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

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Mojca Kos Durjava, Maryline Koub, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pečová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa, Ruud Woutersen, Andrew Chesson, Alberto Mantovani, Jürgen Gropp and Gloria López-Gálvez

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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**Correspondence:** feedap@efsa.europa.eu
Panel members: Giovanna Azimonti, Vasilios Bampidis, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Mojca Kos Durjava, Maryline Koub, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa and Ruud Woutersen.

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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 | Na2EDTA CAS No: 6381-92-6, Origanum oil CAS No: 8007-11-2, Thyme oil CAS No: 8007-46-3, Castanea sativa 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 origanum oil) 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:

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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 (Na$_2$EDTA) is the major constituent of DSP$^\circledast$ 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 Na$_2$EDTA (EFSA FEEDAP Panel, 2016).

The applicant has established that bioaccumulation is unlikely to occur because log Kow = $-11.7$, 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 Na$_2$EDTA. 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 H$_4$EDTA (ethylenediaminetetraacetic acid), its tetrasydronum salt (Na$_4$EDTA) or metal complexes were used as test substance. In order to present comparable results, all effect values were calculated as H$_4$EDTA. No data were reported for the Na$_2$EDTA (the component of DSP$^\circledast$); however, it can be considered acceptable to extrapolate the predicted no-effect concentration (PNEC) for aquatic organisms from the available data (Table 2).

| Test organism          | Compound    | NOEC (mg/L) | PEC(4) (µg/L) | PNEC (µg/L) | Safety factor | PEC/PNEC |
|------------------------|-------------|-------------|---------------|-------------|---------------|-----------|
| *Danio rerio* (1)      | H$_4$-EDTA  | 26.8        | 21.7          | 850         | 10            | 0.03      |
| *Daphnia magna* (2)    |             | 22          |               |             |               |          |
| *Scenedesmus quadricauda* (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.

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3 Value specified in EU-RAR on the basis of $K_{psoil} = 75$ 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. 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 ≤ 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 | Average initial body weight and age | Composition basal diet |
|-------------|-----|-----------------|---------------------|------------------------------------|------------------------|
| 1<sup>6</sup> (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<sup>2</sup>) |                                    |                        |
| 2<sup>7,8</sup> Danish Landrace | 1   | 70              | 50 (25)             | 30 kg 90 days                      | Maize, barley and sunflower |
| 3<sup>9,10</sup> 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.

<sup>5</sup> In this study, pigs were fattened in three batches overlapping in time.
<sup>6</sup> Technical Dossier/Section IV/45_Annexes_IV_FT1_data.pdf, 46_Annexes_IV_FT2_data.pdf, 47_Annexes_IV_FT1_data.pdf.
<sup>7</sup> Technical Dossier/Supplementary Information November 2019/51_Annexes_IV_FT_Serbia.pdf.
<sup>8</sup> Technical Dossier/Supplementary Information November 2019/50_Annexes_IV_TPDS_Serbia.pdf, 52_Annexes_IV_StatAnal_Serbia.pdf.
<sup>9</sup> Technical Dossier/Supplementary Information November 2019/53_Annexes_IV_FT_Slovakia.pdf.
<sup>10</sup> Technical Dossier/Supplementary Information November 2019/54_Annexes_IV_TPDS_Slovakia.pdf, 55_Annexes_IV_StatAnal_Slovakia.pdf.
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® (Na₂EDTA, Castanea sativa, 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. Issues: safety for the environment and efficacy |
| 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. Issues: Efficacy |
| 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 |

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 |
| 1     | 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 |
| 2     | 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 |
| 3     | 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.
(*) : 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.

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