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Safety and efficacy of a feed additive consisting of a tincture derived from the roots of *Angelica sinensis* (Oliv.) Diels (dong quai tincture) for use in poultry, horses, dogs and cats (FEFANA asbl)

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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 *Angelica sinensis* (Oliv.) Diels (dong quai tincture) when used as a sensory additive in feed for horses, dogs and cats and in water for drinking for poultry species. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concluded that the additive is safe for horses and dogs at the maximum proposed use level of 123 and 481 mg/kg complete feed, respectively. For cats, the calculated safe concentration is 184 mg/kg complete feed. For the poultry species, the calculated safe concentration in water for drinking is 79 mg/kg for chickens for fattening, 117 mg/kg for laying hens and 106 mg/kg for turkeys for fattening. No safety concern would arise for the consumer from the use of dong quai tincture up to the highest safe levels in feed. The additive under assessment should be considered as irritant to skin and eyes, and as a dermal and respiratory sensitiser. The use of the dong quai tincture as a flavour in animal feed was not expected to pose a risk for the environment. Since the root of *A. sinensis* has flavouring properties and its function in feed would be essentially the same as that in food, no further demonstration of efficacy is considered necessary.

Keywords: sensory additives, flavouring compounds, *Angelica sinensis* (Oliv.) Diels, dong quai tincture, phthalides, safety

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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 seven years after the entry into force of this Regulation.

The European Commission received a request from Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)[2] for authorisation/re-evaluation of 29 preparations (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 preparations (dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, opoponax oil,[3] parsley oil, hares ear tincture, taiga root extract (sb), ajowan oil[4] and parsley tincture[5]) and requested a change in the species limiting the application for authorisation to poultry, horses, dogs and cats.[6] During the course of the assessment, this application was split and the present opinion covers only one out of the 20 remaining preparations under application: dong quai tincture from *Angelica sinensis* (Oliv.) Diels for all animal species.

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 *Angelica sinensis* (Oliv.) Diels (dong quai tincture), when used under the proposed conditions of use (see Section 3.2.3).

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

1.2. Additional information

Dong quai tincture from *Angelica sinensis* (Oliv.) Diels 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.

[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, 1,050 Brussels, Belgium.
[3] On 27 February 2019, EFSA was informed by the applicant about the withdrawal of the applications on dill seed extract, celery seed extract (oleoresin), caraway oleoresin/extract, and opoponax oil.
[4] On 2 April 2020, EFSA was informed by the applicant about the withdrawal of the applications on parsley oil, hares ear tincture, taiga root extract (sb), ajowan oil.
[5] On 9 December 2020, the applicant informed EFSA about the withdrawal of the application on celery tincture.
[6] Technical dossier/Supplementary information September 2021/ SIn reply_dong_quai_tincture.

There is no specific EU authorisation for any *A. sinensis* preparation when used to provide flavour in food. However, according to Regulation (EC) No 1334/2008[7] flavouring preparations produced from food may be used without an evaluation and approval as long as 'they do not, on the basis of the scientific evidence available, pose a safety risk to the health of the consumer, and their use does not mislead the consumer.'

The World Health Organization (WHO) issued a monograph on 'Radix Angelicae Sinensis' (WHO, 2002).

'Angelica sinensis root (Angelicae sinensis radix)' is described in a monograph of the European Pharmacopoeia 10.0 (PhEur, 2020). They are defined as the whole or fragmented roots of *Angelica sinensis* (Oliv.) Diels, which have been harvested in late autumn, separated from adventitious roots and dried by smoking.

For human medicinal uses, the European Medicines Agency (EMA) issued an assessment report on *Angelica sinensis* (Oliv.) Diels, radix (EMA, 2013a). A community herbal monograph could not be established since the requirements for the establishment of such a monograph were not fulfilled (EMA, 2013b).

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 dong quai tincture as a feed additive.

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 2.[9]

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the phytochemical markers in the additive. The evaluation report is related to the methods of analysis for each feed additive included the group BDG 02 (Apiales and Austrobaileyales). In particular, for the characterisation of taiga root tincture, the EURL recommended a method based on high-performance liquid chromatography with diode array detection (HPLC-DAD) for the quantification of the phytochemical markers *ferulic acid* and *chlorogenic acid* in *dong quai tincture*.[10]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of dong quai tincture is in line with the principles laid down in Regulation (EC) No 429/2008[11] 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), compendium of botanicals that have been reported to contain toxic, addictive, psychotropic or other substances of concern (EFSA, 2012), guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012b), guidance on the 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

[7] Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Regulation (EC) No 1601/91 of the Council, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34.

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

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

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

[11] 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.

additives (EFSA FEEDAP Panel, 2018), 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), guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (EFSA SC, 2019c), general approach to assess the safety for the target species of botanical preparations which contain compounds that are genotoxic and/or carcinogenic (EFSA FEEDAP Panel, 2021).[12]

3. Assessment

The additive under assessment, dong quai tincture, is obtained from the dried roots of *Angelica sinensis* (Oliv.) Diels. It is intended for use as a sensory additive (functional group: flavouring compounds) for poultry, horses, dogs and cats.

3.1. Origin and extraction

Angelica sinensis (Oliv.) Diels is a perennial herb belonging to the family Apiaceae. It is indigenous to China but was early introduced into other regions of Asia. The dried root is extensively used in the traditional medicines of China and Japan and referred to as dong quai or, in relation to its role in the treatment of gynaecological conditions, as 'female' ginseng. The plant has no culinary uses unlike other species of *Angelica* whose roots and stems may be used to introduce flavour into liqueurs and other alcoholic drinks and the stems candied and used as food decoration.

In the manufacturing process, the roots are cleaned mechanically using water and then dried naturally directly under sunlight.[13] The tincture is obtained by extraction of the dried roots of *A. sinensis* using an ethanol/water mixture (60/40, v/v). The ratio of dry raw material to solvent is 1:5 (w:v). Following maceration for 21 days, the tincture is obtained by pressing to remove solid material and filtration.

3.2. Characterisation

3.2.1. Characterisation of the tincture

The tincture under assessment has a density of 974–987 kg/m^3 (982 kg/m^3 on average).[14] By specification, the product is an ethanol/water (60/40, v/v) solution, which contains 0.001–0.01% 4-hydroxy-3-methoxycinnamic acid (herein referred to as ferulic acid) and 0.0001–0.01% chlorogenic acid. The tincture has a dry matter (DM) content of 5–10%.[15]

Table 1 summarises the results of the proximate analysis of five batches of the additive (of Chinese origin) expressed as % (w/w).[16] The DM content ranged between 5.6 and 8.6 g/100 mL (average 6.6 g/100 mL).[17] Subtraction of the identified gross constituents from the DM content provides an indication of the magnitude in which other components (secondary metabolites) not identified by proximate analysis are present. On average, this represents 0.47 g/100 mL of the tincture or 7.1% of the DM content.

[12] https://www.efsa.europa.eu/sites/default/files/2021-05/general-approach-assessment-botanical-preparations-containing-genotoxic-carcinogenic-compounds.pdf
[13] Technical dossier/Supplementary information July 2022/Annex_II.
[14] Technical dossier/Supplementary information September 2021/Annex_IV_Angelica_Gravitational Analysis_Dry Matter_Density
[15] Technical dossier/Supplementary information September 2021/ SIn reply_dong_quai_tincture.
[16] Technical dossier/Supplementary information September 2021/Annex_III_Angelica_Nutritional Analysis_Microbial_Dioxins and Annex_IV_Angelica_Gravitational Analysis_Dry Matter_Density.
[17] Technical dossier/Supplementary information September 2021/Annex_IV_Angelica_Gravitational Analysis_Dry Matter_Density.

Table 1: Proximate analysis of dong quai tincture (*Angelica sinensis* (Oliv.) Diels) based on the analysis of five batches (mean and range). The results are expressed as % (w/w)

	Mean	Range
	% (w/w)	% (w/w)
Dry matter	6.78	5.62–8.69
Lipids	< 0.3	< 0.3
Protein	0.86	0.5–1.3
Fibre	< 0.5	< 0.5
Sugars	5.06	3.4–7.2
Ash	0.24	0.2–0.3
Solvent (ethanol/water, 60/40, v/v)	93.22	91.31–94.38

The fraction of secondary metabolites was characterised in the same batches of the additive and the results are summarised in Table 2. Phenols determined by spectrophotometry (at λ 760 nm) are expressed as gallic acid equivalents.[18] Individual compounds were determined by high-performance liquid chromatography (HPLC) with ultraviolet (UV) detector: phenolic acids and esters (at 325 nm),[19] organic acids (at 210 nm)[20] and phthalides (at 322 nm).[21] Comparable results for phthalides were obtained when determined by gas chromatography–mass spectrometry (GC–MS).[22] Analytical results are expressed as μg/mL and are shown in Table 2.

The sum of identified secondary metabolites (4,669 μg/mL) accounts on average for 7.0% of the dry matter fraction of the tincture and essentially covers the fraction which could not be identified by the proximate analysis (7.1% of DM).

Table 2: Characterisation of the fraction of secondary metabolites of dong quai tincture (*Angelica sinensis* (Oliv.) Diels) based on the analysis of five batches (mean and range). The results are expressed as μg/mL of dong quai tincture

Constituent	CAS No	FLAVIS No	Mean	Range
			μg/mL	μg/mL
Phenols (total, by photometry)	–		643	491–762
Phenolic acids (HPLC)				
Chlorogenic acid	327-97-9	–	31.7	8.6–57.7
Ferulic acid	1135-24-6	08.089	54.5	34.9–70.7
Coniferyl ferulate	63644-62-2	–	7.9	1.9–12.4
Total hydroxycinnamic acids			94.1	73.3–114.6
Other organic acids				
Oxalic acid	110-17-8	08.025	1,288	896–1,878
Fumaric acid	144-62-7	–	26.5	6.1–72.1
Total other organic acids			1,315	905–1,895
Phthalides (HPLC)				
Senkyunolide I	94596-28-8	–	381	306–520
Senkyunolide H	94596-27-7	–	71.7	54.7–102
(Z)-Ligustilide + *(E)*-Ligustilide	81944-09-4 81944-08-3	–	1,235	713–1,703
3-Butylidenephthalide[(a)]	–	–	55.8	37.2–78.1
Total phthalides (HPLC)			1,743	1,264–2,101

[18] Technical dossier/Supplementary information September 2021/Annex_VI_Angelica_Total_Phenols.
[19] Technical dossier/Supplementary information September 2021/Annex_II_Angelica_HPLC_Analysis_Chlorog Ac._Ferul Ac.Coniferylferulate.
[20] Technical dossier/Supplementary information September 2021/Annex_VII_Angelica_ HPLC_Organic Acids.
[21] Technical dossier/Supplementary information September 2021/Annex_V_Angelica_HPLC_Phthalides_Ligustilide.
[22] Technical dossier/Supplementary information September 2021/Annex_X_dong_quai_tincture_GC-MS.

Constituent	CAS No	FLAVIS No	Mean µg/mL	Range µg/mL
Phthalides (GC–MS)				
3-Butylphthalide	6066-49-5	10.025	36.0	22.1–47.1
(Z)-3-Butylidenephthalide	72917-31-8	–	118.0	92.7–147.2
Senkyunolide A + *(E)*-3-Butylidenephthalide	62006-39-7 76681-73-7	– –	59.8	17.7–116
(Z)-Ligustilide	81944-09-4	–	1,340	920–1,763
(E)-Ligustilide	81944-08-3	–	131.0	65.2–189.4
Senkyunolide I	94596-28-8	–	173.7	125.1–232.2
Senkyunolide H	94596-27-7	–	22.4	16.5–30.2
Total phthalides (GC–MS)			1,881	1,431–2,357
Other constituents (GC–MS)				
Spathulenol	6750-60-3	–	3.0	0–5.8
Hexadecanoic acid	57-10-3	08.014	191.4	165.3–256.7
Ethyl hexadecanoate	628-97-7	09.193	51.2	44.6–63.9
Octadeca-9,12-dienoic acid	60-33-3	08.041	414.8	356.7–471.3
Ethyl octadeca-9,12-dienoate	544-35-4	09.204	156.3	126.8–187.9
Unknown fatty acid derivatives			13.4	10.3–15.1
Total fatty acids			830	733–984
Total identified(b)			4,669	3,861–5,556

(a): named butylidenephthalide in the analytical report, isomers not specified.
(b): considering the sum of total phenols (by photometry), organic acids, total phthalides (by GC–MS) and other organic constituents.

Substances of concern

The applicant made a literature search for the chemical composition of *A. sinensis* (Olive.) Diels and its preparations and the identity of any recognised substances of concern.[23] The occurrence of bergapten, psoralen, safrole and carvacol has been reported (but not quantified) in the essential oil from the roots and other underground parts of *A. sinensis* (EFSA compendium; based on one reference: Teresawa et al., 1985).[24] Carvacrol and safrole were not detected by GC–MS in five batches of the additive under assessment (limit of detection, LOD, 1 mg/kg).

The applicant submitted a certificate of analysis for the screening of coumarins and furocoumarins in dong quai tincture by HPLC with diode array detection (DAD) following a method developed by the international fragrance association method (IFRA).[25] Five standards were used (umbelliferone, scopoletin, xanthotoxin, bergapten and isopimpinellin) and none of these were found in a 10-fold concentrated mixture of the five batches. Six unidentified compounds were detected and were tentatively identified as coumarins based on their UV-spectra. However, these compounds were detected in trace concentrations (i.e. between 0.00004% and 0.0004%) and together accounted for < 0.02% of the DM fraction. A complementary analysis was performed to screen for furocoumarins and other constituents including phthalides using GC–MS.[26] No furocoumarins could be detected (LOD, 1 mg/kg).

Impurities

Data on impurities were provided for three batches of dong quai tincture. Lead (0.003–0.006 mg/kg), cadmium (0.001–0.003 mg/kg) and arsenic (0.007–0.009 mg/kg) were detected in all batches, whereas mercury was below the corresponding limit of quantification (LOQ, 0.002 mg/kg). In the same batches, mycotoxins were below the corresponding LOQ and pesticides were not detected in a multiresidue analysis. When specifically analysed, diethyltoluamide (DEET, 0.07–0.12 mg/L) was detected in all three

[23] Technical dossier/Supplementary information September 2021/Literature search_dong_quai_tincture.
[24] Online version: https://www.efsa.europa.eu/en/data-report/compendium-botanicals.
[25] Technical dossier/Supplementary information September 2021/Annex_IX_dong_quai_tincture_coumarins_HPLC.
[26] Technical dossier/Supplementary information September 2021/Annex_X_dong_quai_tincture_GC-MS.

batches and piperonylbutoxide was < 0.01 mg/kg.[27] Polychlorinated dibenzo-p-dioxin (PCDD) and polychlorinated dibenzofuran (PCDF) were below the corresponding LOQ. The calculated upper bond for the sum of dioxins was 31.6 ng WHO PCDD/F-TEQ (toxic equivalents)/kg, the sum of dioxin and dioxin like polychlorinated biphenyls (PCBs) was 33 ng WHO PCCD/F + PCB TEQ/kg.[28]

Analysis of microbial contamination of five batches of dong quai tincture indicated that *Salmonella* spp. were absent in 25 g, and *E. coli* and *Enterobacteriaceae* were < 1 and < 10 colony forming unit (CFU)/g, respectively.[23]

The detected amounts of the above-reported substances do not raise safety concerns.

3.2.2. Shelf-life

The applicant states that the typical shelf-life of flavourings is at least 12 months, when stored in tightly closed containers under standard conditions. No stability studies were performed.

3.2.3. Conditions of use

Dong quai tincture is intended to be used in water for drinking in poultry species at maximum proposed use levels of 0.5, 0.75 and 0.67 mL/L water for drinking for chickens for fattening, laying hens and turkeys for fattening, respectively (corresponding to 492, 734 and 660 mg tincture/kg water for drinking). It is also intended for use in complete feed for horses, dogs and cats at maximum proposed use levels of 1.0, 0.125 and 0.05 mL tincture/head and day, respectively, corresponding to 123, 481 and 818 mg tincture/kg complete feed.[29]

3.3. Safety

The safety assessment of the additive is based on the highest proposed use levels (see Section 3.2.3).

No studies to support the safety for target animals, consumers and users were performed with the additive under assessment. The applicant submitted a repeated dose (28 days) oral toxicity study in rat performed with an extract (70% ethanol) obtained from the roots of *A. sinensis*, with a content of *(Z)*-ligustilide similar to that of the additive under assessment. The study is described below.

The additive under assessment, dong quai tincture, consists of 93.2% (w/w) of a water/ethanol mixture. The concentration of plant-derived compounds is about 6.8% (w/w) of the tincture. The dry matter included minerals (expressed as ash), protein, lipids and carbohydrates, which are not of concern and are not further considered.

Among the identified secondary plant metabolites, 0.01% (w/w) of the tincture is constituted by hydroxycinnamic acids (three compounds), 0.134% (w/w) by oxalic and fumaric acid and 0.085% (w/w) by fatty acid derivatives (4 compounds). Organic acids including hydroxycinnamic acids, oxalic acid and fumaric acid, as well as fatty acids (e.g. hexadecanoic acid and its ester ethyl hexadecanoate, oleic acid) will be readily metabolised and excreted and are not expected to accumulate in animal tissues and products. They also do not raise concern for genotoxicity. Organic acids including hydroxycinnamic acids, oxalic acid and fumaric acid, as well as fatty acids are not of concern at the present concentration and are not further considered in the assessment.

Eight phthalide derivatives (3-butylphthalide, senkyunolide I, H and A; *(Z)*- and *(E)*-ligustilide, and *(Z)*- and *(E)*-3-butylidenephthalide) have been identified in dong quai tincture and together account on average for 0.178% (w/w, when measured by HPLC-UV) or 0.192% of the tincture (when measured by GC–MS). These phthalide derivatives are structurally related or identical to 3-butylphthalide [10.025], 3-butylidenephthalide [10.024] and 3-propylidenephthalide [10.005]. These compounds have been previously assessed and considered safe for use as flavourings and are currently authorised for

[27] Technical dossier/Supplementary information September 2021/Annex_VIII_Angelica_Heavy Metals, Mycotoxins, Pesticides. LOQ for heavy metals and arsenic: < 0.005 mg/kg for arsenic, < 0.002 mg/kg for mercury and < 0.0004 mg/kg for cadmium; LOQ for individual pesticides: 0.001–0.005 mg/L; LOQ 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 cytrochalasin E and sterigmatocystin, < 5 μg/kg for nivalenol, fusarenon X and diacetoxyscirpenol, and < 10 for deoxynivalenol, deoxynivalenol-3-glycoside, 3-acetyldeoxynivalenol, 15-acetyldeoxynivalenol, citrinin, patulin and fumonisins B1, B2 and B3.

[28] Technical dossier/Supplementary information September 2021/Annex_III_Angelica_Nutritional Analysis_Microbial_Dioxins and Supplementary information July 2022.

[29] Transformation into kg complete feed as provided by the applicant: Technical dossier/Supplementary information September 2021/Annex_XIII.

use in food[30] without limitations and for use in feed[31] at individual use levels higher than those resulting from the intended use of the tincture in feed (EFSA FEEDAP Panel, 2012c).

Information on the absorption, distribution, metabolism and excretion (ADME) and on the toxicology of phthalides is summarised in the next sections, based on the information 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

ADME data available for 3-propylidenephthalide indicate that the γ-lactone is hydrolysed *in vivo* in mammals to 2-(2-hydroxyalkyl)benzoic acid which may be excreted directly, or the side chain oxygenated functional group (alcohol or enolic alcohol) may be oxidised (alcohol) or reduced (enol). The reduced form is subsequently conjugated and excreted. The benzoic acid moiety may conjugate with glycine or other amino acids (e.g. ornithine in birds) and be excreted mainly as the hippurate, while the ketone function may be reduced to the corresponding alcohol and excreted as the glucuronic acid conjugate (EFSA FEEDAP Panel, 2012c). A similar pathway is expected for *(Z)*- and *(E)*-3-butylidenephthalide.

Pharmacokinetic studies are available for senkyunolide A (Yan et al., 2007) and for *(Z)*-ligustilide (Yan et al., 2008). After oral administration to rats, senkyunolide A was rapidly absorbed, but showed a low bioavailability (8%) (Yan et al., 2007). After 100 mg/kg senkyunolide A administration, plasma c_{max} was 1.66 μg/mL at a t_{max} of 0.21 h, being $t_{1/2}$ of 0.52 h. *In vitro* assays performed in simulated gastric and intestinal fluids indicated that senkyunolide A was unstable, resulting in more than 60% loss of the compound, this being partly responsible for its low bioavailability. In S9 and microsomes from rat liver, the compound was partly biotransformed, pointing to a role of first-pass metabolism of the compound, also contributing to its low bioavailability. In the *in vivo* study, five minor metabolites were detected in plasma, although only for 3-butylphthalide, the structure was unequivocally established by HPLC coupled with mass spectrometry (HPLC-MS). Two metabolites were tentatively identified as 11-hydroxysenkyunolide A and 11-hydroxy-3-butylphthalide, and two as glutathione and cysteine conjugates of 7-hydroxysenkyunolide A. The three non-conjugated metabolites were also identified *in vitro*.

(Z)-Ligustilide was rapidly absorbed by rats after oral administration although the bioavailability was very low (2.6%) (Yan et al., 2008). After administration of 500 mg/kg body weight (bw), plasma c_{max} was 343 μg/mL at a t_{max} of 0.36 h, with $t_{1/2}$ of 3.43 h. *In vitro*, extensive biotransformation of *(Z)*-ligustilide was observed in S9 and microsomes of rat liver (more than 90%), pointing to an extensive first pass metabolism. No degradation was observed in simulated gastric and intestinal fluids. Eight metabolites of *(Z)*-ligustilide were detected *in vitro*, three of which were unequivocally characterised by HPLC-MS as 3-butylidenephthalide, senkyunolide I and senkyunolide H. 11-Hydroxyligustilide and two isomers of hydroxyligustilide glutathione conjugate were tentatively identified. *In vivo*, among several putative metabolites detected in plasma, eight were common to those formed *in vitro*.

Overall, the available evidence indicates that both senkyunolide A and *(Z)*-ligustilide are poorly absorbed, extensively metabolised, mainly by oxidative pathway, forming hydroxyl compounds that are presumed to be conjugated and rapidly excreted. Some metabolites are themselves constituents of the tincture (3-butylphthalide, 3-butylidenephthalide, senkyunolide I and senkyunolide H). These compounds, being hydroxylated, are expected to be conjugated and excreted.

3.3.2. Toxicology

3.3.2.1. Genotoxicity

The genotoxic potential for three compounds (senkyunolide I and A; *(Z)*-ligustilide) was predicted using the QSAR Toolbox.[32] Structural alerts were found for all the three compounds (acylation, esters). For these compounds, the mutagenicity (Ames test) prediction was made by read-across analyses of

[30] 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.

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

[32] Technical dossier/Supplementary information September 2021/Annex_XIV_SIn reply_dong_quai_tincture_QSAR.

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 consistently negative for all categories of analogues. On this basis, the alerts raised were discounted. The predictions for senkyunolide I and *(Z)*-ligustilide were considered to apply also to senkyunolide H and *(E)*-ligustilide.

3.3.2.2. Repeated dose toxicity studies

The applicant submitted a repeated dose (28 days) oral toxicity study in rats performed with an extract (70% ethanol) obtained from the dried roots of *A. sinensis* (Lim and Kim, 2014), which showed a content of *(Z)*-ligustilide (1.9%, as % of the DM fraction) similar to that of the tincture under assessment (1.3–2.6%).

A total of 30 male and female Sprague–Dawley rats (five males and five females per group) were given 0 (control, distilled water), 1,000 or 2,000 mg dong quai extract/kg body weight (bw) per day via oral administration for 28 days. The study is claimed to be carried out following the OECD Guideline 407 although several limitations were identified (i.e. mainly no information on rats age/feeding and housing conditions, no sensory activity, haematology and histopathology investigations). No deaths and morbidity and no significant differences in growth (i.e. body weight changes) were observed among the groups. The results for blood chemistry,[33] mean organ weight and necropsy findings revealed no evidence of any treatment-related adverse effects. From this study, the highest dose tested (2,000 mg/kg bw per day) was identified by the authors as the no observed adverse effect level (NOAEL).

The FEEDAP Panel considers that the subacute toxicity study with dong quai extract has several limitations, including the short duration, the low number of animals per group, the lack of data on haematology and histopathology, the lack of information on housing conditions. Therefore, the study can be considered as supporting evidence and an NOAEL from the above-mentioned study cannot be derived.

The FEEDAP Panel notes that an NOAEL of 5.4 mg/kg bw and day, the highest dose tested in a 90-day oral toxicity study in rats (Posternak et al., 1969), was identified by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for 3-propylidenephthalide [10.005] (WHO, 2004). This NOAEL was used by the FEEDAP Panel in the assessment of phthalides in CG 11 (EFSA FEEDAP Panel, 2012c).

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 whose individual components are known is based on the safety assessment of each individual component (component-based approach, EFSA SC, 2019a).

The tincture consists of 93.2% (w/w) of a water/ethanol mixture. The concentration of plant-derived compounds is about 6.8% of the tincture. The dry matter included minerals (ash), protein, lipids and carbohydrates, which are not of concern and are not further considered.

Among the identified secondary plant metabolites, 0.010% (w/w) corresponds to hydroxycinnamic acids, 0.134% (w/w) to organic acids (oxalic acid and fumaric acid), 0.178% (w/w, when measured by HPLC) or 0.192% (w/w, when measured by GC–MS) is constituted by phthalides. Total phenols (expressed as gallic acid equivalents) were estimated around 0.066% of the tincture. Other minor constituents identified in the tincture included spathulenol (0.0003%) and fatty acid derivatives (palmitic acid and linoleic acids and their ethyl esters, 0.085%).

Considering that organic acids, such as oxalic and fumaric acids, hydroxycinnamic acids, fatty acids, are naturally occurring in plants at concentrations much higher than those in dong quai tincture, and are compounds of low toxicity, they are not further considered in the assessment.

The safety assessment is therefore based on phthalides derivatives, which are allocated to the same assessment group, based on considerations related to structural and metabolic similarities, and spathulenol. The allocation of the components to the assessment group phthalides is shown in Table 3.

For hazard characterisation, each component of an assessment group was first assigned to the structural class according to Cramer classification. For some components in the assessment group, toxicological data were available to derive no observed adverse effect level (NOAEL) values. Structural and metabolic similarity among the components in the assessment groups were assessed to explore the application of read-across.

[33] Aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyltransferase (GGT), glucose (GLU), blood urea nitrogen (BUN), alkaline phosphatase (ALP), creatinine (CRE), and total protein (TP).

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.

Toxicological data for subchronic studies, from which NOAEL values could be derived, were available for 3-propylidenephthalide [10.005] (see Section 3.3.2.2). Considering the structural and metabolic similarities, the NOAEL for 3-propylidenephthalide was applied using read-across to the compounds belonging to the class of phthalides.

For spathulenol, toxicity studies were not available and read-across was not possible. Therefore, the threshold of toxicological concern (TTC) approach was applied (EFSA FEEDAP Panel, 2017b). Spathulenol belongs to Cramer class I.

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 mg/kg bw per day for Cramer Class I compounds). Reference points selected for each compound are shown in Table 3.

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 approach to the safety assessment of dong quai tincture for the target species is shown in Table 3, where the calculations are shown for chickens for fattening at the proposed use level of 492 mg tincture/kg water for drinking. For the other species, the outcome for the assessment group 'phthalides' is reported in Table 4.

Table 3: Compositional data, intake values (calculated for chickens for fattening at 492 mg/kg water for drinking), reference points and margin of exposure (MOE) for the individual components of dong quai tincture classified according to assessment group

Tincture composition			Exposure		Hazard characterisation		Risk characterisation	
Assessment group	**FLAVIS-No**	**Highest conc. in the tincture**	**Highest conc. water**	**Intake[a]**	**Cramer class[b]**	**NOAEL[c]**	**MOE**	**MOET**
Constituent	–	**(μg/mL)**	**mg/L**	**mg/kg bw**	–	**mg/kg bw**	–	–
Phthalides								
3-Butylphthalide	10.025	47	0.023	0.0062	(III)	5.4	865	
(Z)-3-Butylidenephthalide	–	147	0.072	0.0195	(III)	5.4	277	
Senkyunolide A + *(E)*-3-Butylidenephthalide	–	116	0.057	0.0154	(III)	5.4	351	
(Z)-Ligustilide	–	1763	0.867	0.2336	(III)	5.4	23	
(E)-Ligustilide	–	189	0.093	0.0251	(III)	5.4	215	
Senkyunolide I	–	232	0.114	0.0308	(III)	5.4	176	
Senkyunolide H	–	30	0.015	0.0040	(III)	5.4	1,348	
MOET								16
Other constituents								
Spathulenol	–	5.8	0.003	0.0008	I	*3*	3,773	

(a): Intake calculations for the individual components are based on the use level of 492 mg tincture/kg water for drinking for chickens for fattening, assuming a water intake threefold higher than feed intake. 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 an 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.

Table 4: The combined margin of exposure (MOET) for phthalides calculated for the different target animal categories at the proposed use level of the additive in water for drinking or in feed and maximum safe use levels of the additive calculated to ensure a MOET ≥ 100 (500 for cats)

Animal category	Body weight	Water intake[(a)]	Proposed use level	MOET	Maximum safe use level
	(kg)	(g/day)	(mg additive/kg water)		(mg additive/kg water)
Chicken for fattening	2	474	492	16	79
Laying hen	2	318	734	16	117
Turkey for fattening	3	528	660	16	106
		Feed intake	**(mg additive/kg feed)**		**(mg additive/kg feed)**
Horse	400	8,000	123	755	–
Dog	15	250	481	231	–
Cat	3	60	818	113	184[(b)]

(a): Calculated from the default values for feed intake (EFSA FEEDAP Panel, 2017b) assuming a water intake threefold higher than feed intake (EFSA FEEDAP Panel, 2010).
(b): For cats, the maximum safe level in feed is calculated to ensure an MOET > 500, because of the reduced capacity of glucuronidation.

As shown in Table 4, for poultry species at the proposed use levels in water for drinking a MOET of 16 was calculated for the assessment group phthalides assuming that the water intake is up to threefold higher than feed intake. For poultry species, the maximum safe use level in water for drinking was recalculated in order to ensure an MOET ≥ 100 (Table 4). For the other species (horses, dogs and cats), the MOET for the assessment group phthalides was calculated at the proposed use levels in feed. For cats, considering their unusually low capacity for glucuronidation of compounds (Court and Greenblatt, 1997; Lautz et al., 2021), the maximum safe use level in feed was recalculated in order to ensure an MOET > 500.

3.3.3.1. Conclusions on safety for the target species

The additive is safe for horses and dogs at the maximum proposed use level of 123 and 481 mg/kg complete feed, respectively. For cats, the calculated safe concentration is 184 mg/kg complete feed. For the poultry species, the calculated safe concentration in water for drinking is 79 mg/kg for chickens for fattening, 117 mg/kg for laying hens and 106 mg/kg for turkeys for fattening.

3.3.4. Safety for the consumer

There is no evidence for the use in food of dong quai tincture from *A. sinensis* in the Fenaroli's Handbook of Flavour Ingredients; however, '*Angelica*' roots, seeds and stems, originating from *Angelica archangelica* L., and their preparations are recognised to flavour food (Burdock, 2009). The WHO monograph and the commentary of the PhEur describes the root of *A. sinensis* as having a strong characteristic aromatic flavour with a sweet, pungent and slightly bitter taste. In addition, several components of the tincture are authorised food and feed flavourings.

No data on residues in products of animal origin following the use of the tincture under assessment were made available. The phenolic compounds, including hydroxycinnamic acids, present in the additive at concentrations below the thresholds for Cramer Class I compounds, will be readily metabolised and excreted and are not expected to accumulate in animal tissues and products. For phthalides, the available data indicate that they are poorly absorbed, metabolised and rapidly excreted, and consequently, they are not expected to accumulate in animal tissues and products (see Section 3.3.1). Therefore, a relevant increase of the uptake of the individual constituents by humans consuming products of animal origin is not expected.

Consequently, no safety concern would be expected for the consumer from the use of dong quai tincture up to the use level in feed considered safe for the target animals.

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[34] concerning the presence of ethanol in the tincture.[35]

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

3.3.6. Safety for the environment

A. sinensis is not native to Europe. Organic acids (oxalic acid and fumaric acid), phenols (including hydroxycinnamic acids) and fatty acids are components which are present in many plants indigenous of Europe. At the maximum proposed use level of 123 mg/kg complete feed for horses, the concentration of total phthalides in feed would be < 0.3 mg/kg. For poultry species, the concentration of phthalides resulting from the use of the additive in water for drinking at the concentrations considered safe for the target species would be in the range 0.19–0.28 mg/kg water for drinking. Since the concentration of total phthalides in feed is below 0.5 mg/kg, the threshold below which the trigger value for the predicted environmental concentration (PEC_{soil}) of 10 μg/kg is not exceeded, the use of the dong quai tincture from *A. sinensis* as a flavour in animal feed is not expected to pose a risk for the environment.

3.4. Efficacy

Angelica sinensis is not listed in the Fenaroli's Handbook of Flavour Ingredients or by FEMA as a flavouring agent.

However, the WHO monograph (WHO, 2002) and the Comments on the PhEur (2019) indicate that the root of *Angelica sinensis* has flavouring properties (a strong characteristic aromatic flavour with a sweet, pungent and slightly bitter taste). In addition, several individual components of the tincture are recognised food and feed flavourings. Overall, the FEEDAP Panel considers that *A. sinensis* can influence sensory properties of feedingstuffs.

4. Conclusions

Dong quai tincture from *Angelica sinensis* (Oliv.) Diels may be produced from plants of different origins and by various processes resulting in preparations with different composition and toxicological profiles. Thus, the following conclusions apply only to dong quai tincture which contains ≤ 1 mg/kg safrole and furocoumarins and is produced by ethanol/water extraction from the roots of *A. sinensis*.

The additive is safe for horses and dogs at the maximum proposed use level of 123 and 481 mg/kg complete feed, respectively. For cats, the calculated safe concentration is 184 mg/kg complete feed. For the poultry species, the calculated safe concentration in water for drinking is 79 mg/kg for chickens for fattening, 117 mg/kg for laying hens and 106 mg/kg for turkeys for fattening.

No safety concern would arise for the consumer from the use of dong quai tincture in animal nutrition up to the highest safe levels in feeds.

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

The use of dong quai tincture as a flavour in animal feed is not considered to be a risk for the environment.

Since the root of *A. sinensis* has flavouring properties and its 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.

5. Recommendations

The specification should ensure that the concentration of safrole and furocoumarins should be as low as possible and should not exceed 1 mg/kg dong quai tincture.

[34] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging 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. 1–1,355*.

[35] Technical dossier/Supplementary information September 2021/Annex_XV_SIn reply_dong_quai_tincture_MSDS. H319: moderate eye irritation.

6. 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: characterisation, 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
07/09/2021	Reception of supplementary information from the applicant (partial dataset on dong quai tinture) - Scientific assessment remains suspended
27/09/2022	Reception of supplementary information from the applicant (clarifications on dong quai tinture) - Scientific assessment remains suspended
16/09/2022	The application was split and a new EFSA-Q-2022-00568 was assigned to the preparation included in the present assessment
31/10/2022	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives - Scientific assessment re-started
22/11/2022	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment for the preparation included in the present assessment. The assessment of other preparations is still ongoing

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Abbreviations

ADME	Absorption, distribution, metabolism and excretion
BDG	botanically defined group
bw	body weight
CAS	Chemical Abstracts Service
CD	Commission Decision
CDG	chemically defined group
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CFU	colony-forming unit
CG	chemical group
CV	coefficient of variation
DAD	diode array detection
DEET	diethyltoluamide
DM	dry matter
ECHA	European Chemicals Agency
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
FEMA	Flavour and Extract Manufactures Association
FFAC	Feed Flavourings authorisation Consortium of FEFANA (EU Association of Specialty Feed Ingredients and their Mixtures)
FGE	food group evaluation
FLAVIS	The EU Flavour Information System
FL-No	FLAVIS number
HPLC	high performance liquid chromatography
HPLC-MS	high performance liquid chromatography-mass spectrometry
IFRA	International Fragrance Association
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LOD	limit of detection
LOQ	limit of quantification
MOE	margin of exposure
MOE(T)	(Combined) margin of exposure
MW	molecular weight
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PCBs	polychlorinated biphenyls

PCDD	polychlorinated dibenzo-p-dioxin
PCDF	and polychlorinated dibenzofuran
PEC	predicted environmental concentration
PhEur	European Pharmacopoeia
QSAR	Quantitative Structure–Activity Relationship
RH	relative humidity
sb	solvent-based
SC	EFSA Scientific Committee
TEQ	toxic equivalent
TTC	threshold of toxicological concern
UF	uncertainty factor
UV	ultraviolet
WHO	World Health Organization