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Assessment of the feed additive consisting of *Pediococcus pentosaceus* DSM 23376 for all animal species for the renewal of its authorisation (Agri-King, Inc.)

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Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the assessment of the application for renewal of *Pediococcus pentosaceus* DSM 23376, as a technological additive to improve ensiling of forage for all animal species. The applicant has provided evidence that the additive currently on the market complies with the existing conditions of authorisation. There is no new evidence that would lead the FEEDAP Panel to reconsider its previous conclusions. Thus, the Panel concludes that the additive remains safe for all animal species, consumers and the environment under the authorised conditions of use. Regarding user safety, the additive is not irritant to skin or eyes but owing to its proteinaceous nature, it should be considered a respiratory sensitiser. No conclusions can be drawn on the skin sensitisation potential of the additive. There is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

Keywords: technological additive, silage, *Pediococcus pentosaceus* DSM 23376, safety, efficacy, QPS, renewal

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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 14(1) of that Regulation lays down that an application for renewal shall be sent to the Commission at the latest one year before the expiry date of the authorisation.

The European Commission received a request from Agri-King, Inc., represented in the EU by Agri-king Limited[2] for the renewal of the authorisation of the additive consisting of *Pediococcus pentosaceus* DSM 23376, when used as a feed additive for all animal species (category: technological additives; functional group: silage additives).

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 14(1) (renewal of the authorisation). 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 13 April 2022.

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 feed additive consisting of *Pediococcus pentosaceus* DSM 23376, when used under the proposed conditions of use (see **Section 3.1.3**).

1.2. Additional information

The additive consists of viable cells of *Pediococcus pentosaceus* DSM 23376 and is currently authorised as a feed additive for all animal species in the European Union (1k2105).[3]

EFSA issued one opinion on the safety and efficacy of this product when used in forages for all animal species (EFSA FEEDAP Panel, 2012a).

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[4] in support of the authorisation request for the use of *Pediococcus pentosaceus* DSM 23376 as a feed additive.

In accordance with Article 38 of the Regulation (EC) No 178/2002[5] and taking into account the protection of confidential information and of personal data in accordance with Articles 39 to 39e of the same Regulation, and of the Decision of EFSA's Executive Director laying down practical arrangements concerning transparency and confidentiality,[6] a non-confidential version of the dossier has been published on Open.EFSA.[7]

According to Article 32c(2) of Regulation (EC) No 178/2002 and to the Decision of EFSA's Executive Director laying down the practical arrangements on pre-submission phase and public consultations,[6] EFSA carried out a public consultation on the non-confidential version of the application from 30 November to 21 December 2022 for which no comments were received.

[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] Agri-King Inc. represented in the EU by Agri-king Limited, P25 DD21, Glenawilling, Ballymacoda, Co. Cork.
[3] Commission Implementing Regulation (EU) No 1119/2012 of 29 November 2012 concerning the authorisation of preparations of *Pediococcus acidilactici* CNCM MA 18/5 M DSM 11673, *Pediococcus pentosaceus* DSM 23376, NCIMB 12455 and NCIMB 30168, *Lactobacillus plantarum* DSM 3676 and DSM 3677 and *Lactobacillus buchneri* DSM 13573 as feed additives for all animal species OJ L 330, 30.11.2012, p. 14–18.
[4] FEED dossier reference: FEED-2021-2494.
[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, pp. 1–48.
[6] Decision available at: https://www.efsa.europa.eu/en/corporate-pubs/transparency-regulation-practical-arrangements
[7] Available at: https://open.efsa.europa.eu/dossier/FEED-2021-2494

In addition, the confidential version of the technical dossier was subject to a target consultation of the interested Member States from 13 April to 13 July 2022 for which received comments that were considered for the assessment.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment are valid and applicable for the current application.[8]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of *Pediococcus pentosaceus* DSM 23376 is in line with the principles laid down in Regulation (EC) No 429/2008[9] and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012b), Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018) and Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2021).

3. Assessment

The product consisting of viable cells of *Pediococcus pentosaceus* DSM 23376 is authorised as a technological additive (functional group: silage additives) for use in forages for all animal species. This assessment regards the renewal of the authorisation of the above-mentioned additive.

3.1. Characterisation

3.1.1. Characterisation of the additive

The additive is currently authorised with a minimum content of the active agent (*P. pentosaceus* DSM 23376) of 1.5×10^{11} colony forming units (CFU)/g of additive. The product consists of [redacted] cell concentrate and [redacted] maltodextrin as a carrier.[10] The applicant stated that the manufacturing process has not been modified since the first authorisation was granted[11] and declared that no antimicrobials are used during product manufacturing.[12]

Analysis of five recent batches showed compliance with specifications (mean: 1.60×10^{11} CFU/g additive, range $1.56–1.65 \times 10^{11}$ CFU/g additive).[13]

Analysis of three batches of the additive showed compliance with the specifications set for coliforms (< 10 CFU/g), *Escherichia coli* (< 10 CFU/g), yeasts and filamentous fungi (< 10 CFU/g) and *Salmonella* spp. (no detection in 25 g). Three batches were also tested for aflatoxins (B1, B2, G1, and G2), arsenic, mercury, lead and cadmium, showing levels below the respective limits of quantification (LOQs) of the analytical methods.[14] The same batches were tested for polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and coplanar dioxin-like polychlorinated biphenyls (Co-planar PCBs). The calculated (upper bound) levels of dioxins and the sum of dioxins and dioxin-like-PCBs ranged 0.0602–0.0832 ng WHO-PCDD/F-TEQ/kg and 0.0924–0.127 ng WHO-PCDD/F-PCB-TEQ/kg, respectively (in all three batches).[15]

The detected amounts of the above-described impurities do not raise safety concerns.

No new data were provided regarding the physico-chemical properties of the additive. The data described in the previous opinion (EFSA FEEDAP Panel, 2012a) still applies.

[8] The full report is available on the EURL website: https://joint-research-centre.ec.europa.eu/system/files/2013-02/FinRep-FAD-2010-0127%252B0252%252B0259%252B0280.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] Annex_II.1.3.1 composition_fermentation_media_additive.

[11] Annex_II.3.1.1 Manufacturing_process and Annex_II_1_3_3 product_formulation.

[12] Manufacturing_process.

[13] Annex_II.1.3.2 batch variation.

[14] LOQ: aflatoxins B1, B2, G1 and G2: 5.0 μg/kg, As: 0.01 mg/kg, Hg: 0.01 mg/kg, Pb: 0.01 mg/kg and Cd: 0.01 mg/kg.

[15] Annex_II.1.4.1b purity_test_protocol.

3.1.2. Characterisation of the active agent

The strain was originally isolated from natural forage and is deposited in the Deutsche Sammlung von Mikro-organismen und Zellkulturen (DSMZ) under the accession number DSM 23376.[16] It has not been genetically modified.

The strain DSM 23376 was identified at species level as *P. pentosaceus* by bioinformatic analysis of the whole genome sequence (WGS). [redacted][17]

The antimicrobial susceptibility of the strain DSM 23376 was tested against the battery of antibiotics recommended by the FEEDAP Panel (EFSA FEEDAP Panel, 2018). All the minimum inhibitory concentration (MIC) values for the strain were equal or fell below the corresponding cut-off values.[18] Therefore, the strain is considered to be susceptible to all relevant antibiotics.

The WGS of the strain DSM 23376 was interrogated for the presence of antimicrobial resistance (AMR) genes against [redacted][17] and [redacted][19] databases. No hits of concern were identified.

3.1.3. Conditions of use

The additive is currently authorised for use in forages for all animal species. Under other provisions of the authorisation, it is specified that:

- In the directions for use of the additive and premixture, indicate the storage temperature and storage life.
- Minimum dose of the additive when used without combination with other micro-organisms as silage additives: 1×10^8 CFU/Kg fresh material.
- For safety: it is recommended to use breathing protection and gloves during handling.

The applicant has requested to maintain the same conditions of use.[20]

3.2. Safety

The applicant declares that no adverse effects including accidents for target animals, consumers, users and/or the environment have been reported since the approval of the additive.[21]

3.2.1. Safety for the target species, consumers and environment

In the previous opinion, the Panel concluded that following the Qualified Presumption of Safety (QPS) approach to safety assessment, the use of this strain in the production of silage is considered safe for the target species, consumers and the environment (EFSA FEEDAP Panel, 2012a). In the context of the current application, the identity of the strain as *Pediococcus pentosaceus* was confirmed, and evidence was provided that the strain does not show acquired antimicrobial determinants for antibiotics of human and veterinary importance (EFSA, 2007; EFSA BIOHAZ Panel, 2023). Consequently, the conclusions already reached are still valid and *Pediococcus pentosaceus* DSM 23376 is considered safe for the target species, consumers and the environment.

3.2.2. Safety for the user

In the previous assessment (EFSA FEEDAP Panel, 2012a), the Panel concluded regarding user safety: '*preparations containing the strains may cause irritation on prolonged contact with skin, and eye irritation upon direct contact. A significant fraction of these products with particles that are potentially inhalable means that exposure via the respiratory route is a hazard*' and '*given the proteinaceous nature of the active agents, to treat all six additives as skin and respiratory sensitisers*'.

[16] Annex II.2.1.2.13 strain_deposit.
[17] Annex II.2.1.2.1_WGS_report.
[18] Annex_II.2.1.2.17 Phenotypic_AMR.
[19] Annex_II.2.1.2.14_WGS_Addendum.
[20] Conditions of use.
[21] Safety Statement_P_pentosaceus and Annex_III_1_Conf_Statement_adverse_events.

The applicant has submitted a skin irritation[22] and an eye irritation[23] studies in order to address the safety for the user.

The skin irritation potential of the additive was investigated in an *in vitro* skin irritation study according to OECD TG 439. The results indicated that the additive is non-irritant to the skin in accordance with UN GHS "No Category".[22]

The eye irritation potential of the additive was investigated in an *in vitro* eye irritation study according to OECD TG 492. Based on the results of the study the additive is classified as non-irritant to eyes in accordance with UN GHS 'No Category'.[23]

The FEEDAP Panel notes that the OECD test guidelines available at present are designed to assess the skin sensitisation potential of chemical substances only and that currently no validated assays for assessing the sensitisation potential of microorganisms are available.[24] The additive should be considered a potential respiratory sensitiser.

3.2.3. Conclusions on safety

The FEEDAP Panel concludes that there is no new evidence that would lead to reconsider the previous conclusions that *Pediococcus pentosaceus* DSM 23376 is safe for the target species, consumers and the environment under the authorised conditions of use. Regarding user safety, *Pediococcus pentosaceous* DSM 23376 is not irritant to skin or eyes but owing to its proteinaceous nature, it is considered a respiratory sensitiser. No conclusions can be drawn on the potential of the additive to cause skin sensitisation.

3.3. Efficacy

The present application for renewal of the authorisation does not include a proposal for amending or supplementing the conditions of the original authorisation that would have an impact on the efficacy of the additive. Therefore, there is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

4. Conclusions

The applicant has provided evidence that the additive currently on the market complies with the existing conditions of authorisation.

The Panel concludes that *Pediococcus pentosaceous* DSM 23376 remains safe for all animal species, consumers and the environment under the authorised conditions of use. Regarding user safety, the additive is not irritant to skin or eyes, but should be considered a respiratory sensitiser. No conclusions can be drawn on the skin sensitisation potential of the additive.

There is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

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[22] Annex_III.2 skin_irritation.
[23] Annex_III.3_eye_irritation.
[24] https://www.efsa.europa.eu/sites/default/files/2022-07/feedap20220629-30_m.pdf

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Abbreviations

AMR	antimicrobial resistance
CFU	colony forming unit
dDDH	digital DNA–DNA hybridisation
DSM	Deutsche Sammlung von Mikroorganismen und Zellkulturen
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
LOQ	limit of quantification
MIC	minimum inhibitory concentration
OECD	Organisation for Economic Co-operation and Development
PCB	polychlorinaed biphenyl
PCDD	polychlorinated dibenzodioxin
PDCF	polychlorinated dibenzofuran
QPS	Qualified Presumption of Safety
TEQ	toxic equivalents
WGS	whole genome sequence
WHO	World Health Organization