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SCIENTIFIC OPINION

Safety and efficacy of a feed additive consisting of a tincture derived from the roots of *Panax ginseng* C.A.Mey. (ginseng tincture) for horses, dogs and cats (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** | **Roberto Edoardo Villa** | **Ruud Woutersen** | **Paul Brantom** | **Andrew Chesson** | **Josef Schlatter** | **Johannes Westendorf** | **Yvette Dirven** | **Paola Manini** | **Birgit Dusemund**

Correspondence: feedap@efsa.europa.eu

Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of a tincture from the roots of *Panax ginseng* C.A.Mey. (ginseng tincture), when used as a sensory additive in feed for horses, dogs and cats. The product is a water/ethanol (40:60 v/v) solution, with a dry matter content of no more than 6% and a content of 0.01%–0.5% (w/w) for the sum of the two triterpene saponins ginsenoside Rb1 and ginsenoside Rg1. The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concluded that the tincture is safe for horses, dogs and cats at the maximum proposed use level of 48.6, 228.7 and 162 mg/kg complete feed, respectively. The Panel also concluded that the additive is considered safe for consumers when used at the proposed conditions of use in feed for horses. Ginseng tincture should be considered as an irritant to skin and eyes, and as a dermal and respiratory sensitiser. The use of the ginseng tincture as a flavour in feed for horses was not expected to pose a risk for the environment. Since the roots of *P. ginseng* and its preparations were recognised to flavour food and their function in feed would be essentially the same, no demonstration of efficacy was considered necessary.

KEYWORDS

flavouring compounds, ginseng tincture, ginsenoside Rb1, ginsenoside Rg1, *Panax ginseng* C.A.Mey., safety, sensory additives

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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)[2,3] for authorisation/re-evaluation of 29 additives (namely dill herb oil, dill seed extract, dill tincture, dong quai tincture, celery seed oil, celery seed extract (oleoresin), celery tincture, hares ear tincture, caraway seed oil, caraway oleoresin/extract, coriander oil, cumin oil, taiga root extract (solvent-based, sb), taiga root tincture, fennel oil, fennel tincture, common ivy extract (sb), opoponax oil, ginseng tincture, parsley oil, parsley tincture, anise oil, anise tincture, ajowan oil, *Ferula assa-foetida* oil, anise star oil, anise star tincture, anise star terpenes and omicha tincture) belonging to botanically defined group (BDG) 02 – Apiales/Austrobaileyales when used as feed additives for all animal species (category: sensory additives; functional group: flavourings). During the assessment, the applicant withdrew the application for nine additives.[4] These additives were deleted from the register of feed additives.[5] During the course of the assessment, this application was split and the present opinion covers only one out of the 20 remaining additives under application: a tincture from the roots of *Panax ginseng* C.A.Mey.[6] (ginseng tincture) for all animal species. During the assessment, the applicant requested a change in the species limiting the application for authorisation to horses, cats and dogs.[7]

The remaining 19 additives belonging to botanically defined group (BDG) 02 – Apiales/Austrobaileyales under application are assessed in separate opinions.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 24 June 2019.

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 a tincture from the roots of *P. ginseng* (ginseng tincture), when used under the proposed conditions of use (see Section 3.2.3).

1.2 | Additional information

A tincture from *Panax ginseng* C.A.Mey. (ginseng tincture) is currently authorised as a 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). It has not been assessed as a feed additive in the EU.

'Ginseng (Ginseng radix)' is described in a monograph of the European Pharmacopoeia 11.0 (PhEur, 2022b). It is defined as the whole or cut dried root, designated white ginseng; treated with steam and then dried, designated red ginseng, of *Panax ginseng* C.A.Mey, with a minimum content of 0.40% for the sum of ginsenosides Rg1 and Rb1 (dried drug).

'Ginseng dry extract (Ginseng extractum siccum)' is described in the European Pharmacopoeia 11.0 (PhEur, 2022a) and defined as the dry extract produced from 'Ginseng' with a minimum content of 4.0% of the sum of ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg1 and Rg2, expressed as ginsenoside Rb1 (dried extract).

The European Medicines Agency (EMA) describes an assessment report and a community herbal monograph on 'Panax ginseng C.A. Meyer, radix' for human medicinal use (EMA, 2014a, 2014b). The two documents are currently under revision. The EMEA has also issued summary reports on ginseng for veterinary use in 1999 and 2006 (EMA, 1999, 2006).

[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 the applicant company changed to FEFANA asbl, Avenue Louise 130 A, Box 1, 1050 Brussels, Belgium.

[3]On 27 February 2019, EFSA was informed by the applicant about the transfer of contact point for this application to Manghebati SAS, zone de la Basse Haye – BP 42133 – 35221 Chateaubourg Cedex.

[4]Dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, opoponax oil (27 February 2019); parsley oil, hares ear tincture, taiga root extract (sb), ajowan oil (2 April 2020); celery tincture (9 December 2020).

[5]Register of feed additives, Annex II, withdrawn by OJ L162, 10.05.2021, p. 5.

[6]*Panax ginseng* C.A.Mey.; synonym: *Panax ginseng* C.A. Meyer.

[7]On 25 September 2023, the applicant withdrew the application for certain animal species.

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 ginseng tincture from *P. ginseng* as a feed additive. The dossier was received on 29 January 2024 and the general information and supporting documentation is available at https://open.efsa.europa.eu/questions/EFSA-Q-2024-00055.[9]

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' knowledge, to deliver the present output.

Several of the components of the tincture under assessment have been already evaluated by the FEEDAP Panel as chemically defined flavourings (CDGs). The applicant submitted a written agreement to reuse the data submitted for the assessment of chemically defined flavourings (dossiers, publications and unpublished reports) for the risk assessment of preparations belonging to BDG 02, including the current one under assessment.[10]

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the active substance/agent in animal feed. The evaluation report is related to the methods of analysis for each feed additive included in BDG 02 (Apiales and Austrobaileyales). During the assessment, the EURL issued a partial report[11] and an addendum of the report,[12] which included the additive under assessment, ginseng tincture. In particular, the EURL recommended a high-performance liquid chromatography with ultraviolet detection (HPLC-UV) method based on the European Pharmacopoeia monograph 01/2008:1523 for ginseng radix for the quantification of the phytochemical markers ginsenoside Rb1 and ginsenoside Rg1 in ginseng tincture.[13]

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of ginseng tincture from *P. ginseng* is in line with the principles laid down in Regulation (EC) No 429/2008[14] and the relevant guidance documents: Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA SC, 2009), Guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a), Guidance on 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 consumer (EFSA FEEDAP Panel, 2017c), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018), Guidance on the assessment of the safety of feed additives for the users (EFSA FEEDAP Panel, 2023), Guidance document on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA SC, 2019a), Statement on the genotoxicity assessment of chemical mixtures (EFSA SC, 2019b) and Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (EFSA SC, 2019c).

3 | ASSESSMENT

The additive under assessment, ginseng tincture, is obtained from the roots of *Panax ginseng* C.A.Mey. It is intended for use as a sensory additive (functional group: flavouring compounds) in feed for horses, dogs and cats.

3.1 | Origin and extraction

P. ginseng C.A.Mey. (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. The term 'ginseng' is used to describe the roots and the *plant itself*. White ginseng is the roots after peeling and drying, while red ginseng refers to the unpeeled steam-treated roots.

[8]FEED dossier reference: FAD-2010-0221.

[9]The original application EFSA-Q-2010-01286 was split on 29/01/2024 and a new EFSA-Q-2024-00055 was generated.

[10]Technical dossier/Supplementary information/Letter dated 29/04/2021.

[11]Preparations included in the partial report: dill herb oil, dill tincture, dong quai tincture, cumin oil, fennel tincture, parsley tincture, anise tincture, star anise tincture and ferula assa-foetida oil.

[12]Preparations included in the addendum: celery seed oil, caraway seed oil, coriander oil, taiga root tincture, fennel oil, common ivy extract (sb), ginseng tincture, anise oil, anise star oil, anise star terpenes and omicha tincture.

[13]The full report is available on the EURL website: https://joint-research-centre.ec.europa.eu/publications/fad-2010-0221_en.

[14]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.

The tincture is produced from the roots of *Panax ginseng* C.A.Mey. cleaned by steam treatment. Tincture extraction is achieved by extended extraction for 3 weeks under ambient conditions with a water/ethanol (40:60, v/v) solvent mixture and a plant to solvent ratio of 1:5 (w/v). The tincture is then recovered by pressing to separate solid and liquid phases and the extracted solution is then clarified by filtration.

3.2 | Characterisation

3.2.1 | Characterisation of the tincture

The tincture under assessment has a density of 956–981 kg/m^3 (972 kg/m^3 on average).[15] By specification, the product is a water/ethanol (40/60, v/v) solution, with a dry matter (DM) content of no more than 6% (w/w) and a content of 0.01%–0.5% (w/w) for the sum of the two triterpene saponins ginsenoside Rb1 and ginsenoside Rg1. The analysis of five batches demonstrated compliance with the proposed specification.

Table 1 summarises the results of the proximate analysis of five batches of the additive (of Chinese origin) expressed as % (w/w).[16] The solvent represents on average 95.36% of the additive leaving a DM content of 4.74%.[17] The DM consists of inorganic material measured as ash (5.0%, on average) and a plant-derived organic fraction (70.0% on average), which includes lipids, protein, fibre and sugars.

TABLE 1 Proximate analysis of ginseng tincture derived from the roots of *Panax ginseng* C.A.Mey. based on the analysis of five batches. The results are expressed as % of the tincture (w/w).

Constituent	Method	Mean % (w/w)	Range % (w/w)
Dry matter	Gravimetry	4.74	4.07–5.34
Ash	Gravimetry	0.24	0.1–0.3
Organic fraction			
Lipids	Weibull–Stoldt	0.54	0.5–0.7
Protein	Kjeldahl	0.80	0.6–0.9
Fibre	Gravimetry	< 0.5	< 0.5
Sugars	Luff-Schoorl	1.98	1.4–2.2
Solvent (water/ethanol, 40/60, v/v)	Difference	95.36	94.66–95.83

The fraction of secondary metabolites was characterised in the same batches of the tincture and the results are summarised in Table 2. Phenols were determined by spectrophotometry with the Folin–Ciocalteu reagent and expressed as gallic acid equivalents.[18] Dicarboxylic acids[19] and ginsenosides[20] were determined by HPLC with ultraviolet (UV) detector. In addition, several volatiles including lipophilic compounds were identified and quantified in the tincture by gas chromatography–mass spectrometry (GC–MS),[21] including the polyacetylenes panaxynol (falcarinol) and panaxydol, specific for the roots of *P. ginseng*.

[15]Technical dossier/Supplementary information September 2023/Annex_IV_Ginseng_Gravitational Analysis_Dry Matter_Density.
[16]Technical dossier/Supplementary information September 2023/Annex_II_Ginseng_Nutritional Analysis_Microbiol_Dioxins.
[17]Technical dossier/Supplementary information September 2023/ Annex_IV_Ginseng_Gravitational Analysis_Dry Matter_Density.
[18]Technical dossier/Supplementary information September 2023/Annex_V_Ginseng_Total Phenols.
[19]Technical dossier/Supplementary information September2023/Annex_VI_Ginseng_Organic Acids.
[20]Technical dossier/Supplementary information September 2023/Annex_II_Ginseng_HPLC_Ginsenosides.
[21]Technical dossier/Supplementary information September 2023/Annex_VIII_Panax_GC-MS_lipophilic_compounds.

TABLE 2 Characterisation of the fraction of secondary metabolites of ginseng tincture derived from the roots of *Panax ginseng* C.A.Mey. based on the analysis of five batches (mean and range). The results are expressed as µg/mL of ginseng tincture.

Constituent	CAS no	FLAVIS no	Mean µg/mL	Range µg/mL
Phenols (total, by photometry)	–	–	347	315–375
Ginsenosides (HPLC-UV)				
Ginsenoside Rb1	41753-43-9	–	1600	677–2582
Ginsenoside Rb2	11021-13-9	–	788	217–1158
Ginsenoside Rc	11021-14-0	–	1006	353–1476
Ginsenoside Rd	52705-93-8	–	650	132–1055
Ginsenoside Re	52286-59-6	–	811	328–1210
Ginsenoside Rf	52286-58-5	–	173	105–218
Ginsenoside Rg1	22427-39-0	–	444	376–492
Ginsenoside Rg2	52286-74-5	–	85	30–119
Unknown ginsenoside	–	–	470	270–631
Total ginsenosides			6027	2528–8936[a]
Dicarboxylic acids (HPLC-UV)				
Oxalic acid			1088	906–1525
Malic acid			1175	853–1621
Fumaric acid			27	10–43
Total dicarboxylic acids			2353	1850–3181
Total identified[b]			8728	4693–12,491[a]
Volatiles including lipophilic compounds (GC–MS)				
Spathulenol	6750-60-3	–	14.65	10.73–19.03
α-Himachalene	3853-83-6	–	2.27	1.63–3.39
β-Gurjunene	73464-47-8	–	1.86	0.93–3.92
β-Patchoulene	514-51-2	–	1.68	1.19–2.21
cis-Muurola-4(14),5-diene	157477-72-0	–	0.32	0.29–0.37
Guaia-6,9-diene	–	–	2.17	1.29–2.55
β-Caryophyllene epoxide	1139-30-6	16.043	1.17	0.51–1.69
Humulene oxide II	19888-34-7	–	1.79	0.82–2.95
Ethyl octadeca-9,12-dienoate	544-35-4	09.204	42.69	12.64–131.62
Ethyl hexadecanoate	628-97-7	09.193	22.55	6.25–61.90
Octadeca-9,12-dienoic acid	60-33-3	08.041	78.72	16.14–121.27
Hexanoic acid, 2-hydroxy-1-(hydroxymethyl)- ethyl ester	–	–	3.11	0.68–6.34
2-Monolinolenin	55268-58-1	–	3.09	0.41–9.29
Palmitic acid	57-10-3	08.014	50.82	10.88–88.36
Panaxynol (falcarinol)	21852-80-2	–	46.41	2.74–84.50
Panaxydol	72800-72-7	–	73.73	7.64–135.28
Di-isooctylphthalate	27554-26-3	–	4.86	1.42–7.96
Unknown sesquiterpene	–	–	1.23	0.53–1.71
Unknown sesquiterpene	–	–	2.42	1.28–3.42
Unknown sesquiterpene	–	–	3.79	1.25–6.05
Unknown sesquiterpene	–	–	0.64	0.35–1.09
Unknown fatty acid derivative	–	–	4.86	1.42–7.96
Total volatiles and lipophilic compounds			363.39	225.96–469.64[b]

[a]The values given for total are the lowest and the highest values of the sum of the components in the batches analysed.
[b]Considering the sum of phenols, lignans and dicarboxylic acids.

The tincture was shown to contain phenolic compounds up to 0.039% (w/w)[22] (0.036% on average), accounting for 0.85% of the DM (0.76% on average). As no analytical data were provided on the occurrence of flavonoids in the tincture, it is assumed that the fraction phenolic compounds include flavonoids. Dicarboxylic acids accounted for up to 0.33% (w/w) of the tincture (0.24% on average) corresponding to 6.13% of the DM (5.08% on average). Ginsenosides accounted for up to

[22]For each batch, the values analysed in each individual batch and expressed as µg/mL were converted into g/100 g or % (w/w) considering the value of the density determined for each individual batch. The values expressed as g/100 g are then related to the DM content determined in the corresponding batch. The values reported in the text are the average and the highest value of the range calculated for the five batches.

0.92% (w/w) of the tincture (0.62% on average) corresponding to 17.23% of the DM (12.92% on average). The volatile/lipophilic compounds accounted for up to 0.048% (w/w) of the tincture (0.037% on average), corresponding to 1.04% of the DM (0.78% on average), with the polyacetylenes panaxynol and panaxydol accounting for up to 0.022% (0.012% on average), corresponding to 0.42% of the DM (0.26% on average).

The identified secondary metabolites (9091 µg/mL; range: 4967–12,906 µg/mL) account on average for 19.5% of the DM content of the tincture (range: 11.2%–24.9%).

Ginsenosides are triterpene saponins, with a skeleton of 17 carbons in a four-ring structure, with various sugar moieties (e.g. glucose, rhamnose, xylose, arabinose) attached at C-3 and C-20 positions. Based on the chemical structure, there are two major structural classes of ginsenosides: the 20(S)-protopanaxadiol (PPD) and 20(S)-protopanaxatriol (PPT) derivatives, the latter characterised by the additional hydroxyl group at C-6 of the aglycone. Ginsenosides Rb1, Rb2, Rc and Rd are PPD type, whereas ginsenosides Re, Rf, Rg1 and Rg2 are PPT-type. As an example, the structures of ginsenoside Rb1 and ginsenoside Rg1 as shown in Figure 1.

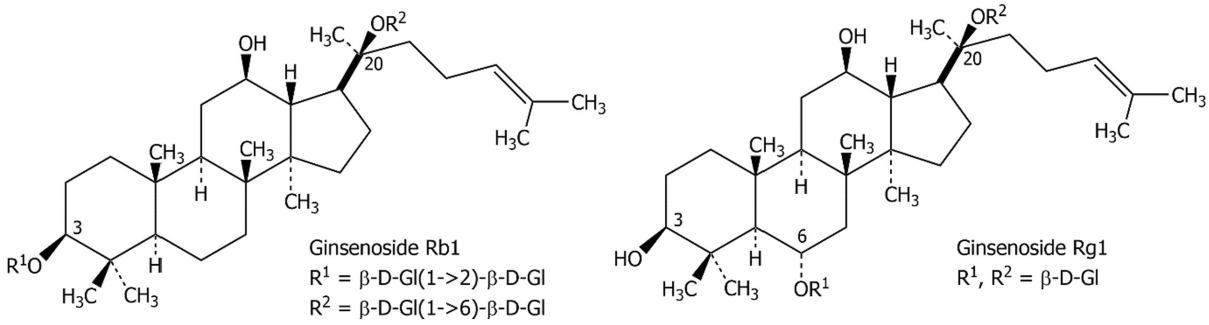

FIGURE 1 Structure of ginsenosides Rb1 and Rg1 as representatives of the two structural classes of 20(S)-protopanaxadiol (PPD) and 20(S)-protopanaxatriol (PPT).

The applicant made a literature search (see Section 3.3) for the chemical composition of *P. ginseng* and its preparations and the identity of any recognised substances of concern.[23] The literature search retrieved 75 publications describing compositional data, none of which reported information on the presence of substances of concern in *P. ginseng* and its preparations.

The FEEDAP Panel notes that in the monographs by EMA (2014a) and the PhEur Commentary (2012) in addition to the components listed in Table 2, the occurrence of polysaccharides/peptidoglycans (panaxans and ginsenans) is described for the root of *Panax ginseng* C.A.Mey.

3.2.1.1 | *Impurities*

Data on impurities were provided for three batches of ginseng tincture.[24] Mercury was below the corresponding limit of quantification (LOQ, 0.002 mg/kg) in the three batches tested. Arsenic was below the corresponding LOQ (0.005 mg/kg) in two batches and was 0.013 mg/kg in one batch. Cadmium was between 0.0007 and 0.0011 mg/kg in three batches. The concentrations of lead ranged between 0.0019 and 0.0042 mg/kg. In the same batches, mycotoxins were below the corresponding LOQ, and pesticides were not detected in a multiresidue analysis, with a few exceptions (diethyltoluamide (DEET) 0.13–0.20 mg/kg and piperonylbutoxide < 0.01 mg/kg). Polychlorinated dibenzo-*p*-dioxins (PCDD), polychlorinated dibenzofurans (PCDF) and dioxin-like polychlorinated biphenyls (DL-PCBs) were analysed in the same batches. The calculated upper bound (UB) concentration was 31.6 ng WHO_{2005}-PCDD/F-TEQ/kg for the sum of PCCD/F, and was in the range between 33.0 and 33.3 ng WHO_{2005}-PCCD/F + PCB TEQ/kg for the sum of PCCD/F and DL-PCBs (expressed as DM).[25]

Analysis of microbial contamination of five batches of ginseng tincture indicated that *Salmonella* spp. was not detected in 25 g of the batches. *Escherichia coli* was detected at < 10 colony forming unit (CFU)/g. Coliform bacteria were not detected.[25]

The FEEDAP Panel considers that the level of microbial contamination and detected impurities do not raise safety concerns.

[23]Technical dossier/Supplementary information September 2023/ Literature_search_ginseng_tincture.

[24]Technical dossier/Supplementary information/September 2023/Annex_VII_Ginseng_Heavy Metals_Mycotoxins_Pesticides. LOQ: < 0.005 mg/kg for arsenic, < 0.002 mg/kg for mercury and < 0.0004 mg/kg for cadmium; LOQs for individual pesticides: 0.01–0.1 mg/kg; LOQs for mycotoxins: < 0.1 µg/kg for aflatoxins B1, B2, G1 and G2, < 1 µg/kg for ochratoxin A, < 2 µg/kg for zearalenone, α- and β-zearalenone, HT2-toxin, T2-toxin cytochalasin E and sterigmatocystin, < 5 µg/kg for nivalenol, fusarenon X and diacetoxyscirpenol, and < 10 µg/kg for deoxynivalenol, deoxynivalenol-3-glycoside, 3-acetyldeoxynivalenol, 15-acetyldeoxynivalenol, citrinin, patulin and fumonisins B1, B2 and B3.

[25]Technical dossier/Supplementary information/September 2023/Annex III_Ginseng_Nutritional Analysis_Microbiol_Dioxins. Upper bound concentrations are calculated on the assumption that all values of the different congeners below the limit of quantification are equal to the limit of quantification. TEQ = toxic equivalency factors for dioxins, furans and dioxin-like PCBs established by WHO in 2005 (van den Berg et al., 2006).

3.2.2 | Shelf-life

The shelf-life of the tincture is declared by the applicant to be at least 12 months when stored in tightly closed containers under standard conditions. No evidence was provided to support this claim.

3.2.3 | Conditions of use

Ginseng tincture is intended for use in feed for horses, dogs and cats at the maximum proposed use levels of 48.6, 228.7 and 162 mg/kg complete feed.[26]

3.3 | Safety

The safety assessment of the additive is based on the proposed use levels in feed.

Several volatile components of the tincture have been already assessed as chemically defined flavourings for use in feed and food by the FEEDAP Panel and the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). The list of flavouring compounds currently authorised for food[27] and feed[28] uses together with the EU Flavour Information System (FLAVIS) number, the chemical group (CG) as defined in Commission Regulation (EC) No 1565/2000[29] and the corresponding EFSA opinion is given in Table 3.

TABLE 3 Flavouring compounds already assessed by EFSA as chemically defined flavourings, grouped according to the chemical group (CG) as defined in Commission Regulation (EC) No 1565/2000, with indication of the EU Flavour Information System (FLAVIS) number and the corresponding EFSA opinion.

CG	Chemical Group	Product – EU register name (common name)	FLAVIS no	EFSA opinion,* year
01	Straight-chain primary aliphatic alcohols/ aldehydes/acids, acetals and esters with esters containing saturated alcohols and acetals containing saturated aldehydes	Hexadecanoic acid (palmitic acid)	08.014	2013
		Ethyl hexadecanoate	09.193	
		Ethyl octadeca-9,12-dienoate[a]	09.204	SCF/CoE
04	Non-conjugated and accumulated unsaturated straight-chain and branched-chain aliphatic primary alcohols, aldehydes, acids, acetals and esters	Octadeca-9,12-dienoic acid[a]	08.041	JECFA
32	Epoxides	β-Caryophyllene epoxide[a]	16.043	2014, CEF

Abbreviations: CoE, Council of Europe; SCF, Scientific Committee on Food.

*FEEDAP opinion unless otherwise indicated.

[a]Evaluated for use in food. According to Regulation (EC) 1565/2000, flavourings evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) before 2000 are not required to be re-evaluated by EFSA.

No studies to support the safety for target animals, consumers and users were performed with the additive under assessment.

The applicant carried out a structured database search to identify data related to the chemical composition and the safety of preparations obtained from *P. ginseng*.[30] Four cumulative databases (LIVIVO, NCBI, OVID and ToxInfo), 13 single databases including PubMed and Web of Science and 12 publishers' search facilities including Elsevier, Ingenta, Springer and Wiley were used. The literature search (no time limits) was conducted in April 2022. The keywords used covered different aspects of safety and the inclusion and exclusion criteria were provided by the applicant.

The additive under assessment, ginseng tincture, consists of 95.26% (w/w) of a water/ethanol mixture. The concentration of plant-derived compounds is about 4.74% (w/w) of the tincture. The dry matter includes minerals (expressed as ash), protein, lipids and carbohydrates, which are not of concern and are not further considered.

[26]Concentrations in complete feed based on the maximum proposed use levels of 0.4, 0.06 and 0.01 mL tincture/head per day for horses, dogs and cats, respectively.

[27]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.

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

[29]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 1 80, 19.7.2000, p. 8.

[30]Technical dossier/Supplementary information/September 2023/Literature_search_ginseng_tincture.

Among the secondary plant metabolites, up to 0.92% (w/w) of the tincture consists of ginsenosides, up to 0.33% (w/w) of dicarboxylic acids, up to 0.039% (w/w) of phenols and up to 0.048% (w/w) of volatile and non-volatile lipophilic compounds (see Section 3.2.1).

Dicarboxylic acids, such as oxalic acid, malic acid and fumaric acid, are ubiquitous in food and feeds of plant origin and are not expected to raise concern for genotoxicity. They will be readily metabolised and excreted, mainly as carbon dioxide, and are not expected to accumulate in animal tissues and products. These compounds are not of concern at concentrations resulting from the use of the additive at the maximum proposed use level in feed and are not further considered in the assessment.

Total phenolic compounds including flavonoids were quantified but not identified. They will be assessed based on considerations at the level of the assessment group (see Section 3.3.4). These compounds are readily metabolised and excreted and are not expected to accumulate in animal tissues and products.

Five out of the 17 identified volatile/lipophilic constituents of ginseng tincture have been previously assessed and considered safe for use as flavourings and are currently authorised for use in food[31] without limitations and for use in feed[32] at individual use levels higher than those resulting from the intended use of the tincture in feed. The list of the compounds already evaluated by the EFSA Panels is given in Table 3.

Twelve additional volatile/lipophilic constituents have not been previously assessed for use as flavourings. The FEEDAP Panel notes that nine[33] of them are aliphatic mono- or sesquiterpenes structurally related to flavourings already assessed in CGs 1, 6, 31 and 32 and a similar metabolic and toxicological profile is expected (EFSA FEEDAP Panel, 2012b, 2013, 2015, 2016a).

In addition, the FEEDAP Panel notes that six out of the 17 volatile/lipophilic constituents (ethyl octadeca-9,12-dienoate, ethyl hexadecanoate, octadeca-9,12-dienoic acid, hexanoic acid, 2-hydroxy-1-(hydroxymethyl)- ethyl ester, 2-monolinolenin and palmitic acid) are medium- and long-chain fatty acids and related esters. These compounds are abundant in the lipid fraction of feed and food and are considered safe as nutrients, in line with the approach followed in the assessment of CG 1 (EFSA FEEDAP Panel, 2013). These compounds are not further considered in the assessment.

The following sections mainly address the ginsenosides (Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg2), the two polyacetylenes (panaxynol, panaxydol) and di-isooctylphthalate, which have not been previously assessed or are not structurally related to flavourings previously assessed, based on the evidence provided by the applicant in the form of literature searches and quantitative structure–activity relationship (QSAR) analysis.

3.3.1 | Absorption, distribution, metabolism and excretion of ginsenosides

Ginsenosides

No absorption, distribution, metabolism and excretion (ADME) studies were submitted with the additive under assessment. The literature search provided by the applicant[34] (see Section 3.3) identified several publications, including reviews on the ADME of ginsenosides, among which those present in the additive. The next paragraphs summarise the available data on the ADME and bioavailability of the ginsenosides when administered by oral route. A study which evaluated the distribution of the labelled compounds in mice after intravenous administration is also described. Nine ginsenosides were detected in the additive (one not identified) with the following ascending order of concentrations: Rb1 > Rc > Re > Rb2 > Rd > Rg1 > unknown>Rf > Rg2.

The pharmacokinetic profile of the ginsenosides Rb1, Rb2 and Rb3 was studied in rats after oral (50 mg/kg) and intravenous (10 mg/kg, through tail vein) administration (Zhao et al., 2012). Blood samples were collected from 5 min (i.v.) and 0.25 h (p.o.) up to 36 h and were analysed by liquid chromatography-electrospray-mass spectrometry (LC-ESI-MS, limit of detection (LOD): 3.0 and 4.0 ng/mL for Rb1 and Rb2, respectively). Rb3 (not detected in the additive) was the most rapidly absorbed being Rb1 the slowest one. The bioavailability after oral administration was low for all tested ginsenosides (0.78% for Rb1, 0.08% for Rb2 and 0.52% for Rb3). The $AUC_{0\text{-}36h}$ of Rb1 (63.5 mg h/L) after oral administration was 10 times higher than that of Rb2 (6.4 mg h/L) and the $t_{1/2}$ was 9.8 and 23.1 h, respectively, for Rb1 and Rb2, showing that these ginsenosides are slowly excreted. T_{max} was 2 and 5 h and C_{max} was 6 and 0.4 mg/L for Rb1 and Rb2, respectively. The pharmacokinetic profile seems to be related to structural features of the ginsenosides, ginsenosides with hexose and hydroxyl groups (e.g. Rb1) showing a slightly higher absorption after oral administration than those with pentose groups (e.g. Rb2, Rb3) in the same glycosylation site.

Similar results were obtained from studies carried out after intravenous administration to rabbits (Yu et al., 2007) and rats (Xia et al., 2008) of 'Shenmai', a combination of *Panax ginseng* and *Ophiopogon japonicus*: ginsenosides Rg1 and Re

[31]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.

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

[33]Hexanoic acid, 2-hydroxy-1-(hydroxymethyl)- ethyl ester and 2-monolinolenin (CG 1); spathulenol (CG 6); α-himachalene, β-gurjunene, β-patchoulene, cis-muurula-4(14),5-diene, guaia-6,9-diene (CG 31); and humulene oxide II (CG 32).

[34]Technical dossier/Supplementary information/September 2023/Literature_search_ginseng_tincture.

(PPT as the basic structure) were eliminated quickly, whereas ginsenosides Rd and Rb1 (PPD as the basic structure) had a relatively long elimination with a $t_{1/2}$ of approximately 22 h. Sun et al. (2012) evaluated the tissue distribution in mice and rats after injection of 50 mg/kg body weight (bw) of ^{3}H-labelled ginsenoside Rd. The highest concentration was observed in the lung, followed by liver, kidney, heart and intestine, the lowest being in the brain. At 24 h, the radioactivity in tissues was reduced nearly by 90%. The urinary excretion of ^{3}H-labelled ginsenoside Rd in mice and rats within 24 h was 60.8% and 37.2% and within 48 h was 62.9% and 39.5% respectively. Faecal excretion in mice and rats within 24 h was 18.45% and 31.7% and within 48 h was 18.8% and 36.6%, respectively.

A study was made by administering by intragastric tube 1 g of the ginsenoside Rg1 to two horses (Chung et al., 2009). Urine samples were collected up to 3 days post-administration. In addition, an in vitro study was carried out in liver microsomes from horses by incubating 1 mg of Rb1 or Rg1 (two ginsenosides present in the additive under assessment). Validated GC-MS and liquid chromatography-mass spectrometry (LC-MS) methods were used for the analysis of samples. In vitro, Rb1 originated the deglycosylated metabolites Rd, Rg3 and Rh2; Rg1 originated Rh1 and PPT. In urine of horses given Rg1, both Rg1 and PPT as conjugate glucuronides were detected. No Rh1 was detected in urine.

Gu et al. (2009) carried out a pharmacokinetics study in Beagle dogs. The animals were administered with a single dose of Rh2 by gavage at 1 mg/kg bw or by i.v. bolus at 0.1 mg/kg bw. Blood was collected at several time points and plasma separated for analysis by LC-MS. The bioavailability of Rh2 was about 16%. A multidose study was also carried out by administering to three male and three female Beagle dogs 1 mg Rh2/kg bw by gavage at 12 h intervals for 7 consecutive days. Blood was collected at the same time points as for the single gavage dose. Multiple-dosing (7 days, 1 mg/kg bw bid, twice a day) did not affect the pharmacokinetics in this animal species, namely T_{max}, $T_{1/2}$ and AUC. The same authors made also carried out an in vitro study in CaCo-2 cells and concluded that the membrane permeability of Rh2 was very low and identified Rh2 as a typical efflux transporter substrate. These findings can contribute for its low bioavailability. Although Rh2 was not identified in the additive, the data obtained both in vivo and in vitro give support to low bioavailability of PPD-type ginsenosides present (e.g. Rb1, Rb2, Rd, Rc).

The metabolism of 20(S)-protopanaxadiol (PPD) (the aglycone of ginsenosides) was evaluated in human liver microsomes and in human cryopreserved hepatocytes (Li et al., 2011). Twenty-four metabolites were detected by LC-MS, and the structure of four of them was elucidated. In the main metabolic pathway, the 24,25-double bond of PPD is oxidised, originating an epoxide. Subsequent hydrolysis and rearrangement gave rise to the formation of the corresponding 24,25-diol- and 20,24-oxide derivatives. Other metabolites were formed by further hydroxylation and dehydrogenation. The formation of a hydroxyl group at C-25 of the side chain is present in all except one phase I metabolites. The authors of the study hypothesised that glucuronide conjugation at the 25-hydroxyl group could explain the presence of the two glucuronide conjugates observed in incubations with human hepatocyte. Data of this in vitro study show the ability of human liver to metabolise the aglycone of the PPD ginsenosides that can be present as residues in meat of horses fed with the additive under assessment.

Polyacetylenes

No data were provided on the ADME of the polyacetylenes panaxynol and panaxydol.

Di-isooctylphthalate

The EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) evaluated several phthalates, including dibutylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and di-isodecylphtalate (DIDP) for use in food contact materials (EFSA CEP Panel, 2019). The consideration made on the ADME of DINP and DIDP is considered relevant to di-isooctylphthalate present in ginseng tincture. In rodents orally exposed to low doses, the gastrointestinal absorption of DINP and DIDP was rapid and around 50% of the dose. The limited distribution data in rodents do not indicate tissue accumulation for phthalates and their metabolites. Long-chain dialkyl phthalates, such as DINP and DIDP, are hydrolysed by esterases to the corresponding monoester. The monoester is further metabolised by $\omega-$ and $\omega-1$ oxidation, resulting in a number of oxidised metabolites which are eliminated in urine as free or conjugated compounds. Only 2%–7% of the dose is excreted as the simple monoester.

Target animals

Metabolism studies in dogs and horses are available for ginsenosides, as described above. There is general evidence that the main metabolic pathways (hydrolysis, oxidation, hydroxylation, dehydrogenation and conjugation with glucuronic acid) are present in the target species (see e.g. Gusson et al., 2006, as reviewed in EFSA FEEDAP Panel, 2016b) except glucuronide conjugation that is limited in cats (Court & Greenblatt, 1997; Lautz et al., 2021). Therefore, food-producing animals (horses) can also be assumed to have the ability to metabolise and excrete the components present in ginseng tincture and there is no evidence that these components or their metabolites would accumulate in tissues.

3.3.2 | Toxicology

3.3.2.1 | *Genotoxicity*

For mixtures containing a substantial fraction of unidentified components, the EFSA Scientific Committee (EFSA SC) recommends that first the chemically defined substances be assessed individually for their potential genotoxicity using all available information, including read-across and QSAR considerations about their genotoxic potential (EFSA SC, 2019b). Therefore, the potential genotoxicity of identified constituents is first considered. Then, in vitro genotoxicity studies performed with ginseng extracts similar to the additive under assessment are taken into account, if deemed relevant.

The genotoxic potential for the eight ginsenosides identified (ginsenoside Rb1, Rb2, Rc, Rd, Re, Rf, RG1 and Rg2), the two polyacetylenes (panaxynol, panaxydol) and di-isooctylphthalate was predicted by the applicant using the Organization for Economic Co-operation and Development (OECD) QSAR Toolbox.[35] Structural alerts for mutagenicity were found for all the compounds[36] and predictions of Ames mutagenicity (with and without S9) were made by 'read-across' analyses of data available for similar substances (i.e. analogues obtained by categorisation). Categories were defined using general mechanistic and endpoint profilers as well as empirical profilers. Mutagenicity read-across-based predictions were found to be consistently negative for all categories of analogues. On this basis, the alerts raised were discounted.

The possible genotoxicity of phthalates was assessed by other bodies (as reviewed in EFSA CEP Panel, 2019). The FEEDAP Panel noted that overall evidence from in vitro and in vivo data on mutagenicity or chromosomal damage for DBP, BBP and DEHP does not give rise to a concern for genotoxicity. The consideration on the genotoxicity of DEHP is considered relevant to di-isooctylphthalate present in ginseng tincture.

Genotoxicity studies with preparations obtained from Panax ginseng C.A.Mey.

The literature search provided by the applicant[37] (see Section 3.3) identified several publications on the genotoxicity of preparations obtained from the roots of *P. ginseng*. The studies considered relevant for the assessment of the genotoxic potential of these preparations were evaluated by the FEEDAP Panel and reported below.

Negative results were obtained in an Ames test performed with Korean Red ginseng oil produced by supercritical CO_2 extraction of secondary products derived from Korean Red Ginseng extract (from unpeeled steam-treated roots of *P. ginseng*). Five concentrations ranging from 312.5 to 5000 µg/plate were tested in Salmonella Typhimurium strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2 uvrA in the presence or absence of metabolic activation (Seo et al., 2017). The FEEDAP Panel noted that the test item, representing a mixture of lipophilic components (fatty acids, phospholipids, phytosterols), was only characterised for the fatty acid composition (linoleic acid 71.4%; palmitic acid 9.39%; linolenic acid 6.24%; oleic acid 5.02%; *cis*-11,14-eicosatyrienoic acid 1.34%) and not for the content of other lipophilic substances; thus, the results of this study were considered of limited relevance.

An extract obtained with boiling water and enzymes from *P. ginseng* roots (containing ginsenoside Rb1 1.5 mg/mL; ginsenoside Rg3-R 3.71 mg/mL; ginsenoside Rg3-S 2.35 mg/mL; ginsenoside Rh1 3.2 mg/mL; ginsenoside Rh2-R 0.45 mg/mL; ginsenoside Rh2-S 2.95 mg/mL; Compound K 5.89 mg/mL) did not induce gene mutations in an Ames test conducted with Salmonella Typhimurium strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2 uvrA in the presence or absence of metabolic activation at 50, 150, 500, 1500 or 5000 µg/plate (Jeong et al., 2016).

Root extract of *P. ginseng* (no further details provided) was also tested in vitro for the induction of gene mutations in mammalian cells using V79 Chinese hamster lung cells. No increase in the mutation frequency was observed at the only concentration tested (0.1 µg/mL) (Rhee et al., 1991).

The potential to induce chromosome damage of an extract from *P. ginseng* roots (obtained with boiling water and enzymes, and described in detail above) was investigated in vitro in Chinese hamster lung cells using 750, 1500 or 3000 µg/mL in a chromosome aberration assay performed following the OECD TG 473 (1997) and applying a short treatment in the presence and absence of metabolic activation as well as a continuous treatment in the absence of metabolic activation. The maximum concentration tested was limited by cytotoxicity. No increase in the frequency of chromosomal aberrations was observed in the presence and absence of metabolic activation (Jeong et al., 2016).

The same test item did not induce chromosome damage in vivo applying the bone marrow micronucleus test with male IRC mice orally administered 1250, 2500 or 5000 mg/kg per day twice a day for 2 days. A preliminary dose range-finding study showed that the ginseng extract did not induce toxic effects up to 5000 mg/kg per day. The highest dose of 5000 mg/kg per day was selected as the maximum tolerated dose. The study was conducted following the OECD TG 474 (1997) (Jeong et al., 2016).

Negative results were also observed in an in vivo micronucleus test performed in male rats treated daily with an oral dose of the Korean ginseng extract (20 mg/kg bw per day for 30 days). The aqueous extract obtained from *P. ginseng* roots with hot water, contained ginsenoside Rg1 0.54 mg/mL; ginsenoside Re 0.95 mg/mL; ginsenoside Rf 1.02 mg/mL;

[35]Technical dossier/Supplementary information September 2023/Annex_XII_Ginseng_QSAR.

[36]The same structural alerts for mutagenicity were found all the ginsenosides (H-acceptor-path3-Hacceptor, menthol). For panaxynol (falcarinol) structural alert was due to the presence of propargyl alcohol group, for panaxydol to the presence of an epoxide and arizidine group, and for di-isooctylphthalate to the presence of high molecular weight phthalate esters, and H-acceptor-path3-Hacceptor.

[37]Technical dossier/Supplementary information/September 2023/Literature_search_ginseng_tincture.

ginsenoside Rh1 0.88 mg/mL; ginsenoside Rg2 3.16 mg/mL; ginsenoside Rb1 3.72 mg/mL; ginsenoside Rc 1.89 mg/mL; ginsenoside Rb2 1.71 mg/mL; ginsenoside Rd 1.32 mg/mL; ginsenoside Rg3 4.04 mg/mL; ginsenoside Rh2 0.11 mg/mL (Abdel-Aziem et al., 2011).

Overall, the available data indicate that preparations from the roots of *P. ginseng* and their components including a broad spectrum of ginsenosides do not induce gene mutations and chromosomal aberrations and thus, do not raise concern for genotoxicity.

3.3.2.2 | *Repeated-dose toxicity studies*

Ginsenosides

The applicant provided a literature search[38] (see Section 3.3) on the toxicity of preparations obtained from *P. ginseng*. The literature search identified 31 references reporting non-clinical studies conducted in rodents (mice, rats) and rabbits made with *P. ginseng* root ethanolic or water extracts (manufacturing process not always specified).

Although none of the studies was performed with the additive under assessment, some of the studies were considered relevant as *P. ginseng* roots were extracted with hot water or 80% ethanol resulting in concentrations of ginsenosides in the test items comparable or higher (from 2% to 10.9%) than in the additive under assessment (1%). From these studies (oral exposure: 28 days up to 2 years), no observed adverse effect level (NOAEL) values were identified in the range 2000–5000 mg/kg bw per day for the test item, ginseng extracts containing 2%–10.9% ginsenosides (Jeong et al., 2016; Lee et al., 2019; NTP, 2011; Park et al., 2013, 2018, 2022).

The FEEDAP Panel reviewed the toxicological information available and selected the NOAEL from the 2-year NTP study in rats as the reference point for ginsenosides for the current assessment. The FEEDAP Panel noted that the ginseng extract tested in the NTP study is the most similar to the additive under assessment, considering both the extraction process (using 80% aqueous ethanol vs. 60% aqueous ethanol used in the manufacturing of the additive) and the qualitative composition in term of the relative proportions of ginsenosides. From the quantitative point of view, the ginsenoside concentrations in the ginseng extract tested in the NTP study are about 10-fold higher than that in the additive under assessment.

The 2-year NTP study in rats tested a ginseng 80% aqueous ethanolic extract from *P. ginseng* roots containing 7.4% ginsenosides (NTP, 2011). Groups of 50 Sprague–Dawley rats of each sex were given the extract dispersed in sterile water by gavage to achieve a dose of 0, 1250, 2500 or 5000 mg extract/kg bw per day on 5 days per week for 2 years. The achieved dose was confirmed by analysis to be within 10% of that intended concentration throughout the study. Survival of the rats given the highest dose was significantly reduced compared with controls and other groups. This followed markedly reduced body weight in that group. Although no specific toxicity was observed in histopathological examination of the high-dose animals, the NOAEL is concluded to be at a dose of 2500 mg extract/kg bw per day. Based on the analysed level of ginsenosides, this NOAEL is equivalent to 185 mg ginsenosides/kg bw per day. It is worthy of note that a 90-day study conducted by NTP on a similar extract but with a 10.9% content of ginsenosides showed no adverse effects at a dose of 5000 mg extract/kg bw per day.

Polyacetylenes

Toxicological data were not provided for the polyacetylenes panaxynol and panaxydol.

Di-isooctylphthalate

For di-isooctylphthalate, the FEEDAP Panel notes that the EFSA CEP Panel assessed several phthalates, including DBP, BBP, DEHP, DINP and DIDP as food contact materials (EFSA CEP Panel, 2019). The CEP Panel established a group tolerable daily intake (TDI) of 50 μg/kg bw per day expressed as DEHP equivalents. This group-TDI is based on reproductive effects of phthalates and was derived applying an uncertainty factor (UF) of 100 to the NOAEL of 4.8 mg/kg bw per day for the target compound DEHP.[39] This group-TDI applies to all phthalates except DIDP, for which a TDI of 150 μg/kg bw per day was established based on liver effects. Considering that the group-TDI for reproductive effects applies to a range of phthalates including DINP, the FEEDAP Panel selected the reference point used to derive the group-TDI, i.e. NOAEL of 4.8 mg/kg bw per day, as the reference point for the assessment of di-isooctylphthalate.

3.3.2.3 | *Conclusions on toxicology*

Based on a QSAR analysis, no concern for genotoxicity has been identified for the individual components of ginseng tincture, the ginsenosides (ginsenoside Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, and Rg2), the polyacetylenes (panaxynol, panaxydol) and di-isooctylphthalate. This conclusion is further supported by experimental data, which showed that preparations from

[38]Technical dossier/Supplementary information/September 2023/Literature_search_ginseng_tincture.

[39]DEHP, for which the most robust database is available, was selected as the target compound. Relative potency factors (RPFs) for the phthalates were established using the health-based guidance values (HBGVs) derived from their respective point of departure (PoD) for the reproductive effects, even though they have related but differing toxicological endpoints in the animal studies.

P. ginseng roots do not induce gene mutations and chromosomal aberrations. Overall, it is concluded that ginseng tincture does not raise concern for genotoxicity.

From the toxicological information available for an aqueous ethanolic extract from *P. ginseng* roots, the FEEDAP Panel derived a NOAEL of 185 mg/kg bw per day for ginsenosides. For di-isooctylphthalate, the FEEDAP Panel selected the NOAEL of 4.8 mg/kg bw used by the CEP Panel to establish a group-TDI for phthalates.

3.3.3 | Safety for the target species

No studies to support the safety for target animals were performed with the additive under assessment.

In the absence of these data, the approach to the safety assessment of a mixture is based on its individual components or group of components (assessment groups). The combined toxicity can be predicted using the dose addition assumption within an assessment group (EFSA SC, 2019a).

The safety assessment is based on phenols, ginsenosides and on the volatile compounds present in the tincture. This fraction also contains lipophilic components, such as panaxynol, and panaxydol and di-isooctylphthalate.

For the group assessment of phenolic compounds, in the absence of data, the threshold of toxicological concern (TTC) is applied to derive maximum safe feed concentrations for the whole group in the tincture (EFSA FEEDAP Panel, 2017b). Since the presence of flavonoids in the phenolic fraction could not be excluded based on analytical data, these compounds were allocated to Cramer Class III.

Based on considerations related to structural and metabolic similarities, ginsenosides were allocated to the same assessment group. For ginsenosides, the FEEDAP Panel identified a NOAEL of 185 mg/kg bw per day.

In the absence of data, the two polyacetylenes panaxynol and panaxydol were allocated to Cramer Class III and assessed as a group. For di-isooctylphthalate, a NOAEL of 4.8 mg/kg bw per day was identified.

The volatile compounds present in the tincture were allocated to three assessment groups, corresponding to the CGs 6, 31 and 32, as defined in Annex I of Regulation (EC) No 1565/2000. The allocation of the components to the (sub-)assessment groups is shown in Table 4 and in the corresponding footnote.

For hazard characterisation, each component of an assessment group was first assigned to the structural class according to the Cramer classification (Cramer et al., 1978). For some components in the assessment group, toxicological data were available to derive NOAEL values. Structural and metabolic similarities among the components in the assessment groups were assessed to explore the application of read-across. If justified, extrapolation from a known NOAEL of a component of an assessment group to the other components of the group with no available NOAEL was made. If sufficient evidence was available for members of a (sub-)assessment group, a (sub-)assessment group NOAEL was derived.

For the volatile components of the tincture, toxicological data for subchronic studies, from which NOAEL values could be derived, were available for β-caryophyllene [01.007] in CG 31 (EFSA FEEDAP Panel, 2015, 2016a) and β-caryophyllene epoxide [16.043] in CG 32 (EFSA CEF Panel, 2014).

The NOAEL of 222 mg/kg for β-caryophyllene was extrapolated to guaia-6,9-diene in CG 31, and the NOAEL of 109 mg/kg for β-caryophyllene epoxide was extrapolated to humulene oxide II in CG 32.

For the remaining eight compounds,[40] toxicity studies were not available and read-across was not possible. Therefore, the TTC approach was applied (EFSA FEEDAP Panel, 2017b). All these compounds belong to Cramer Class I and III.

As the result of the hazard characterisation, a reference point was identified for each component in the assessment group based on the toxicity data available (NOAEL from in vivo toxicity study or read across) or from the 5th percentile of the distribution of NOAELs of the corresponding Cramer Class (i.e. 3, 0.91 and 0.15 mg/kg bw per day, respectively, for Cramer Class I, II and III compounds, Munro et al., 1996). Reference points selected for each compound are shown in Table 4.

For risk characterisation, the margin of exposure (MOE) was calculated for each component as the ratio between the reference point and the exposure. For each assessment group, the combined (total) margin of exposure (MOET) was calculated as the reciprocal of the sum of the reciprocals of the MOE of the individual substances (EFSA SC, 2019a). An MOET > 100 allowed for interspecies- and intra-individual variability (as in the default 10 × 10 uncertainty factor). The volatile compounds (belonging to CGs 6, 31 and 32) resulting individually in an MOE > 50,000 were not further considered in the assessment group as their contribution to the MOE(T) is negligible. They are listed in the footnote.[41]

The approach to the safety assessment of ginseng tincture for the target species is shown in Table 4. The calculations shown in Table 4 were made for horses at the proposed use level of 48.6 mg tincture/kg complete feed.

[40]Spathulenol (CG 6); α-himachalene, β-gurjunene, β-patchoulene, *cis*-muurula-4(14),5-diene (CG 31); panaxynol (falcarinol), panaxydol and di-isooctylphthalate.

[41]Spathulenol (CG 6); α-himachalene, β-gurjunene, β-patchoulene, *cis*-muurula-4(14),5-diene and guaia-6,9-diene (CG 31); β-caryophyllene epoxide and humulene oxide II (CG 32).

TABLE 4 Compositional data, intake values (calculated at the proposed use level of 48.6 mg/kg complete feed for horses), reference points, margin of exposure (MOE) for the individual components of ginseng tincture classified according to assessment group and combined margin of exposure (MOET) for each assessment group.

Additive composition		Exposure		Hazard characterisation		Risk characterisation	
Assessment group	**Highest conc. in the tincture**	**Highest feed conc.**	**Intake[a]**	**Cramer class[b]**	**NOAEL[c]**	**MOE**	**MOET**
Constituent	**(μg/mL)**	**mg/kg**	**mg/kg bw**	**–**	**mg/kg bw**	**–**	**–**
Total phenols	216	0.129	0.0029	(III)	0.15	616	
Ginsenosides							
Ginsenoside Rb1	2582	0.129	0.0029	(III)	185	62,982	
Ginsenoside Rb2	1158	0.058	0.0013	(III)	185	110,218	
Ginsenoside Rc	1476	0.074	0.0017	(III)	185	154,194	
Ginsenoside Rd	1055	0.053	0.0012	(III)	185	134,468	
Ginsenoside Re	1209	0.061	0.0014	(III)	185	750,103	
Ginsenoside Rf	218	0.011	0.0002	(III)	185	330,883	
Ginsenoside Rg1	492	0.025	0.0006	(III)	185	140,474	
Ginsenoside Rg2	119	0.006	0.0001	(III)	185	1,363,223	
Unknown ginsenoside	631	0.032	0.0007	(III)	185	257,930	
MOET							18,201
Lipophilic constituents							
Polyacetylenes							
Panaxynol (falcarinol)	84.5	0.0042	0.000096	III	*0.15*	1567	
Panaxydol	135.3	0.0067	0.000153	III	*0.15*	980	
							603
Phthalate ester							
Di-isooctylphthalate	7.96	0.0004	0.000009	I	*4.8*	521,918	
Unknown							
Unknown sesquiterpene	3.42	0.0002	0.000004	III	*0.15*	38,557	
Unknown sesquiterpene	6.05	0.0003	0.000007	III	*0.15*	21,796	
							13,924

[a]Intake calculations for the individual components are based on the use level of 48.6 mg tincture/kg complete feed for horses. The MOE for each component is calculated as the ratio of the reference point (NOAEL) to the intake. The combined margin of exposure (MOET) is calculated for each assessment group as the reciprocal of the sum of the reciprocals of the MOE of the individual substances.

[b]When a NOAEL value is available or read-across is applied, the allocation to the Cramer Class is put into parentheses.

[c]Values *in italics* are the 5th percentile of the distribution of NOAELs of the corresponding Cramer Class, other values (plain text) are NOAELs extrapolated by using read-across.

As shown in Table 4, for horses at the proposed use levels in complete feed the MOET > 100 for all assessment groups. The lowest MOET was calculated for polyacetylenes. From the lowest MOET of 603 for horses, the MOET for polyacetylenes was calculated for the other target species considering the respective daily feed intake and conditions of use. The results are summarised in Table 5.

TABLE 5 The combined margin of exposure (MOET) for polyacetylenes calculated for the different target animal categories at the proposed use level of the additive in feed.

Animal category	Default values daily feed intake (g DM/kg body weight)	Proposed use level (mg additive/kg complete feed)	MOET
Horses	20	48.6	603
Dogs	17	228.7	154
Cats	20	162	181

Table 5 shows that for all species the MOET exceeds the value of 100. Generally, for cats, a MOET > 500 is considered adequate, considering their unusually low capacity for glucuronidation of compounds (Court & Greenblatt, 1997; Lautz et al., 2021). However, because the MOET for polyacetylenes was derived from Cramer Class III, which is already very

conservative, a value of 100 seems appropriate. Therefore, for all species, no safety concern was identified for ginseng tincture, when used as a feed additive at the proposed use levels.

3.3.3.1 | *Conclusions on safety for the target species*

Ginseng tincture is safe for horses, dogs and cats at the maximum proposed use level of 48.6, 228.7 and 162 mg/kg complete feed, respectively.

3.3.4 | Safety for the consumer

Ginseng roots and their preparations are used in food supplements and herbal remedies (EMA, 2014a; WHO, 2010). Several products are made from ginseng, including many types of ginseng herbal teas, granules and ready-to-drink cans, chewing gums and candies (Burdock, 2009).

No data on residues in products of animal origin were made available for any of the constituents of the tincture. The main constituents of ginseng tincture (ginsenosides) and di-isooctylphthalate are not expected to accumulate in the target animals (horses, see Section 3.3.1). The phenolic compounds and the polyacetylenes panaxynol and panaxydol, present in the additive at concentrations below the thresholds for Cramer Class III compounds, are not expected to be of concern for the consumer.

The FEEDAP Panel considers it is unlikely that consumption of products from animals (horses) given ginseng tincture at the proposed maximum use level would significantly increase human background exposure. No safety concern would be expected for the consumer from the use of ginseng tincture up to the maximum proposed use levels in feed.

3.3.5 | Safety for the user

No specific data were provided by the applicant regarding the safety of the additive for users.

The applicant provided information according to Classification, Labelling and Packaging (CLP) Regulation (EC) 1272/2008[42] concerning the presence of ethanol in the tincture.[43]

The additive under assessment should be considered as irritant to skin and eyes, and presumed to be a dermal and respiratory sensitiser.

3.3.6 | Safety for the environment

P. ginseng is not a species native to Europe. Therefore, the safety for the environment is assessed based on the individual components of the tincture.

Most of the constituents of ginseng tincture (organic acids including fatty acids and volatile constituents in CGs 6, 31 and 32) are ubiquitous compounds naturally present in feed and food and therefore are not expected to be of concern for the environment.

The tincture under assessment also contains low concentrations of ginsenosides. Because of the degradation of ginsenosides by equine metabolism and environmental processes, and considering the small environmental exposure of excreta from horses, the use of the additive in horse feed at the proposed conditions of use is not expected to pose a risk to the environment.

3.4 | Efficacy

Ginseng roots (*P. ginseng*) and its preparations are listed in Fenaroli's Handbook of Flavour Ingredients (Burdock, 2009).

Since ginseng roots and its preparations/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

Ginseng tincture from the roots of *Panax ginseng* C.A.Mey. is safe for horses, dogs and cats at the maximum proposed use level of 48.6, 228.7 and 162.0 mg/kg complete feed, respectively.

The additive is considered safe for consumers when used at the proposed conditions of use in feed for horses.

[42]Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging (CLP) of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. *OJ L 353, 31.12.2008, p. 1–1355*.

[43]Technical dossier/Supplementary information September 2023/Annex_XIII_SIn reply_ginseng_tincture_MSDS. H319: moderate eye irritation; H315: skin irritation.

The additive under assessment should be considered as irritant to skin and eyes, and as a skin and respiratory sensitiser.

The use of ginseng tincture at the proposed use level in feed for horses is not considered to be a risk to the environment.

Since the roots of *P. ginseng* and its preparations/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 for the tincture under assessment.

DOCUMENTATION PROVIDED TO EFSA/CHRONOLOGY

Date	Event
28/10/2010	Dossier received by EFSA. Botanically defined flavourings from Botanical Group 02 – Apiales and Austrobaileyales for all animal species and categories. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)
09/11/2010	Reception mandate from the European Commission
26/02/2013	EFSA informed the applicant (EFSA ref. 7150727) that, in view of the workload, the evaluation of applications on feed flavourings would be re-organised by giving priority to the assessment of the chemically defined feed flavourings, as agreed with the European Commission
24/06/2015	Technical hearing during risk assessment with the applicant according to the "EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products": data requirement for the risk assessment of botanicals
27/02/2019	Partial withdrawal by applicant (EC was informed) for the following additives: dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, and opoponax oil
24/06/2019	Application validated by EFSA – Start of the scientific assessment
03/07/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterization, safety for the target species, safety for the consumer, safety for the user, safety for the environment*
30/09/2019	Comments received from Member States
02/04/2020	Partial withdrawal by applicant (EC was informed) for the following additives: parsley oil, hares ear tincture, taiga root extract (sb), ajowan oil
09/12/2020	Partial withdrawal by applicant (EC was informed) for the following additives: celery tincture
31/10/2022	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives – partial report related to nine additives *(dill herb oil, dill tincture, dong quai tincture, cumin oil, fennel tincture, parsley tincture, anise tincture, star anise tincture and ferula assa-foetida oil)*
16/12/2022	Reception of an addendum of the Evaluation report of the European Union Reference Laboratory for Feed Additives – final report related to 11 additives *(celery seed oil, caraway seed oil, coriander oil, taiga root tincture, fennel oil, common ivy extract (sb), ginseng tincture, anise oil, anise star oil, anise star terpenes and omicha tincture)*
25/09/2023	Reception of supplementary information from the applicant (partial submission: ginseng tincture included in the present assessment)
25/09/2023	Partial withdrawal (target species). Species to be withdrawn: all animal species except horses, cats and dogs
29/01/2024	The application was split and a new EFSA-Q-2024-00055 was assigned to the additive included in the present assessment. Scientific assessment re-started for the additive included in the present assessment
12/03/2024	Opinion adopted by the FEEDAP Panel on ginseng tincture (EFSA-Q-2024-00055). End of the Scientific assessment for the additive included in the present assessment. The assessment of other additives belonging to BDG 02 is still ongoing

ABBREVIATIONS

ADME	absorption, distribution, metabolism and excretion
BBP	butyl-benzyl-phthalate
BDG	botanically defined group
bw	body weight
CAS	Chemical Abstracts Service
CDG	chemically defined group
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CEP	EFSA Panel on Food Contact Materials, Enzymes and Processing Aids
CFU	colony-forming unit
CG	chemical group
CLP	Classification, Labelling and Packaging
CoE	Council of Europe
DBP	di-butylphthalate
DEET	diethyltoluamide
DEHP	bis(2-ethylhexyl)phthalate
DIDP	di-isodecadecylphtalate
DINP	di-isononylphthalate
DL	dioxin-like
DM	dry matter

EEIG	European economic interest grouping
EMA	European Medicines Agency
EURL	European Union Reference Laboratory
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)
FLAVIS	The EU Flavour Information System
GC-MS	gas chromatography-mass spectrometry
HBGVs	health-based guidance values
HPLC	High performance liquid chromatography
HPLC-UV	high performance liquid chromatography-ultraviolet detection
JECFA	Joint FAO/WHO Expert Committee of Food Additives
LC-(ESI)-MS	liquid chromatography-(electrospray)-mass spectrometry (LC-ESI-MS
LOD	limit of detection
LOQ	limit of quantification
MOE	margin of exposure
MOET	combined margin of exposure (total)
NOAEL	no observed adverse effect level
NTP	national toxicology program
OECD	Organization for Economic Co-operation and Development
PCBs	polychlorinated biphenyls
PCDD	polychlorinated dibenzo-*p*-dioxins
PCDF	polychlorinated dibenzofurans
PhEur	European Pharmacopoeia
PoD	point of departure
PPD	20(S)-protopanaxadiol
PPT	20(S)-protopanaxatriol
QSAR	Quantitative Structure–Activity Relationship
RPFs	relative potency factors
SC	EFSA Scientific Committee
SCF	Scientific Committee on Food
TDI	tolerable daily intake
TEQ	toxic equivalent
TG	technical guideline
TTC	threshold of toxicological concern
UF	uncertainty factor
UV	ultraviolet
WHO	World Health Organization

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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.

REQUESTOR

European Commission

QUESTION NUMBER

EFSA-Q-2010-01286 (new EFSA-Q-2024-00055)

PANEL MEMBERS

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

LEGAL NOTICE

Not relevant: Confidentiality claimed for the MSDS, for the identity of the supplier, which is not disclosed.

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