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Safety of 37 feed additives consisting of flavouring compounds belonging to different chemical groups for use in all animal species (FEFANA asbl)

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Abstract

Following a request from the European Commission, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the supplementary information submitted on the safety of 37 compounds belonging to different chemical groups, when used as sensory additives (flavourings) in feed for all animal species formerly assessed by the Panel in the context of the re-evaluation of these feed additives. The FEEDAP Panel concludes that ethyl oleate [09.192] and benzyl cinnamate [09.738] are safe at the proposed use level of 5 mg/kg complete feed for all animal species, the consumer and the environment; ethyl salicylate [09.748] is safe up to the maximum proposed use level of 5 mg/kg complete feed for all animal species and the consumer. No new data were submitted on the safety for the user that would allow the FEEDAP Panel to change its previous conclusion for 26 out of the 37 compounds under assessment. The use of 4-terpinenol [02.072], linalyl butyrate [09.050], linalyl formate [09.080], linalyl propionate [09.130], linalyl isobutyrate [09.423], isopulegol [02.167] and 1,2-dimethoxy-4-(prop-1-enyl)-benzene [04.013] as flavouring additives at the proposed use level of 5 mg/kg in feed for all animal species is considered safe for the environment. The use of 3-methyl-2-cyclopenten-1-one [07.112] at 0.5 mg/kg and methyl dihydrojasmonate [09.520] at 5 mg/kg in feed for all animal species except marine animals is considered safe for the environment.

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Keywords: sensory additives, flavourings, chemical groups, safety, read-across

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1. Introduction

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

Regulation (EC) No 1831/2003¹ establishes the rules governing the Community authorisation of additives for use in animal nutrition and, in particular, Article 9 defined the term of the authorisation by the Commission.

The applicant, FEFANA asbl, is seeking a Community authorisation of 37 products (ethyl oleate, nona-2,6-dien-1-ol, pent-2-en-1-ol, tr-2,cis-6 nonadien-1-ol, 2-dodecenal, nona-2(trans),6(cis)-dienal, nona-2,4-dienal, trans-2-nonenal, 2,4-decadienal, hepta-2,4-dienal, deca-2(trans),4(trans)-dienal, dodec-2(trans)-enal, hept-2(trans)-enal, non-2-enal, nona-2(trans),6(trans)-dienal, undec-2(trans)-enal, trans-2-octenal, trans-2-decenal, tr-2, tr-4-nonadienal, tr-2, tr-4-undecadienal, hex-2(trans)-enyl acetate, hex-2-enyl butyrate, oct-1-en-3-one, 4-terpineol, linalyl butyrate, linalyl formate, linalyl propionate, linalyl isobutyrate, isopulegol, 3-methyl-2-cyclopenten-1-one, methyl 3-oxo-2-pentyl-1-cyclopentylacetate, benzophenone, benzyl cinnamate, ethyl salicylate, 1,2-dimethoxy-4-(prop-1-enyl)-benzene, myrcene and β -ocimene) as feed additives to be used as flavourings compounds for all animal species except in case of methyl 3-oxo-2-pentylacetate and 3-methyl-2-cyclopenten-1-one for which the opinion is requested for all animal species except marine animals (Table 1).

Table 1: Description of the additives

Category of additive	Sensory additive
Functional group of additives	Flavouring compounds
Description	Ethyl oleate Nona-2,6-dien-1-ol Pent-2-en-1-ol tr-2, cis-6 Nonadien-1-ol 2-Dodecenal Nona-2(trans),6(cis)-dienal Nona-2,4-dienal trans-2-Nonenal 2,4-Decadienal Hepta-2,4-dienal Deca-2(trans),4(trans)-dienal Dodec-2(trans)-enal Hept-2(trans)-enal Non-2-enal Nona-2(trans),6(trans)-dienal Undec-2(trans)-enal trans-2-Octenal trans-2-Decenal tr-2, tr-4-Nonadienal tr-2, tr-4-Undecadienal Hex-2(trans)-enyl acetate Hex-2-enyl butyrate Isopulegol Oct-1-en-3-one 4-Terpineol Linalyl butyrate Linalyl formate Linalyl propionate Linalyl isobutyrate 3-Methyl-2-cyclopenten-1-one Methyl 3-oxo-2-pentyl-1-cyclopentylacetate
	Benzophenone Benzyl cinnamate Ethyl salicylate 1,2-Dimethoxy-4-(prop-1-enyl)-benzene

¹ Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

Category of additive	Sensory additive
	Myrcene β-Ocimene
Target animal category	All animal species, except in case of methyl 3-oxo-2-pentylacetate and 3-methyl-2-cyclopenten-1-one for which the opinion is requested for all animal species except marine animals
Applicant	FEFANA asbl
Type of request	New opinion

On 25 April 2021, 13 June 2012, 13 November 2012, 12 March 2013, 1 December 2015, 20 April 2016, 28 February 2019, 10 January 2020 and 28 January 2020, the Panel on Additives and Products or Substances used in Animal Feed of the European Food Safety Authority ("EFSA"), in its opinions on the safety and efficacy of the products (see Table 2), could not conclude on the safety of the 37 flavouring compounds as feed additives for all animal species due to different aspects related to safety for human health, animal health or the environment.

The Commission gave the possibility to the applicant to submit complementary information in order to complete the assessment and to allow a revision of Authority's opinion. The new data have been received on 4 May 2021.

In view of the above, the Commission asks the Authority to deliver a new opinion on the above-mentioned 37 compounds listed in Table 2 as feed additives for all animal species, except in case of methyl 3-oxo-2-pentylacetate and 3-methyl-2-cyclopenten-1-one for which the opinion is requested for all animal species except marine animals, based on the additional data submitted by the applicant, in accordance with Article 29(1) of Regulation (EC) No 178/2002.

The aspects on which the applicant has submitted information and for which a new opinion is requested, the species affected and the use level are indicated in the table below (Table 2).

Table 2: Flavouring compounds (FLAVIS number and EU register name) under assessment, use levels in feed (mg/kg) proposed for the evaluation and aspects for which applicant has submitted supplementary information to be examined by EFSA and species for which the data are intended for

FLAVIS no	Name in EU register of feed additives	Use level (mg/kg) proposed for the evaluation	Aspects for which applicant has submitted supplementary information to be examined by EFSA and species for which the data are intended for
09.192	Ethyl oleate	5	Animal safety, consumer and environmental safety for all animal species (purity and exact composition was not available to conclude on safety)
02.049	Nona-2,6-dien-1-ol	1	User safety all animal species
02.050	Pent-2-en-1-ol	5	User safety all animal species
02.231	tr-2,cis-6 Nonadien-1-ol	1	User safety all animal species
05.037	2-Dodecenal	5	User safety all animal species
05.058	Nona-2(trans),6(cis)-dienal	1	User safety all animal species
05.071	Nona-2,4-dienal	5	User safety all animal species
05.072	trans-2-Nonenal	5	User safety all animal species
05.081	2,4-Decadienal	5	User safety all animal species
05.084	Hepta-2,4-dienal	5	User safety all animal species
05.140	Deca-2(trans),4(trans)-dienal	5	User safety all animal species
05.144	Dodec-2(trans)-enal	5	User safety all animal species
05.150	Hept-2(trans)-enal	5	User safety all animal species
05.171	Non-2-enal	5	User safety all animal species
05.172	Nona-2(trans),6(trans)-dienal	1	User safety all animal species
05.184	Undec-2(trans)-enal	5	User safety all animal species

FLAVIS no	Name in EU register of feed additives	Use level (mg/kg) proposed for the evaluation	Aspects for which applicant has submitted supplementary information to be examined by EFSA and species for which the data are intended for
05.190	trans-2-Octenal	5	User safety all animal species
05.191	trans-2-Decenal	5	User safety all animal species
05.194	tr-2, tr-4-Nonadienal	5	User safety all animal species
05.196	tr-2, tr-4-Undecadienal	5	User safety all animal species
09.394	Hex-2(trans)-enyl acetate	5	User safety all animal species
09.396	Hex-2-enyl butyrate	5	User safety all animal species
02.067	Isopulegol	Cats:1 Other species: 5	User safety and environmental safety all animal species
07.081	Oct-1-en-3-one	Cats:1 Other species: 5	User safety all animal species
02.072	4-Terpineol	5	Environmental safety all animal species
09.050	Linalyl butyrate	5	Environmental safety all animal species
09.080	Linalyl formate	5	Environmental safety all animal species
09.130	Linalyl propionate	5	Environmental safety all animal species
09.423	Linalyl isobutyrate	5	Environmental safety all animal species
07.112	3-Methyl-2-cyclopenten-1-one	Cattle and non-food producing animals 0.5 Pigs and poultry: 0.3 Fresh water fish: 0.5	Environmental safety all animal species, except marine animals
09.520	Methyl 3-oxo-2-pentyl-1-cyclopentylacetate	Other species: 5	Environmental safety all animal species, except marine animals
07.032	Benzophenone	Chickens for fattening, laying hens and piglets: 0.5 Other species: 1	User safety all animal species
09.738	Benzyl cinnamate	5	Animal safety (NOEL), consumer and environmental safety for all animal species
09.748	Ethyl salicylate	5	Safety for humans and animals taking into account that the levels proposed as flavourings is higher than the estimated LOEL for animals and for humans
04.013	1,2-Dimethoxy-4-(prop-1-enyl)-benzene	5	Environmental safety all animal species
01.008	Myrcene	Cats: 4 Other species: 5	User safety all animal species
01.018	β -Ocimene	Cats: 4 Other species: 5	User safety all animal species

1.2. Additional information

The list of the 37 flavouring compounds currently authorised for food² and feed³ uses together with the EU Flavour Information System (FLAVIS) number, the chemical group as defined in Commission Regulation (EC) No 1565/2000⁴ and the corresponding EFSA opinion is given in Table 3.

Table 3: Flavouring compounds under assessment, grouped according to the chemical group (CG) as defined in Commission Regulation (EC) No 1565/2000², with indication of the EU Flavour Information System (FLAVIS) number and the corresponding FEEDAP opinion

CG	Chemical group	Product (EU register name)	FLAVIS no	Year
01	Straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters with esters containing saturated alcohols and acetals containing saturated aldehydes	Ethyl oleate	09.192	2013
03	a, β -Unsaturated (alkene or alkyne) straight-chain and branched-chain aliphatic primary alcohols/aldehydes/ acids, acetals and esters	Nona-2,6-dien-1-ol	02.049	2019a
		Pent-2-en-1-ol	02.050	
		trans-2,c is-6 Nonadien-1-ol	02.231	
		2-Dodecenal	05.037	
		Nona-2(trans),6(cis)-dienal	05.058	
		Nona-2,4-dienal	05.071	
		trans-2-Nonenal	05.072	
		2,4-Decadienal	05.081	
		Hepta-2,4-dienal	05.084	
		Deca-2(trans),4(trans)-dienal	05.140	
		Dodec-2(trans)-enal	05.144	
		Hept-2(trans)-enal	05.150	
		Non-2-enal	05.171	
		Nona-2(trans),6(trans)-dienal	05.172	
		Undec-2(trans)-enal	05.184	
		trans-2-Octenal	05.190	
		trans-2-Decenal	05.191	
trans-2, trans-4-Nonadienal	05.194			
trans-2, trans-4-Undecadienal	05.196			
Hex-2(trans)-enyl acetate	09.394			
Hex-2-enyl butyrate	09.396			
05	Saturated and unsaturated aliphatic secondary alcohol/ketones/esters with esters containing secondary alcohols	Oct-1-en-3-one	07.081	2020a
06	Aliphatic alcohols	4-Terpineol	02.072	2012a
		Linalyl butyrate	09.050	
		Linalyl formate	09.080	
		Linalyl propionate	09.130	
		Linalyl isobutyrate	09.423	

² 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.

³ 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

⁴ 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 180, 19.7.2000, p. 8.

CG	Chemical group	Product (EU register name)	FLAVIS no	Year
08	Secondary alicyclic saturated and unsaturated alcohols, ketones, ketals and esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols	Isopulegol	02.067	2020a
		3-Methyl-2-cyclopenten-1-one	07.112	2016a
		Methyl 3-oxo-2-pentyl-1-cyclopentylacetate (methyl dihydrojasmonate)	09.520	
21	Aromatic ketones, secondary alcohols and related esters	Benzophenone	07.032	2020b
23	Benzyl alcohols, aldehydes, acids, esters and acetals	Benzyl cinnamate	09.738	2012b
		Ethyl salicylate	09.748	
26	Aromatic ethers including anisole Derivatives	1,2-Dimethoxy-4-(prop-1-enyl)-benzene	04.013	2012c
31	Aliphatic and aromatic hydrocarbons and acetals containing saturated aldehydes	Myrcene	01.008	2016b
		β -Ocimene	01.018	

In the context of the re-evaluation of feed flavourings, the FEEDAP Panel issued 39 opinions dealing with 568 compounds. For about 35% of the compounds assessed, in the absence of data (tolerance studies and/or toxicological studies with the additives under assessment from which a no observed adverse effect level (NOAEL) could be derived) or because of the unsuitability of the available toxicological data, the FEEDAP Panel could not conclude on the safety for target animals of the compounds at the maximum use level proposed by the applicant. For a number of compounds (about 9%, 49 compounds) in the absence of specific studies to assess the safety for the user, the FEEDAP Panel cannot conclude on the safety for the users when handling the additives.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of supplementary information to previous applications on the same products.⁵

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment regarding the methods used for the control of the chemically defined groups in animal feed are valid and applicable for the current application.⁶

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of active substance (trade name of the product) is in line with the principles laid down in Regulation (EC) No 429/2008⁷ and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012d); Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a); Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b); Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017c); Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019b).

⁵ FEED dossiers' reference: FAD-2010-0015, FAD-2010-0025, FAD-2010-0028, FAD-2010-0054, FAD-2010-0125, FAD-2010-0411, FAD-2010-0412, FAD-2010-0414, FAD-2010-0416, FAD-2010-0417.

⁶ The full report is available on the EURL website: <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0015.pdf>; <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0022.pdf>; <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0025.pdf>; <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0028.pdf>; <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0054.pdf>; <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0074.pdf>; <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0075.pdf>; <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0124.pdf>; <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0125.pdf>.

⁷ 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.

3. Assessment

The additives under assessment are 37 compounds belonging to several chemical groups, namely CG 01, 03, 05, 06, 08, 21, 23, 26 and 31, intended for use as sensory additives (functional group: flavouring compounds) in feed for all animal species.⁸

In previous opinions of the FEEDAP Panel (EFSA FEEDAP Panel, 2012a,b,c, 2013, 2016a,b, 2019a,b, 2020a,b), the 37 additives under assessment were fully characterised, with the exception of ethyl oleate [09.192], and evaluated for their safety and efficacy as flavouring substances. Ethyl oleate was excluded from further assessment. For benzyl cinnamate [09.738], the FEEDAP Panel could not conclude on the safety for target animals at the maximum use level proposed by the applicant. The Panel, however, was able to identify a safe use level for all animal species, lower than the maximum proposed use level, based on the application of the Threshold of Toxicological Concern (TTC) approach. The Panel also concluded that no safety concern would arise for the consumer or the environment from the use of this compound at the levels considered safe for the target species. For ethyl salicylate [09.748], the FEEDAP Panel already concluded that it is safe at the maximum proposed use level of 5 mg/kg complete feed for all animal species, the consumer and the environment. However, the authorisation was denied because of the similarity of ethyl salicylate with acetyl salicylic acid and the potential medicinal effects at the proposed intake levels as flavouring. Additionally, it was argued that the exposure of the target animals via the use of ethyl salicylate as a feed flavouring is higher than the estimated low observed effect level (LOEL) of 0.167 mg/kg body weight (bw) per day, which was identified for animals and humans by the European Medicines Agency (EMA) in the evaluation of acetyl salicylic acid for veterinary use (EMA, 1999).

For 26 compounds belonging to CGs 03, 05, 08, 21 and 31, no studies to assess the safety for the user were submitted for previous assessments. Therefore, the FEEDAP Panel could not conclude on the safety for the users when handling the additive at that time (EFSA FEEDAP Panel, 2016b, 2019a,b, 2020a,b).

In earlier evaluations, the FEEDAP Panel could not conclude on the safety for the aquatic compartment for five compounds in CG 06 (EFSA FEEDAP Panel, 2012a) and on the safety for the terrestrial compartment for one compound in CG 08 (EFSA FEEDAP Panel, 2016a). For three compounds, methyl 3-oxo-2-pentyl-1-cyclopentylacetate (herein referred to as methyl dihydrojasmonate) [09.520], benzyl cinnamate [09.738] and 1,2-dimethoxy-4-(prop-1-enyl)-benzene [04.013] the Panel had concluded on the safety for the environment at lower use levels (EFSA FEEDAP Panel, 2012b,c, 2016a).

The applicant has provided new data to address the limitations identified in the previous assessments. The new data submitted consist of (i) analytical data for ethyl oleate [09.192], (ii) a proposal for read-across for benzyl cinnamate [09.738], (iii) arguments to confirm the safety of ethyl salicylate [09.748] at the proposed use levels, (iv) evidence of the natural occurrence of 4-terpinenol [02.072], linalyl butyrate [09.050], linalyl formate [09.080], isopulegol [02.067], oct-1-en-3-one [07.081] in European plants in concentrations higher than 5 mg/kg, (v) revised calculations for the safety for the environment for 3-methyl-2-cyclopenten-1-one [07.112], methyl dihydrojasmonate [09.520] and 1,2-dimethoxy-4-(prop-1-enyl)-benzene [04.013]. No new data were submitted on the safety for the user.

The additives are intended for use in feed for all animal species, except in case of methyl 3-oxo-2-pentylacetate [09.520] and 3-methyl-2-cyclopenten-1-one [07.122], for which the opinion is requested for all animal species except marine animals. The use levels for the present assessment are summarised in Table 2.

3.1. Ethyl oleate

Ethyl oleate [09.192] belongs to chemical group 01. In its previous assessment, the FEEDAP Panel was unable to perform an assessment of the safety of ethyl oleate for the target species, the consumer and the environment because of insufficient purity (EFSA FEEDAP Panel, 2013). The applicant has now provided analytical data which include the full characterisation of the additive and show compliance with the proposed specification.

⁸ All animal species, except in case of methyl 3-oxo-2-pentylacetate and 3-methyl-2-cyclopenten-1-one for which the opinion is requested for all animal species except marine animals.

3.1.1. Characterisation of ethyl oleate

Ethyl oleate (synonyms: 9-octadecenoic acid (Z)-, ethyl ester oleic acid, ethyl ester; ethyl cis-9-octadecenoate; ethyl Z-9 octadecenoate) is a colourless to light-yellow oily liquid, with a characteristic floral odour. Ethyl oleate is identified by the Chemical Abstract Service (CAS) number 111-92-6 and with the FLAVIS number [09.192]. It has a molecular formula of $C_{20}H_{38}O_2$ and a molecular weight of 310.5 g/mol. Ethyl oleate is produced by chemical synthesis, e.g. by direct esterification of oleic acid with ethyl alcohol in the presence of hydrochloric or sulfuric acid. The routes of synthesis are described in the dossier.⁹

Ethyl oleate [09.192] is authorised for use in food as flavouring with a purity of at least 99%, as specified by the Joint Food and Agriculture Organization of the United Nations (FAO/WHO) Expert Committee on Food Additives (JECFA) (FAO, 2006). In the original application as feed flavouring, ethyl oleate [09.192] was specified to contain a minimum of 60% ethyl oleate plus unknown amounts of the ethyl derivatives of other fatty acids.

The applicant has now provided analytical data on five batches of the additive which showed compliance with the specification, with a content of ethyl oleate in the range 76.6–85.9%. The applicant provided the full characterisation of the fatty acids profile of the same five batches of the additive by gas chromatography with flame ionisation detector (GC-FID). The main secondary components were cis-linoleic acid (C18:2, 9.9–14.2%), trans-oleic acid (C18:1, 4.0–5.8%), stearic acid (C18:0, 2.15–3.8%), trans-linoleic acid (C18:2, 0.6–3.2%) and palmitic acid (C16:0, 0.2–1.5%).¹⁰ No other impurities were identified. The additive is now considered fully characterised.

The applicant states that potential contaminants are considered as part of the product specification and are monitored as part of the Hazard Analysis and Critical Control Point procedure applied by all consortium members. The parameters considered include residual solvents, heavy metals and other undesirable substances. However, no evidence of compliance was provided for these parameters.

The shelf-life for the compound under assessment is at least 6 months when stored in closed containers under recommended conditions. This assessment is made on the basis of compliance with the original specification over this storage period.

3.1.2. Safety

In the new data submitted, ethyl oleate has been sufficiently characterised and no substances of concern were identified. Ethyl oleate is expected to be hydrolysed to oleic acid and ethanol. Odd numbered straight chain fatty acids are cleaved by beta-oxidation to yield propionyl-CoA, which is further metabolised via methylmalonyl CoA to succinyl CoA, an intermediate of the tricarboxylic acid cycle, which is finally converted to CO_2 . Therefore, the fatty acid moiety of ethyl oleate is not of concern (it is considered a nutrient) and the safety assessment of ethyl oleate is driven by the presence of ethanol.

In the assessment of the safety for the target species of compounds belonging to CG 01, the Panel concluded that ethyl esters with fatty acids with chain lengths from C1 to C14 are safe at the proposed use level of 5 mg/kg complete feed for all animal species, based on a group NOAEL of 1,730 mg/kg body weight (bw) per day for ethanol. Based on the same NOAEL, safe concentrations in feed for the target species were derived for ethyl oleate following the EFSA Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), resulting in concentrations ranging from 193 mg/kg complete feed (chickens for fattening) and 3,383 mg/kg (ornamental fish). Therefore, it is concluded that ethyl oleate is safe at 5 mg/kg complete feed for all animal species.

Regarding the safety for the consumer of all compounds belonging to CG 01, the FEEDAP Panel concluded that 'Straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters with esters containing saturated alcohols, and acetals containing saturated aldehydes are rapidly absorbed, distributed, metabolised and excreted. Mammals, birds and fish share a similar metabolic capacity to handle these compounds. Consequently, no safety concern would arise for the consumer from the use of these compounds up to the highest safe level in feeds' (EFSA FEEDAP Panel, 2013). The same conclusion is extended to ethyl oleate.

Regarding the safety for the environment of all compounds belonging to CG 01, the FEEDAP Panel concluded that 'The compounds considered to be safe for the target species are extensively metabolised by the target species and excreted as innocuous metabolites and carbon dioxide.

⁹ Technical dossier FAD-2010-0015/Section II.

¹⁰ Technical dossier/Annex_1_CDG01_09_192_CoAs.

Therefore, no risk for the safety for the environment is foreseen' (EFSA FEEDAP Panel, 2013). The same conclusion is extended to ethyl oleate [09.192].

3.1.3. Conclusions

The FEEDAP Panel concludes that ethyl oleate [09.192] is safe at the proposed use level of 5 mg/kg complete feed for the target species, the consumer and the environment.

3.2. Benzyl cinnamate

3.2.1. Safety for the target species, the consumer and the environment

Benzyl cinnamate [09.738] belongs to CG 23. In its previous assessment of benzyl cinnamate, in the absence of tolerance and/or toxicological studies, the FEEDAP Panel could not conclude on the safety for the target species, the consumer and the environment at the maximum proposed use level of 5 mg/kg but identified lower safe levels based on the application of the TTC approach. The applicant provided (i) arguments based on the metabolism of benzyl cinnamate to justify a proposal for read-across from cinnamic acid and (ii) a reference point for cinnamic acid (not available at the time of the previous assessment).

Benzyl cinnamate [09.738] is expected to be hydrolysed to cinnamic acid and benzyl alcohol, which is then oxidised to benzoic acid and excreted as hippuric acid. Benzoic acid and benzyl alcohol were considered safe up to 125 mg/kg complete feed (EFSA FEEDAP Panel, 2012b). The Panel on Food Additives and Flavourings (FAF) evaluated benzyl alcohol (E 1519) when used as a food additive and concluded that benzyl alcohol is of low acute toxicity with no concern with respect to genotoxicity and carcinogenicity. The FAF Panel established an acceptable daily intake (ADI) of 4 mg/kg bw per day based on a no observed adverse effect level (NOAEL) of 400 mg/kg bw per day from a carcinogenicity study in rats (EFSA FAF Panel, 2019). The applicant also refers to the assessment of cinnamic acid [08.022] in CG 22, for which an NOAEL of 275 mg/kg bw per day has been established (EFSA FEEDAP Panel, 2017d). Considering the metabolism of benzyl cinnamate, and the toxicity of its metabolites, the NOAEL of cinnamic acid was used to calculate safe concentrations in feed for the target species following the EFSA Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), resulting in concentrations ranging from 31 mg/kg complete feed (chickens for fattening) to 538 mg/kg (ornamental fish). The FEEDAP Panel concludes that benzyl cinnamate is safe for all animal species at 5 mg/kg complete feed.

Regarding the safety for the consumer of the compounds belonging to CG 23, the FEEDAP Panel concluded that for benzoates, benzyl derivative and salicylates 'no safety concern would arise for the consumer from the use of these compounds up to the highest safe level identified in feeds', based on a TTC approach. In laboratory animals, the absorption, metabolism and excretion of benzyl acetate were apparently unaffected by the size or number of doses administered as no evidence of a reduction or saturation of the metabolic capacity was observed as the dose increased. Similarly, the beta-oxidation of cinnamic acid [08.022] was shown not to be limited at doses up to 400 mg/kg bw per day in male rats (EFSA FEEDAP Panel, 2017d). Therefore, it is expected that the previous conclusion that benzyl cinnamate is safe for consumers based on the metabolism of benzyl cinnamate would also apply at the maximum proposed use level of 5 mg/kg complete feed.

Concerning the safety for the environment, the FEEDAP Panel for CG 23 concluded that benzyl derivatives are converted in the target species to benzoic acid, which is then excreted in conjugated form. The conjugate can be converted back to benzoic and so benzoates occur in nature in free and combined forms. Both are readily biodegradable and possess low ecotoxicity (European Commission, 2002). Consequently, the use of benzyl cinnamate as a flavour in feed is not expected to adversely affect the environment (EFSA FEEDAP Panel, 2012b). For cinnamic acid [08.022], evidence from the published literature showed that it occurs in the environment at levels above the application rate of 5 mg/kg (EFSA FEEDAP Panel, 2017d).

Therefore, it is expected that the conclusions reached in the previous assessment (EFSA FEEDAP Panel, 2012b) based on a lower feed concentration (1.5 mg/kg complete feed) are also applicable at the maximum proposed use level of 5 mg/kg complete feed.

3.2.2. Conclusions

The FEEDAP Panel concludes that benzyl cinnamate [09.738] up to the maximum proposed use level of 5 mg/kg complete feed is safe for all animal species, the consumer and the environment.

3.3. Ethyl salicylate

3.3.1. Safety for the target species and the consumer

Ethyl salicylate [09.748] belongs to CG 23. In its previous assessment of ethyl salicylate [09.748], the FEEDAP Panel concluded that it is safe at the maximum proposed use level of 5 mg/kg complete feed for all animal species, the consumer and the environment (EFSA FEEDAP Panel, 2012b).

However, the authorisation of ethyl salicylate was denied by the European Commission on the grounds that it has 'medicinal effects and at the levels proposed, the intake as flavouring is higher than the estimated LOEL for animals and humans'. An LOEL of 0.167 mg/kg bw per day was identified by the European Medicines Agency (EMA, 1999) in the evaluation of acetyl salicylic acid.

The European Commission requested EFSA to reconsider the safety of ethyl salicylate for animals and humans 'taking into account that the level proposed as flavouring is higher than the estimated LOEL for animals and for humans' and considering the arguments provided by the applicant.

In the previous opinion, the safety of ethyl salicylate for the target species was evaluated by applying read-across from methyl salicylate [09.749], for which an NOAEL of 50 mg/kg bw per day was identified from a 2-year study in rats (Webb and Habsen, 1963). On this basis, the FEEDAP Panel reached its conclusion that ethyl salicylate is safe at the maximum proposed use level of 5 mg/kg complete feed for all animal species. A further consideration of the pharmacokinetics of salicylates led to a conclusion that no concern was identified for the consumer from the use of the compounds up to the highest safe level in feeds (EFSA FEEDAP Panel, 2012b).

The applicant provided scientific arguments,¹¹ which indicate that the pharmacological endpoint on which the LOEL of 0.167 mg/kg bw per day identified by EMA (inhibition of platelet aggregation and prolongation of bleeding time) is applicable to acetyl salicylic acid only, as the underlying mode of action (inhibition of thromboxane production by irreversible acetylation of the cyclooxygenases in platelets) requires an acetyl group. Salicylic acid itself or salicylic acid esters with substitutions in the carboxyl group, like methyl salicylate or ethyl salicylate, cannot react by acetylation with the cellular targets and therefore, do not share the resulting biological effects on platelet aggregation with acetyl salicylic acid (Schrör, 2009). The FEEDAP Panel considers that the pharmacological effect described for acetyl salicylic acid on bleeding time is not relevant for the assessment of ethyl salicylate when used as feed flavouring at the proposed conditions of use.

3.3.2. Conclusion

The FEEDAP Panel concludes that ethyl salicylate [09.748] is safe up to maximum proposed use level of 5 mg/kg complete feed for all animal species and the consumer.

3.4. Remaining 34 compounds

3.4.1. Safety for the user of 26 compounds

Regarding the safety for the user, in its previous assessments, for 26 compounds, namely nona-2,6-dien-1-ol [02.049], pent-2-en-1-ol [02.050], trans-2,cis-6 nonadien-1-ol [02.231], 2-dodecenal [05.037], nona-2(trans),6(cis)-dienal [05.058], nona-2,4-dienal [05.071], trans-2-nonenal [05.072], 2,4-decadienal [05.081], hepta-2,4-dienal [05.084], deca-2(trans),4(trans)-dienal [05.140], dodec-2(trans)-enal [05.144], hept-2(trans)-enal [05.150], non-2-enal [05.171], nona-2(trans),6(trans)-dienal [05.172], undec-2(trans)-enal [05.184], trans-2-octenal [05.190], trans-2-decenal [05.191], trans-2, tr-4-nonadienal [05.194], trans-2, tr-4-undecadienal [05.196], hex-2(trans)-enyl acetate [09.394], hex-2-enyl butyrate [09.396], isopulegol [02.067], oct-1-en-3-one [07.081], benzophenone [07.032], myrcene [01.008] and β -ocimene [01.018], in the absence of studies to assess the safety for the user, the FEEDAP Panel could not conclude on the safety for the users when handling the additives (EFSA FEEDAP Panel, 2016b,2019a,b,2020a,b).

¹¹ Technical dossier/FFAC_CDG23_09_748_Ethyl salicylate.

At the time of the previous assessment, the applicant produced the required safety data sheets (SDS), in which hazard for users were identified. The applicant states that 'exposure to such hazards shall be limited accordingly by the operator by taking the precautionary measures stipulated in the respective SDS: (i) use of protective material to avoid contact with skin and eyes for those additives for which hazards for skin and eye contact have been identified; (ii) operators should ensure adequate ventilation and workers shall use appropriate respiratory protectors to avoid inhalation of vapour or mist for those additives for which a hazard for respiratory exposure is recognised'.

The applicant did not provide experimental data on the safety the user for any of the compounds following the requirements of the guidance on user safety (EFSA FEEDAP Panel, 2012d). Reference has been made for some compounds on ongoing or existing evaluations by the European Chemical Agency (ECHA) or the Research Institute for Fragrance Materials (RIFM).

Dodec-2(trans)-enal [05.144] has been preregistered under REACH and the applicant provided information on the classification provided by companies.¹² For benzophenone [07.032], the registration dossiers submitted to ECHA have been evaluated under REACH.¹³ However, the evaluation was not made available.

The applicant provided the RIFM fragrance ingredient safety assessments for nona-2,6-dien-1-oil [02.049], and trans-2-, cis-6-nonadien-1-ol [02.231] and isopulegol [02.067]. For nona-2,6-dien-1-ol [02.049], based on the limited data available and the application of the dermal sensitisation threshold (DST) there was no sensitisation concern (Api et al., 2015a). The same conclusion was reached for trans-2-, cis-6-nonadien-1-ol [02.231] based on the application of the DST (Api et al., 2015b), and for isopulegol [02.067] based on experimental data (Api et al., 2016). However, the relevance of this information is limited and is not considered in the current assessment.

The new information submitted did not include relevant data on the safety for the user that would allow the FEEDAP Panel to change its previous conclusion.

3.4.1.1. Conclusions on safety for the user

Considering that there is no new relevant data, the FEEDAP Panel reiterates that it is not in the position to conclude on the safety for the user for nona-2,6-dien-1-ol [02.049], pent-2-en-1-ol [02.050], trans-2,cis-6 nonadien-1-ol [02.231], 2-dodecenal [05.037], nona-2(trans),6(cis)-dienal [05.058], nona-2,4-dienal [05.071], trans-2-nonenal [05.072], 2,4-decadienal [05.081], hepta-2,4-dienal [05.084], deca-2(trans),4(trans)-dienal [05.140], dodec-2(trans)-enal [05.144], hept-2(trans)-enal [05.150], non-2-enal [05.171], nona-2(trans),6(trans)-dienal [05.172], undec-2(trans)-enal [05.184], trans-2-octenal [05.190], trans-2-decenal [05.191], trans-2, trans-4-nonadienal [05.194], trans-2, trans-4-undecadienal [05.196], hex-2(trans)-enyl acetate [09.394], hex-2-enyl butyrate [09.396], isopulegol [02.067], oct-1-en-3-one [07.081], benzophenone [07.032], myrcene [01.008] and β -ocimene [01.018].

3.4.2. Safety for the environment of 10 compounds

In its previous assessments of environmental safety for 10 compounds, namely 4-terpinenol [02.072], linalyl butyrate [09.050], linalyl formate [09.080], linalyl propionate [09.130], linalyl isobutyrate [09.423], isopulegol [02.167], 3-methyl-2-cyclopenten-1-one [07.112], methyl dihydrojasmonate [09.520], benzyl cinnamate [09.738] and 1,2-dimethoxy-4-(prop-1-enyl)-benzene [04.013], the FEEDAP Panel could not conclude for all compartments or could not conclude at the proposed use levels in feed. The compounds belong to CG 06 (EFSA FEEDAP Panel, 2012a), CG 05 (EFSA FEEDAP Panel, 2020a), CG 08 (EFSA FEEDAP Panel 2016a, 2020a) and CG 26 (EFSA FEEDAP Panel, 2012c).

Chemical group 06

In the previous assessment, the FEEDAP Panel could not conclude on the safety for the aquatic compartments of 4-terpinenol [02.072], linalyl butyrate [09.050], linalyl formate [09.080], linalyl propionate [09.130] and linalyl isobutyrate [09.423], all belonging to CG 06 (EFSA FEEDAP Panel, 2012a).

¹² Technical dossier/Annex_3_ECHA_2020_CG03_2_05_144. According to the classification provided by companies to ECHA in REACH registrations this substance is very toxic to aquatic life, causes serious eye irritation, causes skin irritation and may cause an allergic skin reaction

¹³ Technical dossier/Annex_13_ECHA_2020_CG21_07_032. According to the classification provided by companies to ECHA in REACH registrations this substance may cause damage to organs through prolonged or repeated exposure and is harmful to aquatic life with long lasting effects.

No new experimental data were provided for the compounds under assessment. The applicant provided evidence from the literature that 4-terpinenol, linalyl butyrate and linalyl formate are naturally occurring in European plants in concentrations higher than 5 mg/kg.¹⁴ For linalyl propionate, natural occurrence could be demonstrated only in plants which are uncommon in Europe, and for linalyl isobutyrate, no quantitative data were found. However, the four linalyl esters are expected to be hydrolysed in the target animals into the linalool and the corresponding carboxylic acid, which will be incorporated in normal physiological process such as beta-oxidation and the citric acid cycle. Considering the above (natural occurrence and/or extensive metabolism), a Phase II assessment is not required for these compounds.

Therefore, the FEEDAP Panel concludes that no risk for the environment is expected for 4-terpinenol [02.072], linalyl butyrate [09.050], linalyl formate [09.080], linalyl propionate [09.130] and linalyl isobutyrate [09.423] at the proposed use level of 5 mg/kg complete feed.

Chemical group 05

In its previous assessment, the FEEDAP Panel already concluded that the use of isopulegol [02.167] in animal feed at 5 mg/kg complete feed for all animal species is safe, as the compound is naturally occurring in the European environment (EFSA FEEDAP Panel, 2020a). The applicant provided further evidence of its natural occurrence¹⁵ in *Mentha arvensis* L., *Melissa officinalis* L. and *Citrus sinensis* L. Osbeck (5–120 mg/kg) to support the previous conclusion.

Therefore, the FEEDAP Panel confirms its previous conclusion that the use of isopulegol [02.167] in animal feed at the maximum level of 5 mg/kg is considered safe for the environment.

Chemical group 08

3-Methyl-2-cyclopenten-1-one [07.112] and methyl dihydrojasmonate [09.520] belong to CG 08. In the previous assessment of CG 08, the FEEDAP Panel concluded that 'The concentrations considered safe for the target species are unlikely to have detrimental effects on the terrestrial and freshwater environment, with some exceptions. For five compounds, (...) 3-methyl-2-cyclopenten-1-one [07.112], (...) it was not possible to reach a conclusion on the safety for the terrestrial compartment. For (...) methyl dihydrojasmonate [09.520], the proposed normal use level of 1 mg/kg feed would not cause an environmental risk. For the marine environment, the safe use level for all substances was estimated to be 0.05 mg/kg feed' (EFSA FEEDAP Panel, 2016a). For the current assessment, the applicant proposed a reduced use level in feed of 0.5 mg/kg complete feed for 3-methyl-2-cyclopenten-1-one [07.112] and confirmed the high use level of 5 mg/kg for methyl dihydrojasmonate [09.520]. For both compounds, for which the FEEDAP Panel has identified a potential concern for the marine environment (sea cages), the applicant proposed to limit the concentration in fish feed used in marine aquaculture to 0.05 mg/kg.

In the previous assessment, the PEC_{soil} calculated for 3-methyl-2-cyclopenten-1-one [07.112] at the application rate of 0.5 mg/kg, following the provision of the former guidance on environmental risk assessment (EFSA, 2008) was 11 $\mu\text{g}/\text{kg}$, above the threshold of 10 $\mu\text{g}/\text{kg}$. The applicant provided calculations according to the guidance on the environmental risk assessment (EFSA FEEDAP Panel, 2019a,b), which showed that at the levels in feed considered safe for the target animals (up to 0.5 mg/kg), the PEC_{soil} would be below the threshold of 10 $\mu\text{g}/\text{kg}$. This would exclude the need for further assessment for the terrestrial compartment.

In the previous assessment of methyl dihydrojasmonate [09.520], a dose of 5 mg/kg feed resulted in a $PEC_{soil}/PNEC$ ratio of 0.074 and $PEC_{sw}/PNEC$ ratio of 2.29, suggesting a concern for the freshwater environment. Therefore, it was concluded that the proposed normal use level of 1 mg/kg feed would not cause an environmental risk (EFSA FEEDAP Panel, 2016a). The applicant provided calculations which showed that, at the use level of 5 mg/kg, the $PEC_{sw}/PNEC$ ratio is < 1 for the aquatic compartment (see Table 4).

¹⁴ Technical dossier/Annex_FFAC_CG06_TT_M2_ERA.

¹⁵ Technical dossier/Annex_7_TNO_2019_CDG05_02_067 and Annexes_8- 10.

Table 4: Risk characterisation (PEC/PNEC) for the freshwater compartment

Taxa	PEC _{sw} (µg/L)	E _(r) (L)C ₅₀ (mg/L)	AF	PNEC (µg/L)	PEC/PNEC
Algae, E _r C ₅₀	2.7	8.16	1,000	5.6	0.48
Daphnia, EC ₅₀		15.3			
Fish, LC ₅₀		5.57			

EC₅₀: the concentration of a test substance which results in 50% of the test animals being adversely affected (i.e. both mortality and sublethal effects); LC₅₀: the concentration of a test substance which results in a 50% mortality of the test species.

The PEC/PNEC for surface water was < 1 indicating that there is no risk to the freshwater environment at the level of 5 mg/kg, which is considered safe for target species.

Chemical group 26

In the previous assessment, the FEEDAP Panel could not conclude on the safety for the environment of 1,2-dimethoxy-4-(prop-1-enyl)-benzene [04.013] at the proposed use level of 5 mg/kg (EFSA FEEDAP Panel, 2012c). No new experimental data were provided for this compound under assessment. However, the applicant provided evidence from the literature on the natural occurrence at 5 mg/kg in fennel (up to 10 mg/kg) and pistachio tree (up to 800 mg/kg).¹⁶ Therefore, the Panel accepts that an assessment of Phase II is not needed for this compound.

3.4.2.1. Conclusions on safety for the environment

The use of 4-terpinenol [02.072], linalyl butyrate [09.050], linalyl formate [09.080], linalyl propionate [09.130], linalyl isobutyrate [09.423], isopulegol [02.167] and 1,2-dimethoxy-4-(prop-1-enyl)-benzene [04.013] as flavouring additives at the proposed use level of 5 mg/kg in feed for all animal species is considered safe for the environment.

The use of 3-methyl-2-cyclopenten-1-one [07.112] at 0.5 mg/kg and methyl dihydrojasmonate [09.520] at 5 mg/kg in feed for all animal species except marine animals is considered safe for the environment.

4. Conclusions

The FEEDAP Panel concludes that ethyl oleate [09.192] and benzyl cinnamate [09.738] are safe at the proposed use level of 5 mg/kg complete feed for all animal species, the consumer and the environment; ethyl salicylate [09.748] is safe up to the maximum proposed use level of 5 mg/kg complete feed for all animal species and the consumer.

Considering that there is no new evidence, the FEEDAP Panel reiterates that it is not in a position to conclude on the safety for the user for nona-2,6-dien-1-ol [02.049], pent-2-en-1-ol [02.050], trans-2,cis-6 nonadien-1-ol [02.231], 2-dodecenal [05.037], nona-2(trans),6(cis)-dienal [05.058], nona-2,4-dienal [05.071], trans-2-nonenal [05.072], 2,4-decadienal [05.081], hepta-2,4-dienal [05.084], deca-2(trans),4(trans)-dienal [05.140], dodec-2(trans)-enal [05.144], hept-2(trans)-enal [05.150], non-2-enal [05.171], nona-2(trans),6(trans)-dienal [05.172], undec-2(trans)-enal [05.184], trans-2-octenal [05.190], trans-2-decenal [05.191], trans-2, trans-4-nonadienal [05.194], trans-2, trans-4-undecadienal [05.196], hex-2(trans)-enyl acetate [09.394], hex-2-enyl butyrate [09.396], isopulegol [02.067], oct-1-en-3-one [07.081], benzophenone [07.032], myrcene [01.008] and β-ocimene [01.018].

The use of 4-terpinenol [02.072], linalyl butyrate [09.050], linalyl formate [09.080], linalyl propionate [09.130], linalyl isobutyrate [09.423], isopulegol [02.167] and 1,2-dimethoxy-4-(prop-1-enyl)-benzene [04.013] as flavouring additives at the proposed use level of 5 mg/kg in feed for all animal species is considered safe for the environment.

The use of 3-methyl-2-cyclopenten-1-one [07.112] at 0.5 mg/kg and methyl dihydrojasmonate [09.520] at 5 mg/kg in feed for all animal species except marine animals is considered safe for the environment.

¹⁶ Technical dossier/EFSA_TT_Non-TT_Annex_ERA_CG26/Annex_4_TNO_CDG26_04_013.

5. Documentation provided to EFSA/Chronology

Date	Event
05/05/2021	Dossier received by EFSA. Follow-up opinion linked to EFSA-Q-2010-01031, EFSA-Q-2010-00876, EFSA-Q-2010-00873, EFSA-Q-2010-00702, EFSA-Q-2015-00069, EFSA-Q-2010-01181, EFSA-Q-2016-00344, EFSA-Q-2015-00599, EFSA-Q-2016-00163 and EFSA-Q-2016-00453 – 37 flavouring compounds for all animal species. Submitted by FEFANA asbl
08/10/2021	Reception mandate from the European Commission
10/11/2021	Application validated by EFSA – Start of the scientific assessment
23/03/2022	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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Abbreviations

BW	body weight
CAS	Chemical Abstracts Service
CDG	chemically defined group
CG	chemical group
DM	dry matter
EMA	European Medicines Agency
EURL	European Union Reference Laboratory
FAF	EFSA Panel on Food Additives and Flavourings
FAO	Food Agricultural Organization
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)
FGE	food group evaluation
FLAVIS	The EU Flavour Information System
FL-no	FLAVIS number
GC-FID	gas chromatography-flame ionisation detector
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
MW	molecular weight
NOAEL	no observed adverse effect level
TTC	threshold of toxicological concern
UF	uncertainty factor
WHO	World Health Organization