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Safety and efficacy of DSP[®] (Na₂EDTA, tannin-rich extract of *Castanea sativa*, thyme oil and origanum oil) for pigs for fattening

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Abstract

Following a request from the European Commission, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety for the environment and efficacy of DSP[®] (a mixture of disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA), tannin-rich extract of *Castanea sativa*, thyme oil and origanum oil) as a zootechnical feed additive for pigs for fattening. The European Commission request followed an inconclusive opinion of the FEEDAP Panel published in 2016. The applicant submitted additional information to allow the FEEDAP Panel to complete its assessment; these additional data, related to the safety for the environment and the efficacy of the additive, were the subject of this opinion. Concerning safety for the environment, the risk quotient (PEC/PNEC) value for aquatic organisms was < 1, indicating no concerns of DSP[®] for the aquatic compartment; no toxicity data for terrestrial organisms were provided and consequently no conclusion on the safety of DSP[®] for the terrestrial compartment could be reached, as well as on the risk for groundwater contamination. Based on the results from three studies in pigs for fattening in which final body weight and average daily weight gain were increased, and feed to gain ratio was improved, the FEEDAP Panel concluded that DSP[®] has the potential to be efficacious as a zootechnical additive in pigs for fattening.

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Keywords: zootechnical additives, DSP[®], Na₂EDTA, pigs for fattening, safety, environment, efficacy

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

Regulation (EC) No 1831/2003 establishes rules governing the Community authorisation of additives for animal nutrition and, in particular, Article 9 defines the terms of the authorisation by the Commission.

The applicant, Pharmatéka Preventive Kft., is seeking a Community authorisation of Na₂EDTA CAS No: 6381–92–6, Origanum oil CAS No: 8007–11–2, Thyme oil CAS No: 8007–46–3, tannin-rich extract of *Castanea sativa* Mill. (Pharmatéka) as a feed additive to be used as a gut flora stabiliser for pigs for fattening (Table 1).

Table 1: Description of the substances

Category of additive	Zootechnical additive
Functional group of additive	Gut flora stabiliser
Description	Na ₂ EDTA CAS No: 6381-92-6, Origanum oil CAS No: 8007-11-2, Thyme oil CAS No: 8007-46-3, <i>Castanea sativa</i> Mill. (Pharmatéka)
Target animal category	Pigs for fattening
Applicant	Pharmatéka Preventive Kft
Type of request	New opinion

On 18 May 2016, 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, could not conclude on the safety and efficacy of Na₂EDTA CAS No: 6381–92–6, Origanum oil CAS No: 8007–11–2, Thyme oil CAS No: 8007–46–3, *Castanea sativa* Mill. (Pharmatéka) as a feed additive for pigs for fattening, under the condition of use as proposed by the applicant, assessment of risk for terrestrial and aquatic compartments cannot be completed. Efficacy is also not demonstrated.

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 23 October 2017.

In view of the above, the Commission asks the Authority to deliver a new opinion on Na₂EDTA CAS No: 6381–92–6, Origanum oil CAS No: 8007–11–2, Thyme oil CAS No: 8007–46–3, *Castanea sativa* Mill. (Pharmatéka) as a feed additive for pigs for fattening based on the additional data submitted by the applicant.

1.2. Additional information

The FEEDAP Panel adopted in 2016 an opinion on the safety and efficacy of the DSP® (Na₂EDTA, tannin-rich extract of *C. sativa*, thyme oil and oregano oil) when used as a zootechnical additive for pigs for fattening (EFSA FEEDAP Panel, 2016). At that time, the Panel could not conclude on the safety for the environment owing to the absence of appropriate ecotoxicity data. The FEEDAP Panel was also unable to determine the efficacy of the additive since the submitted studies did not comply with the minimum requirements for an experimental design for the demonstration of efficacy.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of additional information¹ to a previous application of the same product.²

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of DSP® is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance documents:

¹ FEED dossier reference: FAD-2017-0055.

² FEED dossier reference: FAD-2010-0406.

Guidance on zootechnical additives (EFSA FEEDAP Panel, 2012), Technical Guidance for assessing the safety of feed additives for the environment (EFSA, 2008).

3. Assessment

The additive under application is a blend of disodium ethylenediamine tetraacetic acid, a tannin-rich extract from *C. sativa*, thyme oil and origanum oil with an emulsifier (glyceryl polyethyleneglycol ricinoleate), and glucose and wheat flour as carriers. It is intended to be used as a zootechnical additive (functional group: gut flora stabilisers) to positively influence the intestinal microbiota of pigs for fattening, particularly by reducing the incidence of dysentery caused by the bacterial spirochete *Brachyspira hyodysenteriae* and, thus, to improve performance. Although referred to under a different trade name (DSP) to that used in the previous opinion (Diarr-Stop S Plus), it has the same composition and the same proposed conditions of use (1,000 mg/kg complete feed).

In its previous opinion, the FEEDAP Panel was able to establish the safety of the additive for the target species (pigs for fattening) and consumers and to conclude that the additive was a skin and eye irritant (EFSA FEEDAP Panel, 2016). However, the Panel could not conclude on the safety for the environment owing to the absence of appropriate ecotoxicity data and on the efficacy of the additive since the submitted studies did not comply with the minimum requirements for an experimental design for the demonstration of efficacy. The applicant provided additional information related to the safety of the additive for the environment and the efficacy of the additive. The assessment of the new information is the subject of this opinion.

3.1. Safety for the environment

Disodium ethylenediamine tetraacetic acid (Na₂EDTA) is the major constituent of DSP® and is not a naturally occurring substance. In its previous opinion, the FEEDAP Panel identified the need for a phase II environmental risk assessment, however a conclusion could not be reached in the absence of appropriate data on the ecotoxicological effects of Na₂EDTA (EFSA FEEDAP Panel, 2016).

The applicant has established that bioaccumulation is unlikely to occur because $\log Kow = -11.7$,³ so risk due to secondary poisoning is not expected.

The applicant has submitted a risk assessment report (RAR) of the European Union (EU RAR, 2004) on Na₄EDTA.⁴ The document contains relevant ecotoxicological data for the aquatic organisms. In the RAR, as a result of the exposure assessment, it is concluded that over-stoichiometric amounts of metal ions are always present in the environment; thus, there is no uncomplexed EDTA. Therefore, tests with EDTA metal complexes have to be considered as well. Consequently, a number of studies were considered to evaluate the toxicity on aquatic organisms; indeed, either H₄EDTA (ethylenediaminetetraacetic acid), its tetrasodium salt (Na₄EDTA) or metal complexes were used as test substance. In order to present comparable results, all effect values were calculated as H₄EDTA. No data were reported for the Na₂EDTA (the component of DSP®); however, it can be considered acceptable to extrapolate the predicted no-effect concentration (PNEC) for aquatic organisms from the available data (Table 2).

Table 2: Risk characterisation (PEC/PNEC ratio) for aquatic risk assessment

Test organism	Compound	NOEC (mg/L)	PEC ⁽⁴⁾ (µg/L)	PNEC (µg/L)	Safety factor	PEC/PNEC
<i>Danio rerio</i> ⁽¹⁾	H ₄ -EDTA	26.8	21.7	850	10	0.03
<i>Daphnia magna</i> ⁽²⁾		22				
<i>Scenedesmus quadricauda</i> ⁽³⁾		8.5				

NOEC: No Observed Effect Concentration; PEC: Predicted Environmental Concentration.

(1): ELS (Early Life Stage) test.

(2): 21-day study.

(3): 8-day growth inhibition test.

(4): Value taken from the previous opinion (EFSA FEEDAP Panel, 2016).

The applicant has not submitted toxicity data on terrestrial organisms and consequently the PNEC value for terrestrial organisms cannot be calculated. No refinement for groundwater was proposed.

³ Value specified in EU-RAR on the basis of $K_{psoil} = 75 \text{ L/kg}$ ($K_{oc} = K_{psoil}/F_{ocsoil}$). Data taken from the previous dossier submitted by the applicant (FAD-2010-0406).

⁴ Technical Dossier/Supplementary information November 2019/13_Annexes_III_RiskAssRepNa4EDTA.pdf.

3.1.1. Conclusions on safety for the environment

The risk quotient (PEC/PNEC) value for aquatic organisms was < 1, indicating no concerns of DSP® for the aquatic compartment. No toxicity data for terrestrial organisms were provided and consequently no conclusion on the safety of DSP® for the terrestrial compartment can be reached, as well as on the risk for groundwater contamination.

3.2. Efficacy for pigs for fattening

Three efficacy studies with pigs for fattening were submitted. The first study included three runs.⁵ The details on the experimental design of the three studies are provided in Table 3 and the main results in Table 4.

In all studies, pigs for fattening were fed either a non-supplemented diet (control) or a diet containing DSP® at 1,000 mg/kg complete feed (analytically confirmed by analysis of EDTA). Experimental diets were administered for either 70 (studies 1 and 2) or 92 (study 3) days (Table 3). In the three studies, pigs were individually housed; feed (as mash) and water were offered ad libitum to the animals. Health and mortality were recorded during the experimental period. No preventive or therapeutic treatments were applied to the experimental animals in any of the studies. Pigs performance parameters were measured (body weight (bw) and feed intake) or calculated (daily weight gain and feed to gain ratio) at various days during the study, but always at the beginning and at the end of each study. Statistical evaluation was done by an analysis of variance (ANOVA). The significance level was set at $p \leq 0.05$.

Table 3: Summary of the design of the efficacy studies performed in pigs for fattening

Study breed	Run	Duration (days)	Total no of animals ⁽¹⁾ (animals per group)	Average initial body weight and age	Composition basal diet
1 ⁶ (Pietrain × Duroc) × (Large White × Landrace)	1	70	48 (24)	33 kg 90 days	Barley, soybean meal and sunflower
	2		24 (12)		
	3		47 (24/23) ⁽²⁾		
2 ^{7,8} Danish Landrace	1	70	50 (25)	30 kg 90 days	Maize, barley and sunflower
3 ^{9,10} Hungarian breed × Danish Landrace	1	92	50 (25)	24 kg 85 days	Barley, wheat, maize and soybean meal

(1): Distribution by sex. Study 1: same rate of males and females, except in Run 3 (Control 10 males and 14 females, and treatment 10 males and 13 females); study 2: control group 12 males and 13 females, treatment group 12 males and 13 females. Study 3: Control group 12 males and 13 females, treatment group 14 males and 11 females.

(2): 24 Control; 23 Treatment.

⁵ In this study, pigs were fattened in three batches overlapping in time.

⁶ Technical Dossier/Section IV/45_Annexes_IV_FT1_data.pdf, 46_Annexes_IV_FT2_data.pdf, 47_Annexes_IV_FT1_data.pdf.

⁷ Technical Dossier/Supplementary Information November 2019/51_Annexes_IV_FT_Serbia.pdf.

⁸ Technical Dossier/Supplementary Information November 2019/50_Annexes_IV_TPDS_Serbia.pdf, 52_Annexes_IV_StatAnal_Serbia.pdf.

⁹ Technical Dossier/Supplementary Information November 2019/53_Annexes_IV_FT_Slovakia.pdf.

¹⁰ Technical Dossier/Supplementary Information November 2019/54_Annexes_IV_TPDS_Slovakia.pdf, 55_Annexes_IV_StatAnal_Slovakia.pdf.

Table 4: Performance parameters of pigs at the end of the studies

Study	Group	Initial bw (kg)	Final bw (kg)	Average daily weight gain (kg/day)	Average daily feed intake (kg/day)	Feed/gain
1 ⁽¹⁾	Control	33.8	100.7	0.956	3.00	3.14
	DSP® (1,000 mg/kg)	33.7	102.9*	0.988*	2.79*	2.82*
2	Control	30.1	107.8	1.11	3.02	2.72
	DSP® (1,000 mg/kg)	30.0	114.2*	1.20*	3.04	2.53*
3	Control	23.1	81.2	0.632	2.85	4.51
	DSP® (1,000 mg/kg)	24.6	90.8*	0.719*	2.96	4.11*

bw: body weight.

(1): For the study 1, an analysis of the pooled data from the three runs was submitted.¹¹

(*): For a given study and parameter, the symbol (*) denotes a significant difference from control at $p \leq 0.05$.

In the three studies, final body weight and average daily weight gain were increased, and feed to gain ratio was improved, when pigs were fed the diet supplemented with the additive. The FEEDAP Panel notes that the three efficacy studies did not follow the requirements foreseen in the relevant Guidance of the FEEDAP Panel regarding the housing of the animals (i.e. individually housed – thus not reflecting the common farming practices in the EU – instead of in collective pens). However, in this case, the consistent positive results obtained likely suggest a reliable evidence of efficacy.

3.2.1. Conclusion on the efficacy in pigs

Based on the results from three studies in pigs for fattening in which final body weight and average daily weight gain were increased, and feed to gain ratio was improved, the FEEDAP Panel concludes that DSP® has the potential to be efficacious as zootechnical additive in pigs for fattening at the proposed conditions of use.

4. Conclusions

Concerning safety for the environment, the risk quotient (PEC/PNEC) value for aquatic organisms was < 1 , indicating no concerns of DSP® for the aquatic compartment. No toxicity data for terrestrial organisms were provided and consequently no conclusion on the safety of DSP® for the terrestrial compartment can be reached, as well as on the risk for groundwater contamination.

Based on the results from three studies in pigs for fattening in which final body weight and average daily weight gain were increased, and feed to gain ratio was improved, the FEEDAP Panel concludes that DSP® has the potential to be efficacious as zootechnical additive in pigs for fattening.

Documentation provided to EFSA/Chronology

Date	Event
19/09/2017	Dossier received by EFSA. DSP® (Na ₂ EDTA, <i>Castanea sativa</i> , thyme oil and origanum oil) for pigs for fattening. Submitted by Pharmatéka Preventive Kft
22/05/2018	Reception mandate from the European Commission
01/08/2018	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: safety for the environment and efficacy</i>
21/11/2019	Reception of supplementary information from the applicant - Scientific assessment re-started
20/12/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: Efficacy</i>
08/04/2020	Reception of supplementary information from the applicant - Scientific assessment re-started
25/05/2020	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

¹¹ Technical Dossier/Supplementary Information November 2019/57_Annexes_IV_StatAnal_Hungary.pdf.

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- EU RAR (European Union Risk Assessment Report), 2004. Tetrasodium ethylenediaminetetraacetate (Na₄EDTA). Institute for Health and Consumer Protection. European Chemicals. Bureau Existing Substances. European Commission. Directorate General Joint Research Centre. Available online: <https://echa.europa.eu/documents/10162/415c121b-12cd-40a2-bd56-812c57c303ce>

Abbreviations

ANOVA	analysis of variance
bw	body weight
CAS	Chemical Abstracts Service
ELS	Early Life Stage
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
NOEC	No Observed Effect Concentration
PEC	Predicted Environmental Concentration
PNEC	predicted no-effect concentration
RAR	risk assessment report