SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 17 March 2021

doi: 10.2903/j.efsa.2021.6526

Safety and efficacy of a feed additive consisting of a dried extract from the roots of *Panax ginseng* C.A. Meyer (*P. ginseng* dry extract) for use in cats and dogs (C.I.A.M.)

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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 a dried extract prepared from the roots of *Panax ginseng* C.A. Meyer (*P. ginseng* dry extract) when used as a sensory additive in feed for cats and dogs. *P. ginseng* dry extract is specified to contain at least 27–30% total ginsenosides (as ginsenosides RG1). Since uncertainty remains concerning the nature of up to 73% of the extract, the FEEDAP Panel was unable to conclude on the safety of the additive at the proposed use levels of up to 20 mg/kg complete feed for cats and dogs. In the absence of data, no conclusions can be drawn on the safety for the user. Since ginseng and its extracts are recognised to flavour food and their function in feed would be essentially the same as that in food, no further demonstration of efficacy is considered necessary.

Keywords: sensory additives, *Panax ginseng* C.A. Meyer, *Panax ginseng* dry extract, ginsenosides, safety, efficacy

Requestor: European Commission

Question number: EFSA-Q-2018-00320

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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 acknowledge the contribution of Jaume Galobart and Joana Revez to this opinion.

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, Dusemund B, 2021. Safety and efficacy of a feed additive consisting of a dried extract from the roots of *Panax ginseng* C.A. Meyer (*P. ginseng* dry extract) for use in cats and dogs (C.I.A.M.). EFSA Journal 2021;19(4):6526, 9 pp. https://doi.org/10.2903/j.efsa.2021.6526

ISSN: 1831-4732

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

Table of contents

Abstract 1
1. Introduction 4
1.1. Background and Terms of Reference 4
1.2. Additional information 4
2. Data and methodologies 4
2.1. Data 4
2.2. Methodologies 5
3. Assessment 5
3.1. Origin and extraction 5
3.2. Characterisation 5
3.2.1. Characterisation of the extract 5
3.2.2. Stability 6
3.2.3. Conditions of use 6
3.3. Safety for the target species and the user 6
3.4. Efficacy 7
4. Conclusions 7
5. Documentation as provided to EFSA/Chronology 7
References 7
Abbreviations 8
Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis of total ginsenosides in *Panax ginseng* C.A. Mey (Ginseng extract CoE 318) 9

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 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 seven years after the entry into force of this Regulation.

The European Commission received a request from C.I.A.M. S.r.l.[2] for re-evaluation of the product *Panax ginseng* C.A. Meyer (Ginseng extract CoE 318), 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 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 22 May 2018.

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 and the user, and on the efficacy of the product *P. ginseng* dry extract, when used under the proposed conditions of use (see Section 3.2.3).

1.2. Additional information

P. ginseng C.A. Meyer (Ginseng extract CoE 318) is currently listed in the European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003 (2b natural products – botanically defined). It has not been previously assessed by EFSA as a feed additive.

Ginseng is listed by the Council of Europe (CoE) as a natural source of food flavouring (CoE 318).

Ginseng and its standardised extracts and preparations are listed as active medicinal ingredients for all food-producing animal species without a maximum residue limit (MRL).[3] In 2006, the European Medicines Agency (EMEA) committee for medicinal products for veterinary use issued a report on ginseng (EMEA, 2006).

P. ginseng extract from the roots of the ginseng is listed in the European list of Cosmetics and Ingredients and Substances as tonic, hair skin conditioning, emollient and skin protecting agent.[4]

For human traditional medicinal uses, the European Medicines Agency (EMA) issued an assessment report and a herbal monograph on *P. ginseng* C.A. Meyer, radix (EMA, 2014a,b).

Ginseng (*Ginseng radix*) is described in a monograph of the European Pharmacopoeia (PhEur, 2020, 7/2019:1523).[5] Whole or cut dried root of *P. ginseng* C.A. Meyer is designated white ginseng, whereas treated with steam and then dried is designated red ginseng. Furthermore, a Ginseng dry extract (*Ginseng extractum siccum*) is described in the European Pharmacopoeia (PhEur, 2020, 1/2013:2356).

Radix Ginseng (*P. ginseng* C.A. Meyer) is described in a WHO monograph (WHO, 1999).[6]

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 re-evaluation of *P. ginseng* dry extract as a feed additive.

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) used the data provided by the applicant together with data from other sources, such as previous risk

[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] C.I.A.M. S.r.l., via Piemonte 4, 63100 Ascoli Piceno (AP), Italy.
[3] Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. OJ L 15/1, 20.1.2010, p. 15.
[4] Commission Decision 2006/257/EC of 9 February 2006 amending Decision 96/335/EC establishing an inventory and a common nomenclature of ingredients employed in cosmetic products, OJ L 97, 5.4.2006, p. 1–528.
[5] Technical dossier/Section II/Ref_II_1_02.
[6] Technical dossier/Section II/Ref_II_1_04.
[7] FEED dossier reference: FAD-2010-0308.

assessments by EFSA or other expert bodies, peer-reviewed scientific papers, other scientific reports 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 additive's phytochemical markers 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 *P. ginseng* dry extract, is in line with the principles laid down in Regulation (EC) No 429/2008[9] 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) and Guidance on the assessment of additives intended to be used in pets and other non-food-producing animals (EFSA FEEDAP Panel, 2011).

3. Assessment

The additive under assessment, *P. ginseng* dry extract, is prepared from the roots of *P. ginseng* C.A. Meyer and is intended for use as a sensory additive (functional group: flavouring compounds) in feed for cats and dogs.

3.1. Origin and extraction

P. ginseng C.A. Meyer (ginseng) is a perennial herb, belonging to the family of Araliaceae and is native to the mountain regions of East Asia. It is cultivated for medicinal purposes in Russia, Japan, China and Korea where its roots and their extracts have a long history as an herbal remedy. White ginseng is the roots after peeling and drying, while red ginseng refers to the unpeeled steam-treated roots.

P. ginseng extract is prepared from roots by exhaustive extraction with ethanol at 60°C in a multi-stage process. The extract is then separated from the insoluble plant biomass and concentrated by evaporation. The concentrated extract is homogenised, pasteurised and dried. Maltodextrin is added to the dried extract as carrier and the mix is ground, sieved and packed for distribution.

3.2. Characterisation

3.2.1. Characterisation of the extract

P. ginseng dry extract is identified by the CoE number 318, the Chemical Abstract Service (CAS) number 84650-12-4 and the European Inventory of Existing Commercial chemical Substances (EINECS) number 283-493-7. The additive is described as a yellow brown fine powder, with a characteristic odour. It has a density of 450–650 kg/m^3. The additive is partially soluble in water and organic solvents.

According to the specification proposed by the applicant, *P. ginseng* dry extract contains 27–30% total ginsenosides (expressed as ginsenosides RG1, selected as the marker compounds). Loss on drying is specified to be ≤ 5%, and ash ≤ 5%. Data were provided for five batches of the *P. ginseng* dry extract, which showed an average content of ginsenosides (as ginsenosides RG1) of 28.3% (range 27.2–29.7%).[10] However, certificates of analysis were not provided.

The applicant did not provide the full characterisation of the additive, despite being requested. Although the additive contains maltodextrin, the amount added is unknown and, as a result, uncertainty remains concerning the nature of up to 73% of the extract.

The applicant provided a commercial information sheet for five batches of the *P. ginseng* dry extract,[11] which includes the limits applied for chemical impurities and microbiological contamination. Specifications for chemical impurities include heavy metals (lead ≤ 3.0 mg/kg, cadmium ≤ 1.0 mg/kg

[8] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/finrep-fad-2010-0308-panax_ginseng.pdf

[9] 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.

[10] Technical dossier/Section II/Annex II_1_02_ Analysis batches.

[11] Technical dossier/Section II/Annex II_1_01_Data_sheet_Ginseng extract.

and mercury ≤ 0.1 mg /kg), mycotoxins (aflatoxin B1 ≤ 5.0 μg/kg, aflatoxins B1, B2, G1 and G2 ≤ 10.0 μg/kg), residual solvents (ethanol ≤ 0.5%, below the thresholds proposed by International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (EMA, 2010)) and pesticide residues (which are declared to comply with the maximum limits of Regulation (EU) No 396/2005[12]). Specifications for microbial contamination include aerobic bacteria ≤ 50,000 colony forming unit (CFU)/g, fungi (yeast/moulds) ≤ 500 CFU/g, bile-tolerant Gram-negative bacteria ≤ 100 CFU/g, *Salmonella* spp. absent in 25 g, *Escherichia coli* absent in 1 g. However, analytical data supported by certificates of analysis were not provided. The FEEDAP Panel notes that the specification for aerobic bacteria is very high.

Particle size analysis (by sieving) of the additive showed that 90% of particles passed a 300 μm sieve. The fraction of particles < 50 μm was 73% in one batch and fraction of particles < 75 μm was 65 and 76% in two additional batches of *P. ginseng* dry extract. No data were provided on the dusting potential of the additive.

3.2.2. Stability

The applicant stated that the typical shelf-life of *P. ginseng* dry extract is at least three years when stored in closed containers protected from heat, light and humidity.[13] Stability studies provided showed that the content of total ginsenosides (the marker compound) was on average 90% of the initial content in two batches of *P. ginseng* dry extract after 3-year storage (storage conditions not reported).[14]

Stability in feedingstuffs of *P. ginseng* dry extract was tested in cat feed at 25°C.[15] After 18-month storage, 89.3% of the initial content of total ginsenosides was present in feed. When the stability in cat feed was tested at different temperatures, the total ginsenosides content was 93, 87, 87 and 74% of the initial content after 59-day storage at 25, 45, 60 and 80°C, respectively.

3.2.3. Conditions of use

P. ginseng dry extract is intended for use in feedingstuffs, premixtures and complementary feed for cats and dogs, up to the maximum use level of 20 mg/kg complete feed.

3.3. Safety for the target species and the user

Tolerance studies and/or toxicological studies made with the additive under application were not submitted. In addition, the additive was not sufficiently characterised to allow an assessment based on the individual components.

No specific studies were provided on absorption, distribution, metabolism and excretion with the extract under assessment or with the individual constituents.

The applicant makes reference to the EMEA assessment of 'ginseng' for veterinary medical use (EMEA, 2006). The administration of a 'standardised ginseng extract' (no specification given) for 90-day up to 15 mg/kg body weight (bw) per day did not induce toxic effects in Beagle dogs. No effects in reproductive parameters were observed in rats administered 'a standardised ginseng extract' (no specification given) up to 10 mg/kg bw per day in a 33-week two-generation study.

Since uncertainty remains concerning the nature of up to 73% of the extract and in the absence of adequate toxicological data, the FEEDAP Panel cannot conclude on the safety of the additive for cats and dogs.

No specific data were provided by the applicant regarding the safety of the additive for the user and, consequently, no conclusions can be drawn on the additive's potential to be dermal/eye irritant or skin sensitiser. The additive contains about 70% of the particles < 50 μm. In the absence of data on their dusting potential it is not possible to estimate exposure of users to dust.

In the absence of adequate data, the FEEDAP Panel cannot conclude on the safety of the additive under assessment for the target animals or the users.

[12] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EECText with EEA relevance. OJ L 70, 16.3.2005, p. 1–16.
[13] Technical dossier/Section II/Annex II_4_01_Stability statement of supplier.
[14] Technical dossier/Section II/Annex II_4_02_Stability shelf life.
[15] Technical dossier/Section II/Annex II_4_03_Stability feedingstuff.

3.4. Efficacy

Ginseng is listed in Fenaroli's Handbook of Flavour Ingredients (Burdock, 2010) and is recognised by the Flavour and Extract Manufactures Association (FEMA) to have an earthy flavour, however is without a FEMA number. Ginseng is listed by the Council of Europe as natural source of food flavouring (CoE 318).

Since ginseng and its extracts are recognised to flavour food and their function in feed would be essentially the same as that in food, no further demonstration of efficacy is considered necessary.

4. Conclusions

Since uncertainty remains concerning the nature of up to 73% of the extract, the FEEDAP Panel cannot conclude on the safety of the dry extract derived from the roots of *P. ginseng* at the proposed use levels of up to 20 mg/kg complete feed for cats and dogs.

In the absence of data, no conclusions can be drawn on the safety for the user.

Since ginseng and its extracts are recognised to flavour food and their function in feed would be essentially the same as that in food, no further demonstration of efficacy is considered necessary.

5. Documentation as provided to EFSA/Chronology

Date	Event
05/11/2010	Dossier received by EFSA. *Panax ginseng* C.A. Meyer (Ginseng extract CoE 318) for cats and dogs. Submitted by C.I.A.M. S.r.l.
24/04/2018	Reception mandate from the European Commission
22/05/2018	Application validated by EFSA – Start of the scientific assessment
22/06/2018	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 the target species, safety for the user, efficacy*
23/08/2018	Comments received from Member States
11/10/2019	The applicant informed the European Commission on the impossibility to provide the information requested in line with Article 8(1)(2) of Regulation (EC) No 1831/2003
19/01/2021	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives - Scientific assessment re-started
17/03/2021	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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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. https://doi.org/10.2903/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

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WHO (World Health Organization), 1999. Radix ginseng. WHO monographs on selected medicinal plants. Vol 1 ISBN 92-4-154517-8, pp. 168–182.

Abbreviations

bw	body weight
CAS	Chemical Abstracts Service
CFU	colony forming unit
CoE	Council of Europe
EINECS	European Inventory of Existing Commercial chemical Substances
EMA	European Medicines Agency
EURL	European Union Reference Laboratory
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
FEMA	Flavour and Extract Manufactures Association
MRL	maximum residue limit
WHO	World Health Organization

Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis of total ginsenosides in *Panax ginseng* C.A. Mey (Ginseng extract CoE 318)

In the current application an authorisation is sought under Article 10(2) for the botanically defined *Panax ginseng C.A. Mey. (Ginseng extract CoE 318)* under the category/functional group (2 b) "sensory additives"/"flavouring compounds", according to the classification system of Annex I of Regulation (EC) No 1831/2003. Specifically, the *feed additive* is sought to be used for cats and dogs.

The Applicant indicated *total ginsenosides* (expressed as *ginsenoside* Rg1) as phytochemical marker for *Panax ginseng C.A. Mey. (Ginseng extract CoE 318)* specifying a range of its relative mass fraction in the *feed additive* corresponding to 27–30%.

The *feed additive* is intended to be incorporated directly into *feedingstuffs* or through *premixtures*. The Applicant did not propose a minimum or a maximum level of the *feed additive*. However, a maximum content of 20 mg *feed additive* / kg *feedingstuffs* was suggested by the Applicant.

For the determination of the phytochemical marker in the *feed additive* the Applicant submitted a spectrophotometric method described in the journal Deutsche Apotheker-Zeitung, which is equivalent to the procedure described in the "Farmacopea Ufficiale della Repubblica Italiana/Pharmacopoea Italica (X edition)", where the *total ginsenosides* are determined and expressed as *ginsenoside* Rg1.

The EURL recommends for official control the spectrophotometric method proposed by the Applicant for the quantification of *total ginsenosides* (phytochemical marker) in the *feed additive*.

As the unambiguous determination of the *feed additive* added to *premixtures* and *feedingstuffs* is not achievable experimentally, the EURL cannot evaluate or recommend any method for official control for the determination of *Panax ginseng C.A. Mey. (Ginseng extract CoE 318)* in these matrices.

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, as last amended by Regulation (EU) 2015/1761) is not considered necessary.