

ADOPTED: 23 March 2022

doi: 10.2903/j.efsa.2022.7248

Safety of feed additives consisting of β -damascone [07.083] and (E)- β -damascone [07.224] belonging to chemical group 8 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 β -damascone [07.083] and (E)- β -damascone [07.224] belonging to chemical group 8, when used as sensory additives (flavourings) in feed for all animal species. The additives are already authorised for use in all animal species. According to previous assessments, the additives were considered safe for the target species, the consumer and the freshwater environment. For the marine environment, the safe use level for the two substances was estimated to be 0.05 mg/kg feed. Hazards for skin and eye contact, and respiratory exposure were recognised for the majority of the compounds belonging to chemical group 8. In the absence of ecotoxicity data, the FEEDAP Panel could not conclude on the safety of β -damascone [07.083] and (E)- β -damascone [07.224] for the terrestrial compartment. The applicant has provided new data (a chronic toxicity test on earthworms) to address the issue previously identified regarding the environmental safety of β -damascone [07.083] for the terrestrial compartment. The use of β -damascone [07.083] and (E)- β -damascone [07.224] as feed additives is considered safe for the terrestrial and freshwater environment.

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Keywords: sensory additives, flavouring compounds, β -damascone, (E)- β -damascone, chemical group 8, safety, environment

Requestor: European Commission

Question number: EFSA-Q-2021-00520

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

Acknowledgements: The Panel wishes to thank the following for the support provided to this scientific output: Antonio Finizio, Jaume Galobart, Matteo Lorenzo Innocenti, Ivana Teodorovic and Maria Vittoria Vettori.

Suggested citation: EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Bampidis V, Azimonti G, Bastos ML, Christensen H, Dusemund B, Fašmon Durjava M, Kouba M, López-Alonso M, López Puente S, Marcon F, Mayo B, Pechová A, Petkova M, Ramos F, Sanz Y, Villa RE, Woutersen R, Tarrés-Call J and Manini P, 2022. Scientific Opinion on the safety of feed additives consisting of β -damascone [07.083] and (E)- β -damascone [07.224] belonging to chemical group 8 for use in all animal species (FEFANA asbl). EFSA Journal 2022;20(4):7248, 9 pp. <https://doi.org/10.2903/j.efsa.2022.7248>

ISSN: 1831-4732

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



Table of contents

Abstract.....	1
1. Introduction.....	4
1.1. Background and Terms of Reference as provided by the requestor.....	4
1.2. Additional information.....	4
2. Data and methodologies.....	5
2.1. Data.....	5
2.2. Methodologies.....	5
3. Assessment.....	5
3.1. Safety for the environment.....	6
3.1.1. Conclusions on safety for the environment.....	8
4. Conclusions.....	8
5. Documentation provided to EFSA/Chronology.....	8
References.....	8
Abbreviations.....	9

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 defines the terms of the authorisation by the Commission.

The European Commission (EC) received a request from (FEFANA asbl)² for the authorisation and the re-evaluation of an authorisation of the product Chemically defined flavourings Group 02 - Branched-chain primary aliphatic alcohols/aldehydes/acids, acetal and esters when used as a feed additive for all animal species (category: sensory additives; functional group: flavouring compound) (Table 1).

Table 1: Description of the substances

Category of additive	Sensory additive
Functional group of additive	Flavouring
Description	β -damascone [07.083] and (E)- β -damascone [07.224]
Target animal category	All animal species
Applicant	FEFANA Asbl
Type of request	New opinion

On 18 November 2020, the Panel on Additives and Products or Substances used in Animal Feed of the European Food Safety Authority ("Authority"), in its opinion on the safety and efficacy of the product,³ could not conclude on the safety of these two additives for the environment when used in terrestrial species: β -damascone [07.083] and (E)- β -damascone [07.224] from Chemically defined flavourings Group 08.⁴

During the discussions with the Member States at a meeting of the Standing Committee on Plants, Animals, Food and Feed (Animal Nutrition section), it was suggested to check for the possibility to demonstrate the safety for the environment of the additives.

The Commission gave the possibility to the applicant to submit supplementary information and data in order to complete the assessment and to allow a revision of the EFSA's opinion. The new data have been received on 20 July 2021.

In view of the above, the Commission asks the Authority to deliver a new opinion on the safety of β -damascone [07.083] and (E)- β -damascone [07.224] from Chemically defined flavourings Group 08 as feed additives for all animal species based on the additional data submitted by the applicant.

1.2. Additional information

The EFSA FEEDAP Panel issued two opinions on the safety and efficacy of β -damascone [07.083] and (E)- β -damascone [07.224] when used in feed for all animal species (EFSA FEEDAP Panel, 2016, 2020). In both assessments, the FEEDAP Panel could not reach a conclusion on the safety of β -damascone [07.083] and (E)- β -damascone [07.224] for the terrestrial compartment in the absence of ecotoxicity data.

The additives are currently authorised for food⁵ and feed⁶ uses.

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 FEFANA asbl, Avenue Louise 130 A, Box 1, 1050 Brussels, Belgium.

³ <https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2020.6338>

⁴ In the mandate, the two compounds were allocated to chemically defined flavourings Group 02 - Branched-chain primary aliphatic alcohols/aldehydes/acids, acetal and esters. The two compounds belong to chemically defined flavourings Group 08. The correct chemical group has been indicated in the letter with the acceptance of the mandate (letter dated 1 October 2021).

⁵ 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.

⁶ 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

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 in support to previous applications on the same products.⁷

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 active substances β -damascone [07.083] and (E)- β -damascone [07.224] in animal feed are valid and applicable for the current application.⁸

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 429/2008⁹ and the relevant guidance documents: Guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019), Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment (EFSA Scientific Committee, 2019).

3. Assessment

The additives under assessment, β -damascone [07.083] and (E)- β -damascone [07.224] are two compounds belonging to chemical group 8, secondary alicyclic saturated and unsaturated alcohols, ketones, ketals and esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols, intended for use as sensory additives (functional group: flavouring compounds) in feed for all animal species at the proposed use level of 5 mg/kg complete feed, except for the marine environment (0.05 mg/kg complete feed).

β -Damascone [07.083] is authorised for use in food as flavouring with a purity of at least 90% (sum of cis- and trans-isomers), as specified by the Joint Food and Agriculture Organization of the United Nations (FAO/WHO) Expert Committee on Food Additives (JECFA) (FAO, 2006).¹⁰

In the first assessment (EFSA FEEDAP Panel, 2016), β -damascone [07.083] and (E)- β -damascone [07.224] were considered safe for the target species, the consumer and the freshwater environment at the use level of 1.5 mg/kg complete feed. For the marine environment, the safe use level for the two substances was estimated to be 0.05 mg/kg feed. For both compounds, the predicted environmental concentration in soil (PEC_{soil}) arising from the application rate of 1.5 mg/kg (considered safe for the target species) exceeded the threshold of 10 μ g/kg. In the absence of any information on the effects on terrestrial organisms, it was not possible to reach a conclusion on the safety for the terrestrial environment. Hazards for skin and eye contact, and respiratory exposure were recognised for both compounds.

In the second opinion, based on the outcome of tolerance studies in chickens for fattening, piglets and cattle for fattening with a mixture of 22 flavourings which included β -damascone [07.083], the additives were considered safe for the target species, the consumer and the freshwater environment at the proposed use level of 5 mg/kg complete feed. For the marine environment, the safe use level for β -damascone [07.083] and (E)- β -damascone [07.224] was confirmed to be 0.05 mg/kg. Concentrations of β -damascone [07.083] in manure samples collected during the tolerance trials¹¹ were provided to refine the calculations for PEC_{soil}. However, in the absence of an ecotoxicity study on earthworms, from which a predicted no effect concentration (PNEC) estimate for the terrestrial compartment could be derived, the FEEDAP Panel could not reach a conclusion on the safety of

⁷ FEED dossier reference: FAD-2010-0125 and FAD-2019-0095.

⁸ The full report is available on the EURL website: <https://ec.europa.eu/jrc/sites/default/files/FinRep-FAD-2010-0125.pdf>

⁹ Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

¹⁰ Food and Agricultural Organization of the United Nations (FAO), 2006. "Specification for flavourings": Online edition: <https://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-flav/details/en/c/338/>

¹¹ The % fraction of β -damascone in manure was 4.2% in poultry, 9.1% in pigs and 3.7% in cattle for fattening (EFSA FEEDAP Panel, 2020).

β -damascone [07.083] and (E)- β -damascone [07.224] for the terrestrial compartment (EFSA FEEDAP Panel, 2020).

The applicant has now provided a chronic study on earthworms, to address the issue previously identified regarding the environmental safety of β -damascone [07.083] for the terrestrial compartment. The applicant also provided calculations performed according to the current Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019) to confirm that the proposed use level of 5 mg/kg complete feed is safe for the freshwater environment. The applicant also proposes to extrapolate the conclusions to (E)- β -damascone [07.224]. 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.

3.1. Safety for the environment

Exposure assessment

As a first step, the predicted environmental concentrations (PECs) were calculated at the proposed use level of 5 mg β -damascone/kg complete feed for the different compartments.

PECs calculation – terrestrial animals

The PEC for the different compartments was calculated using the modelled values for physico-chemical properties using EPIWEB 4.1 (EFSA FEEDAP Panel, 2016), including the half-life of the additive (DT_{50}) and the organic carbon sorption constant (K_{oc}).

The highest PEC values obtained for terrestrial animals are reported in Table 2.

Table 2: Predicted environmental concentration of β -damascone [07.083] in soil, groundwater, surface water and sediment

Input	Value
Dose	5
Molecular weight	192.3
Vapour pressure (Pa)	1.7
Solubility (mg/L) at pH 7	7.986
K_{oc} (L/kg)	713
DT_{50} in soil at 12°C (days)	25
Output	
PEC _{soil} (μ g/kg)	101
PEC _{groundwater} (μ g/L)	1.75
PEC _{surface water} (μ g/L)	0.6
PEC _{sediment} (μ g/kg)	43.7

The calculated PEC values indicate that all the thresholds are exceeded and therefore further assessment is needed for terrestrial animals.

PECs calculation – land-based aquaculture

The use of the additive in fish feed land-based aquaculture systems gives a predicted environmental concentration of the additive (parent compound) in surface water (PEC_{swaq}) varying between 0.006 and 0.013 μ g/L, well below the trigger value of 0.1 μ g/L. The assessment for land-based aquaculture stops in Phase I.

Ecotoxicity studies

Effects of β -damascone [07.083] on the reproduction of the earthworm *Eisenia fetida* were investigated in artificial soil by a good laboratory practice (GLP) compliant study following the Organization for Economic Co-operation and Development (OECD) Guideline 222 (2016). The experimental setup included eight test item treatment groups (3.7, 6.0, 9.5, 15.3, 24.4, 39.1, 62.5, 100 mg test item/kg soil dry weight) and an untreated control group, eight replicates in the control group and four replicates in each test item treatment group. Adult worm mortality, behavioural effects and biomass development were recorded after 28 days and reproduction rate after an additional

28 days (assessed 56 days after application). There was no statistically significant effect on mortality compared to the control group at any concentration tested. At a concentration of 100 mg test item/kg soil dry weight (d.w.), the biomass change (−11.5%) was significantly lower compared to the control group (+22.1%). Statistically significant negative effects on reproduction, expressed as the number of juveniles compared to the control group were recorded at concentrations of 39.1 (16.6%, reduction of reproduction compared to control), 62.5 (45.1%) and 100 mg test item/kg soil d.w. (100%). Calculated EC_{10} reproduction (Probit method) is 38.9 mg/kg soil d.w. (95% confidence interval 34.3–44.1) while the no observed effect concentration for reproduction ($NOEC_{\text{reproduction}}$) is 24.4 mg/kg soil d.w. Since the $NOEC_{\text{reproduction}}$ is lower than EC_{10} , it is used for risk characterisation.

Effects on freshwater organisms

For freshwater organisms, the assessment is based on toxicity values in fish, daphnids and algae modelled by ECOSAR 1.11, as reported in the previous assessment (EFSA FEEDAP Panel, 2016).

Risk characterisation (PEC/PNEC ratio)

Terrestrial animals

The predicted no effect concentration (PNEC) for terrestrial environment ($PNEC_{\text{soil}}$) was determined by dividing the $NOEC$ for earthworms by an assessment factor (AF) of 10. The risk characterisation for terrestrial compartment is reported in Table 3

Table 3: Risk characterisation (PEC/PNEC ratio) for the terrestrial compartment

Taxa	PEC_{soil} ($\mu\text{g}/\text{kg}$)	$NOEC$ (mg/kg)	AF	PNEC ($\mu\text{g}/\text{kg}$)	PEC/PNEC
Earthworm	101	24.4	10	2,440	0.04

$NOEC$: no observed effect concentration.

The PEC/PNEC ratio for earthworms was < 1 indicating that there is no risk for the terrestrial compartment at the level of 5 mg/kg considered safe for target species.

The risk characterisation for the aquatic compartment is reported in Table 4.

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

Taxa	PEC_{sw} ($\mu\text{g}/\text{L}$)	$E_{(r)}(L)C_{50}$ (mg/L)	AF	PNEC ($\mu\text{g}/\text{L}$)	PEC/PNEC
Algae, E_rC_{50}	0.6	0.83	1,000	0.8	0.75
Daphnia, EC_{50}		0.87			
Fish, LC_{50}		2.77			

EC_{50} : the concentration of a test substance which results in 50% of the test animals being adversely affected (i.e. both mortality and sublethal effects); LC_{50} : the concentration of a test substance which results in a 50% mortality of the test species; $NOEC$: no observed effect concentration.

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 considered safe for target species.

Bioaccumulation and risk for secondary poisoning

To assess bioaccumulation and risk for secondary poisoning, the method proposed in the relevant Guidance from the European Medicines Agency (EMA) was considered (EMA, 2016). Based on the $\log K_{ow}$ of 4.42, β -damascone has the potential for bioaccumulation in aquatic and terrestrial food chain. Since there were no bioaccumulation data available for aquatic and terrestrial organisms, the FEEDAP Panel made an assessment on secondary poisoning of β -damascone for aquatic and terrestrial food chain. The lowest chronic no observed adverse effect level (NOAEL) was estimated from the threshold of toxicological concern (TTC) concept and for Cramer class I compounds (EFSA Scientific Committee, 2019). This is a very conservative value as it represents the 5th percentile of the distribution of the NOAEL for the compounds belonging to this class. The database consisted of data on rodents and rabbits, with the majority of the studies in rats. The NOAEL was determined as 3 mg β -damascone/kg body weight (bw) per day. $NOEC$ for β -damascone was 30 mg/kg feed and was calculated from the NOAEL taking into account conversion factor of 10 for rats. Using an assessment factor of 30, the corresponding $PNEC_{\text{oral}}$ was equivalent to 1.0 mg/kg feed. This value is higher than the estimated concentration in fish and in earthworms of

0.68 mg/kg and 0.51 mg/kg, respectively, which are based on PECs presented in Table 2. The PEC/PNEC ratios are presented in Table 5.

Table 5: The assessment of secondary poisoning for β -damascone via aquatic and terrestrial food chain based on the 100% of the proposed recommended dose

	PEC _{fish} ¹ (mg/kg)	PEC _{worm} ² (mg/kg)	PNEC _{oral} (mg/kg)	PEC _{fish} /PNEC _{oral}	PEC _{worm} /PNEC _{oral}
β -Damascone	0.68	0.51	1.0	0.68	0.51

1: PEC_{fish} (oral,predator) for the assessment of secondary poisoning via the aquatic food chain.

2: PEC_{worm} (oral,predator) for the assessment of secondary poisoning via the terrestrial food chain.

A risk for secondary poisoning for worm/fish-eating birds and mammals is not likely to occur.

The FEEDAP Panel considers that the conclusions reached for β -damascone [07.083] can be extrapolated to (E)- β -damascone [07.224].

3.1.1. Conclusions on safety for the environment

The use of β -damascone [07.083] and (E)- β -damascone [07.224] in animal nutrition at the proposed conditions of use (5 mg/kg complete feed) is not expected to have a detrimental effect on the terrestrial and freshwater environment. A risk for secondary poisoning for worm/fish-eating birds and mammals is not likely to occur.

4. Conclusions

The use of β -damascone [07.083] and (E)- β -damascone [07.224] as feed additives at the proposed conditions of use (5 mg/kg complete feed) is considered safe for the terrestrial and freshwater environment.

5. Documentation provided to EFSA/Chronology

Date	Event
20/07/2021	Dossier received by EFSA. Follow-up opinion linked to EFSA-Q-2020-00175 - β -damascone [07.083] and (E)- β -damascone [07.224] from chemically defined flavourings Group 08 for all animal species. Submitted by FEFANA asbl
16/08/2021	Reception mandate from the European Commission
13/09/2021	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

AF	Assessment factor
BW	body weight
CG	chemical group
DT ₅₀	half-life of additive (by BioWin3)
EC ₁₀	the concentration of a test substance which results in 10% of the test animals being adversely affected
EC ₅₀	half-maximal effective concentration
EEIG	European Economic Interest Grouping
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
FFAC	Feed Flavourings authorisation Consortium of FEFANA (EU Association of Specialty Feed Ingredients and their Mixtures)
FGE	food group evaluation
FLAVIS	The EU Flavour Information System
FL-no	FLAVIS number
GLP	Good Laboratory Practice
K _{OC}	organic carbon sorption constant
LC ₅₀	half-maximal lethal concentration
NOAEL	no observed adverse effect level
NOEC	No observed effect concentration
PEC	predicted environmental concentration
PEC _{soil}	predicted environmental concentration for soil
PEC _{pore water}	predicted environmental concentration for pore water
PEC _{surface water}	predicted environmental concentration for surface water
PEC _{swaq}	predicted environmental concentration of the additive (parent compound) in surface water
PNEC	predicted no effect concentration
PNEC _{aquatic}	predicted no effect concentration for aquatic compartment
PNEC _{soil}	predicted no effect concentration for terrestrial environment
OECD	Organization for Economic Co-operation and Development
TTC	threshold of toxicological concern