | 9 | 45 |
| Piglet | 20 | 880 | 60 | 60 |
| Pig for fattening | 60 | 2,200 | 180 | 72 |

[redacted]

| Animal category | Default values | | Maximum safe intake/concentration | |
|---|---|---|---|---|
| | Body weight (kg) | Feed intake (g DM/day) | Intake (mg/day) | Concentration in feed (mg/kg feed)(1) |
| Sow lactating | 175 | 5,280 | 525 | 94 |
| Veal calf (milk replacer) | 100 | 1,890 | 300 | 150 |
| Cattle for fattening | 400 | 8,000 | 1,200 | 132 |
| Dairy cow | 650 | 20,000 | 1,950 | 86 |
| Sheep/goat | 60 | 1,200 | 180 | 132 |
| Horse | 400 | 8,000 | 1,200 | 132 |
| Rabbit | 2 | 100 | 6 | 53 |
| Salmon | 0.12 | 2.1 | 0.4 | 151 |
| Dog | 15 | 250 | 45 | 158 |
| Cat(2) | 3 | 60 | 0.18 | 29 |
| Ornamental fish | 0.012 | 0.054 | 0.04 | 587 |

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.

At the maximum proposed use level for the additive of 100 mg/kg complete feed, the concentration of hydroxycinnamic acids is estimated to be ~ 11 mg/kg complete feed. This concentration is below the maximum safe concentration of hydroxycinnamic acids calculated for the different animal categories (Table 2) and therefore the FEEDAP Panel concludes that the additive is considered safe for all animal species at the maximum proposed use level of 100 mg/kg complete feed with an additional margin of safety of at least 2.6 (in cat) and up to 53 (in ornamental fish). This would account for the uncertainty in the read-across and for the presence of unidentified compounds in the phenolic fraction.

The FEEDAP Panel considers that the use in water for drinking is safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed (EFSA FEEDAP Panel, 2010).

### 3.2.3. Safety for the consumer

In the previous opinion, the FEEDAP Panel concluded that the use of the additive in animal feed would not appreciably increase the existing human exposure to the constituents of the additive. However, in the absence of adequate data on the genotoxicity, the FEEDAP Panel could not conclude on the safety of the use of the additive in animal feed for the consumer.

Since the new data indicated that there is no concern for genotoxicity, the FEEDAP Panel concludes that no safety concern would be expected for the consumer from the use of the additive up to the maximum proposed use level in animal feed.

### 3.2.4. Safety for the user

In the original application dossier, no specific information other than dusting potential were provided by the applicant regarding the safety of the additive for users. In the absence of such data, the FEEDAP Panel could not conclude on the safety for the users when handling the additive (EFSA FEEDAP Panel, 2020).

In the current application dossier, the applicant has provided particle size analysis of one batch of the additive, which showed the fractions of particles below 10, 25 and 100 μm amounted, respectively, to about 3%, 12% and 83% (v/v).[12] The applicant provided calculations of exposure by inhalation in a premixture factory, according to the Guidance on studies concerning the safety of the use for users/ workers (EFSA FEEDAP Panel, 2012).

Assuming that 1% of premixtures contain the additive and that the concentration of the active substance in the dust is the same as in the additive (11% for hydroxycinnamic acids including 5.4% for rosmarinic acid), and considering a dusting potential of 1.5 g/m$^3$, the inhalation exposure of workers/users was calculated to be 0.91 mg/day for hydroxycinnamic acids and 0.47 mg/day for rosmarinic acid.

[12] Technical dossier/Annex_9_Laser granulometry.

The additive is completely soluble in water and it is therefore expected that the inhaled dust will be dissolved by the fluid of the respiration tract and the constituents will be absorbed. This would result in a maximum systemic exposure of 0.90 mg/day or 15 μg/kg bw per day for hydroxycinnamic acids and of 0.47 mg/day or 7.8 μg/kg bw per day for rosmarinic acid (assuming a bw of 60 kg). This would not be of concern as it would be sufficiently below the level of 3 mg/kg bw calculated from the NOAEL of 300 mg/kg bw per day for rosmarinic acid referenced earlier in this opinion (Section 3.2.2).

In the current application dossier, no new data have been provided on the effects of the additive on eyes or skin.

In the absence of such data, no conclusion can be drawn on the irritant properties of the additive for eyes or skin. Due to the nature of the additive, it may be assumed to be potentially both a skin and respiratory sensitiser.[13]

**Conclusions on the safety for the user**

The exposure to dusts from the additive is not of concern. No data are provided on irritant properties for eyes or skin, thus no conclusion can be drawn on these aspects. Due to the nature of the additive, it may be assumed to be potentially both a skin and respiratory sensitiser.

## 4. Conclusions

The new data submitted identified luteolin 3′-glucuronide as the only flavonoid determined in the additive and allowed to improve the characterisation of the hydroxycinnamates fraction. The FEEDAP Panel considers that the additive is sufficiently characterised. The new data submitted demonstrated that the additive is not genotoxic.

The additive under assessment is safe up to the maximum proposed use level of 100 mg/kg complete feed for all animal species. The use in water for drinking is safe provided that the total daily intake of the additive does not exceed the daily amount that is considered safe when consumed via feed.

No safety concern would arise for the consumer from the use of the additive up to the maximum proposed use level in animal feed.

The exposure of users to dusts from the additive is not of concern. No data are provided on irritant properties for eyes or skin, thus no conclusion can be drawn on these aspects. Due to the nature of the additive, it may be assumed to be potentially both a skin and respiratory sensitiser.

## 5. Documentation provided to EFSA/Chronology

| Date | Event |
|---|---|
| **25/02/2021** | Dossier received by EFSA. *Melissa officinalis* dry extract (Nor-Balm®) for all animal species and categories. Submitted by Nor-Feed SAS |
| **23/03/2021** | Reception mandate from the European Commission |
| **12/04/2021** | Application validated by EFSA – Start of the scientific assessment |
| **28/05/2021** | Spontaneous submission of information by the applicant. *Issues: characterisation* |
| **29/09/2021** | Opinion adopted by the FEEDAP Panel. End of the Scientific assessment |

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[13] According to the classification provided by companies to ECHA in CLP notifications *Melissa officinalis*, ext. causes serious eye damage, skin irritation and may cause allergic skin reactions. https://echa.europa.eu/it/substance-information/-/substanceinfo/100.074.528

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## Abbreviations

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| bw | body weight |
| CAS | Chemical Abstracts Service |
| DAD | diode array detection |
| DM | dry matter |
| EURL | European Union Reference Laboratory |
| FEEDAP | EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed |
| GLP | Good Laboratory Practice |
| HPLC | high-performance liquid chromatography |
| NOAEL | no observed adverse effect level |
| OECD | Organisation for Economic Co-operation and Development |
| RAE | rosmarinic acid equivalent |
| UF | uncertainty factor |
| UV | ultraviolet |