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Safety and efficacy of APSA PHYTAFEED® 20,000 GR/L (6-phytase) as a feed additive 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, Maryline Kouba, Mojca Kos Durjava, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa, Ruud Woutersen, Jaume Galobart, Orsolya Holczknecht, Paola Manini, Elisa Pettenati, Fabiola Pizzo, Jordi Tarrés-Call and Montserrat Anguita

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 safety and efficacy of APSA PHYTAFEED® 20,000 GR/L (6-phytase) as a feed additive for pigs for fattening. The additive is a preparation of 6-phytase produced by a genetically modified strain of *Komagataella phaffii* and has been previously assessed by the FEEDAP Panel in the context of three applications for its use in different species. The Panel concluded in those opinions that the production strain is safe, and that the use of the additive as a feed additive would raise no safety concerns for the consumers and the environment. The additive was also considered not to be irritant to skin or eyes or a dermal sensitiser but it should be considered as a respiratory sensitiser. The Panel considered that the new use in pigs for fattening would not modify the previously drawn conclusions with respect to the consumers, users and the environment. A tolerance trial in weaned piglets and a subchronic oral toxicity study were made available to support the safety for the new target species. From the results obtained, the Panel concluded that the additive is safe for pigs for fattening at the level of 1,000 U/kg feed. The applicant submitted three efficacy trials to support the efficacy of the additive. In two trials the apparent faecal digestibility of phosphorus and bone ash/phosphorus content were measured and in the third the effects on the performance of the animals were studied. The results of the studies submitted showed an improvement on the faecal digestibility of phosphorus in two trials, with no improvements on the bone mineralisation. Significant improvements on zootechnical parameters were found in the performance of pigs for fattening that were fed 1,000 U/kg feed in the long-term trial. Since significant effects in relevant parameters were found only in one trial the FEEDAP Panel could not conclude on the efficacy of the product in pigs for fattening.

Keywords: safety, efficacy, zootechnical additives, digestibility enhancers, phytase, pigs for fattening

Requestor: European Commission

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Correspondence: feedap@efsa.europa.eu

Panel members: Giovanna Azimonti, Vasileios Bampidis Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Maryline Kouba, Mojca Kos Durjava, 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

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of a feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from Andrés Pintaluba S.A.[2] for authorisation of the product APSA PHYTAFEED® 20,000 GR/L (6-phytase), when used as a feed additive for pigs for fattening (category: zootechnical additives; functional group: digestibility enhancers).

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 21 June 2019.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the product APSA PHYTAFEED® 20,000 GR/L (6-phytase), when used under the proposed conditions of use (see Section 3.1).

1.2. Additional information

The FEEDAP Panel adopted three opinions on the product, one on the safety and efficacy of APSA PHYTAFEED® 20,000 GR/L (6-phytase) as a feed additive for chickens for fattening or reared for laying and minor poultry species for fattening or reared for laying (EFSA FEEDAP Panel, 2019a), the second on the use in turkeys for fattening or reared for breeding (EFSA FEEDAP Panel, 2019b) and a third one regarding its use in weaned piglets and minor porcine species (EFSA FEEDAP Panel, 2019c).

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[3] in support of the authorisation request for the use of APSA PHYTAFEED® 20,000 GR/L (6-phytase) as a feed additive for pigs for fattening.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA.

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 APSA PHYTAFEED® 20,000 GR/L (6-phytase) in animal feed are valid and applicable for the current application.[4]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of APSA PHYTAFEED® 20,000 GR/L (6-phytase) is in line with the principles laid down in Regulation (EC) No 429/2008[5] and the relevant guidance documents: Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017) and Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018).

[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.
[2] Andrés Pintaluba S.A. Pol. Ind. Agro Reus, c/ Prudenci Bertrana, 5, Reus 43206, Spain.
[3] FEED dossier reference: FAD-2019-0021.
[4] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/fin_report_fad-2018-0031_phytafeed.pdf
[5] 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 additive APSA PHYTAFEED® 20,000 GR/L contains 6-phytase activity (EC 3.1.3.26; phytase) and is intended to be used in feed for pigs for fattening as a zootechnical additive (functional group: digestibility enhancers).

3.1. Characterisation

The phytase present in the additive is produced by a genetically modified strain of the yeast *Komagataella phaffii* that has been deposited in the China General Microbiological Culture Collection Centre (CGMCC) with the deposit number 12056. The additive is available in two formulations, a solid one, APSA PHYTAFEED® 20,000 GR, and a liquid one, APSA PHYTAFEED® 20,000 L. The two formulations of the additive ensure a guaranteed minimum phytase activity of 20,000 U[6]/g or mL of product.

In a previous opinion, the Panel described the additive and its manufacturing process including the production strain (EFSA FEEDAP Panel, 2019a).

The additive is to be used in feed for pigs for fattening at a minimum recommended level of 1,000 U/kg feed.

3.2. Safety

The safety aspects regarding the use of this additive in feed including the safety of the genetic modification of the production strain, the safety for the consumers, for the user and for the environment have been previously assessed (EFSA FEEDAP Panel, 2019a). The Panel concluded that the use of the product as a feed additive raises no concerns for consumer safety and for the environment. Regarding the safety for the user, the Panel concluded that the additive is not irritant for skin or eye and it is not a dermal sensitiser, but it is considered a potential respiratory sensitiser. The FEEDAP Panel is not aware of any new information that would lead it to reconsider the conclusions drawn previously and considers that the extension of use to the new species for which the application is made would not have an impact on the safety aspects already considered.

However, the safety for the new target species needs to be addressed. The applicant provided a tolerance study in weaned piglets and a subchronic oral toxicity study. The FEEDAP Panel evaluated the tolerance trial in weaned piglets in a previous opinion (EFSA FEEDAP Panel, 2019c) and concluded that no adverse effects were found in weaned piglets when fed with the phytase up to 100,000 U/kg feed. However, the Panel noted that the control group in that study showed reduced growth. The subchronic oral toxicity study in rats, that has been assessed by the FEEDAP Panel (EFSA FEEDAP Panel, 2019a), was also provided.[7] The results of that study indicate a no observed adverse effects level (NOAEL) of 119,228 U/kg body weight and day in rats. Using this NOAEL, and applying the procedure detailed in the guidance on the safety for the target species (EFSA FEEDAP Panel, 2017), the maximum safe level for pigs for fattening is calculated to be 28,356 U/kg feed. This value is approximately 28 times higher than the proposed use level in pigs for fattening and would support the conclusion that the additive is safe for pigs for fattening at the recommended level of 1,000 U/kg feed.

3.3. Efficacy for pigs for fattening

Two digestibility studies that included bone measurements and a trial evaluating zootechnical performance parameters were submitted for the assessment.

The two digestibility trials had a similar trial design and were conducted in different trial sites.[8] In each study, a total of 35 pigs for fattening (males and females, initial body weight of approximately 70 kg) were individually penned and allocated to one of the five treatments (representing 7 replicates/treatment). Basal diets based on maize and soya bean meal were either not supplemented (control) or supplemented with APSA PHYTAFEED® 20,000 GR to provide 250, 500 or 1,000 U/kg feed. The enzyme activities were confirmed by analysis. However, the Panel notes that the analysis of the diet containing 1,000 U/kg feed in trial 2 showed an enzyme activity similar to 1,400 U/kg feed. In the two trials, a positive control diet with a content of phosphorus higher than in the basal diet was also

[6] One Unit (U) is defined as the amount of enzyme that releases 1 μmol of inorganic phosphate from phytate per minute at pH 5.5 and 37°C.
[7] Technical dossier/Section III/Annex III.2.2.3.
[8] Technical dossier/Section IV/Annex IV.2.1 and Annex IV.2.2.

considered (see Table 1). Diets were offered to the animals for 29 days in pelleted form in trial 1 or in mash form in trial 2. The diets contained an external marker (titanium dioxide) to determine the digestibility. Mortality and health status of the piglets were checked every day. Animals were weighed and feed intake was measured throughout the study period. Spot samples of faeces were collected in days 26–28. Feed and the faeces collected were analysed for the phosphorus content and external marker in order to study the digestibility. On the last day of the study, all animals were killed and the *os metacarpale* was collected from each animal to analyse it for ash and phosphorus content (only in trial 2). An analysis of variance was done with the data and group means were compared with Dunnett test in trial 1 or Tukey test in trial 2. The significance level was set at 0.05. The results on the apparent faecal digestibility and bone mineralisation of the pigs for fattening are reported in Table 1.

Table 1: Effect of APSA PHYTAFEED® 20,000 on the apparent faecal phosphorus digestibility and *os metacarpale* bone ash and phosphorus content

Trial	Diets		Faecal apparent digestibility of phosphorus (%)	Bone content (%)	
	Phytase (units/kg feed)	Total P/Ca (g/kg feed)(1)		Ash	Phosphorus
1	0	3.4/9.2	15.3	46.0	–
	250	3.4/9.2	26.7*	44.2	–
	500	3.4/9.2	31.1*	46.6	–
	1,000	3.4/9.2	40.4*	46.5	–
	Positive control	4.7–8.2	28.0*	47.5	–
2	0	3.1/5.2	32.1^{b}	59.5	9.7^{b}
	250	3.1/5.2	36.2^{ab}	59.9	9.7^{b}
	500	3.1/5.2	39.8^{ab}	60.9	9.9^{ab}
	1,000	3.1/5.2	49.2^{a}	60.4	9.8^{ab}
	Positive control	4.3/−5.2	44.4^{ab}	61.2	10.0^{a}

(1): Intended values for the diets administered during the period in which collection of faeces was done.
*: Values are significantly different ($p < 0.05$) to the control group (0 U/kg feed).
a,b: Values within the same trial and column with different superscript are significantly different ($p < 0.05$).

The general status of the animals was good and no major incidences were reported. The apparent faecal digestibility of phosphorus was higher compared to control from levels of 250 U/kg feed and above in trial 1, and with 1,000 U/kg feed in trial 2. In trial 1, the total amount of ash/bone was higher in the animals receiving 1,000 U/kg feed (5.02 g ash/bone) compared to control (4.22 g ash/bone) but the percentage of ash/phosphorus in bone showed no differences between the animals receiving the unsupplemented diet and the animals receiving the phytase in any of the two studies.

The third trial[9] was a long-term trial in which a total of 96 male pig for fattening (DanBred) 70 days old (initial body weight of 29 kg) were penned in groups of two animals and the pens were allocated to one of the six dietary treatments (representing a total of eight replicates pens/treatment). The experimental diets were obtained from three basal diets (grower I, grower II and finisher) based on maize and soya bean meal (total phosphorus 4.3, 3.8 and 3.6 g/kg, total calcium 6.4, 5.5 and 5.1 g/kg, respectively) which were either not supplemented (control) or supplemented with APSA PHYTAFEED® 20,000 GR to provide 250, 500, 750 or 1,000 U/kg feed (confirmed by analysis). A positive control diet was also included (total phosphorus 5.3, 4.8 and 4.6 g/kg, total calcium 6.4, 5.5 and 5.1 g/kg, respectively). Diets were offered on *ad libitum* basis in mash form for 70 days. Mortality and health status were checked daily. Animals were individually weighed on days 0, 21, 42 and 70, feed intake was registered per pen and feed to gain ratio calculated. An analysis of variance was done with the performance data (pen basis) and considering the treatment as the effect. Group means were compared with Tukey test. The significance level was set at 0.05.

During the study, two pigs died[10] and four were culled.[11] The results on the performance of the animals are presented in Table 2. The final body weight and daily weight gain were significantly higher

[9] Technical dossier/Section IV/Annex IV.3.1 and supplementary information December 2019.
[10] One for the positive control and another one in the 1,000 U/kg feed group.
[11] Two in the control diet, one in the 500 U/kg feed group and another one in the 1,000 U/kg feed group.

in pigs fed with 1,000 U/kg feed compared to control. No differences were observed in the feed to gain ratio between the treatments.

Table 2: Effect of APSA PHYTAFEED® 20,000 on the performance of pigs for fattening

Groups (FTU/kg feed)	Average daily feed intake (kg)	Initial body weight (kg)	Final body weight (kg)	Daily weight gain (kg)	Feed to gain ratio
Control	2.50	28.9	91.1^{b}	0.887^{b}	2.81
250	2.59	29.2	95.5^{ab}	0.948^{ab}	2.74
500	2.62	29.2	96.9^{ab}	0.970^{ab}	2.70
750	2.58	28.9	95.2^{ab}	0.944^{ab}	2.73
1,000	2.64	29.4	98.4^{a}	0.987^{a}	2.69
Positive control	2.61	29.2	96.5^{ab}	0.965^{ab}	2.71

a,b: Values within the same column with different superscript are significantly different ($p < 0.05$).

The results of the two short-term trials showed a significant improvement of the apparent faecal digestibility of phosphorus in pigs fed the additive; however, no significant improvements on the bone mineralisation were observed and therefore the studies do not support the efficacy of the additive. In the long-term trial, significant improvements were found in the performance of pigs for fattening that were fed with the phytase at 1,000 U/kg feed. Owing to the limited evidence of efficacy in the studies submitted, the FEEDAP Panel cannot conclude on the efficacy of the additive APSA PHYTAFEED® GR/L in pigs for fattening.

3.4. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation[12] and Good Manufacturing Practice.

4. Conclusions

APSA PHYTAFEED® 20,000 GR/L is safe pigs for fattening at the recommended dose.

The FEEDAP Panel concludes that there are no concerns for consumer safety and no risks for the environment are expected from the use of APSA PHYTAFEED® 20,000 GR/L in pigs for fattening. The additive is not a skin or eye irritant, and it is not a dermal sensitiser but it should be considered a respiratory sensitiser.

The FEEDAP Panel cannot conclude on the efficacy of APSA PHYTAFEED® 20,000 GR/L as a feed additive for pigs for fattening.

Documentation as provided to EFSA/Chronology

Date	Event
08/03/2019	Dossier received by EFSA. APSA PHYTAFEED® 20,000 GR/L. Submitted by Andrés Pintaluba S.A
06/05/2019	Reception mandate from the European Commission
21/06/2019	Application validated by EFSA – Start of the scientific assessment
26/09/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: Characterisation*
04/10/2019	Reception of supplementary information from the applicant - Scientific assessment re-started
21/09/2019	Comments received from Member States
12/12/2019	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

[12] Regulation (EC) No 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

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Abbreviations

CGMCC	China General Microbiological Culture Collection Centre
EFSA FEEDAP	Panel EFSA Panel on Additives and Products or Substances used in Animal Feed
EURL	European Union Reference Laboratory
NOAEL	no observed adverse effects level