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Assessment of the feed additive consisting of *Lactiplantibacillus plantarum* (previously *Lactobacillus plantarum*) DSM 19457 for all animal species for the renewal of its authorisation (Biomin GmbH)

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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 assessment of the application for renewal of authorisation of *Lactiplantibacillus plantarum* (previously *Lactobacillus plantarum*) DSM 19457 as a technological additive for use in 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 evidence to lead the FEEDAP Panel to reconsider its previous conclusions. Thus, the Panel concluded 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. In the absence of data, no conclusions could 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 additive, *Lactiplantibacillus plantarum* DSM 19457, 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 Biomin GmbH[2] for the renewal of the authorisation of the additive consisting of *Lactiplantibacillus plantarum* (previously *Lactobacillus plantarum*) DSM 19457, 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 21 December 2021.

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 *Lactiplantibacillus plantarum* (previously *Lactobacillus plantarum*) DSM 19457, when used under the proposed conditions of use (see Section 3.1.3).

1.2. Additional information

The additive consists of viable cells of *Lactiplantibacillus plantarum* (previously *Lactobacillus plantarum*) DSM 19457. EFSA has adopted one opinion on the safety and efficacy of this product for all animal species (EFSA FEEDAP Panel, 2012a). It is currently authorised as a feed additive in the European Union (1 k20718).[3]

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 *Lactiplantibacillus plantarum* (previously *Lactobacillus plantarum*) DSM 19457 as a feed additive.

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 are valid and applicable for the current application.[5]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of *Lactiplantibacillus plantarum* (previously *Lactobacillus plantarum*) DSM 19457 is in line with the principles laid down in Regulation

[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] Biomin GmbH, Erber Campus 1, 3,131 Getzersdorf, Austria.
[3] Commission Implementing Regulation (EU) No 1065/2012 of 13 November 2012 concerning the authorization of preparations of Lactobacillus plantarum (DSM 23375, CNCM I-3235, DSM 19457, DSM 16565, DSM 16568, LMG 21295, CNCM MA 18/5 U, NCIMB 30094, VTT E-78076, ATCC PTSA-6139, DSM 18112, DSM 18113, DSM 18114, ATCC 55943 and ATCC 55944) as feed additives for all animal species OJ L 314, 14.11.2012, p. 15.
[4] FEED dossier reference: FAD-2021-0048.
[5] The full report is available on the EU Science Hub website: https://joint-research-centre.ec.europa.eu/publications/20-fad-dossiers_en (FAD-2010-0048).

(EC) No 429/2008[6] and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012a), 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, 2013).

3. Assessment

The product consisting of viable cells of *L. plantarum* DSM 19457 is currently authorised for use as technological additive (functional group: silage additives) in forages for all animal species. This assessment regards the renewal of the authorisation of *L. plantarum* DSM 19457 for the above-mentioned animal species.

3.1. Characterisation

3.1.1. Characterisation of the additive

The additive currently authorised consists of a powder containing the active agent (*L. plantarum* DSM 19457) at the minimum concentration of 1×10^{10} colony forming units (CFU)/g of additive. The additive may also contain cryoprotectants [redacted], approx. 65%) and fermentation medium residues (approx. 6%).[7]

The applicant declared that no modifications have been made to the composition or manufacturing process of the additive since the first authorisation was granted.

Analysis of five batches showed a mean value of 1.7×10^{10} CFU/g (range $1.5–1.8 \times 10^{10}$ CFU/g).[8]

Specifications are set for coliforms (<1,000 CFU/g), *Escherichia coli* (< 10 CFU/g), *Salmonella* spp. (not detected in 25 g), yeasts and filamentous fungi (< 1,000 CFU/g), arsenic (< 2 mg/kg), lead (< 5 mg/kg), cadmium (< 0.5 mg/kg) and mercury (< 0.1 mg/kg). Analysis of six batches showed compliance with these limits and Enterobacteriaceae counts (based on three batches) < 10 CFU/g.[9] Three batches were also tested for aflatoxin B1 concentration and showed levels below the limit of quantification of the analytical method.[10]

Three batches of the additive (carrier [redacted]) were tested for dusting potential using the Stauber-Heubach method and showed a mean value of 3.1 g/m^3 (range: 3.0–3.2 g/m^3).[11]

3.1.2. Characterisation of the active agent

The active agent was isolated from silage and is deposited in the Deutsche Sammlung von Mikro-organismen und Zellkulturen (DSMZ) with the accession number DSM 19457.[12] It has not been genetically modified.

The taxonomical identification of the active agent was confirmed by a bioinformatic analysis of its whole genome sequence (WGS) data.[13] The taxonomic assignment was based on an average nucleotide identity (OrthoANI) value of 99.16% with the type strain of the species (*L. plantarum* ATCC 14917^T). The strain was predicted to harbour at least three plasmids based on WGS analysis (PlasmidFinder).

Susceptibility of the strain to antimicrobials was tested using broth microdilution method and including the set of antimicrobials recommended by EFSA (EFSA FEEDAP Panel, 2018).[14] All the minimum inhibitory concentration values were below the cut-off values, except for kanamycin and erythromycin, which were one dilution higher. However, exceeding the cut-off by one dilution is considered within the experimental error of the method, and therefore, the strain is considered to be susceptible to all the relevant antibiotics.

[6] 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.

[7] Technical dossier/Section II/Annex II_27.

[8] Technical dossier/Section II/Annexes II_04-II_08 and Supplementary information September 2022/Answers to Supplementary Information Request.

[9] Technical dossier/Section II/Annexes II_06-II_011 and Supplementary information September 2022/Answers to Supplementary Information Request/ Annexes (i) – (vi).

[10] Technical dossier/Section II/Annexes II_12-II_014 and Supplementary information September 2022/Answers to Supplementary Information Request. Limit of quantification: 0.23 μg/kg.

[11] Technical dossier/Supplementary information September 2022/Answers to Supplementary Information Request and Annex (vii).

[12] Technical dossier/section II/Annex II_02.

[13] Technical dossier/section II/Annex II_22–23.

[14] Technical dossier/section II/Annex II_24.

The WGS data of the strain were interrogated for the presence of antimicrobial resistance (AMR) genes against the NCBI Bacterial Antimicrobial Resistance Reference Gene database and ResFinder, using the search tools AMRFinderPlus, ABRIcate and Diamond for NCBI and ABRIcate and tblastn for ResFinder, with a threshold of 70% similarity and 60% length coverage.[13] No genes of concern were identified.

3.1.3. Conditions of use

The additive is currently authorised for use in forages for all target 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 microorganisms as silage additives: 5×10^7 CFU/kg fresh material.
- For safety: It is recommended to use breathing protection and gloves during handling.

The additive can be incorporated into the forage either directly or sprayed after dissolving in water.
The applicant has requested to maintain the same conditions of use.

3.2. Safety

In the previous opinion, the Panel concluded that following the Qualified Presumption of Safety (QPS) approach, the use of *L. plantarum* DSM 19457 in the production of silage was considered safe for target species, consumers and the environment (EFSA FEEDAP Panel, 2012b). In the context of this application, the identity of the strain as *L. plantarum* DSM 19457 was confirmed and evidence that the strain does not show acquired antimicrobial resistances for antibiotics of human and veterinary importance was provided. Consequently, the conclusions already reached are still valid and *L. plantarum* DSM 19457 is safe for the target species, consumers and the environment.

In the previous assessment (EFSA FEEDAP Panel, 2012b), the Panel concluded regarding user safety: 'The generic material safety data sheet proposed for the 18 strains indicates that preparations containing the strains may cause irritation on prolonged contact with skin and eyes. The dusting potential of formulations tested is generally high. This, coupled with the significant fraction of these products with particles that are potentially inhalable, means that exposure via a respiratory route is a hazard. Although users at the farm level are exposed to the additive for only a short period of time when preparing the aqueous suspension, the FEEDAP Panel considers it prudent, given the proteinaceous nature of the active agents, to treat all 18 additives as skin and respiratory sensitisers'.

Recent data on dusting potential of the additive (range: 3.0–3.2 g/m^3) showed that exposure by inhalation is likely. Owing to the proteinaceous nature of the active agent, the additive is assumed to be a respiratory sensitiser.

The applicant has also submitted a skin irritation[15] and an eye irritation[16] study in order to address the safety for the user.

The *in vitro* skin irritation study was performed with *L. plantarum* DSM 19457 (carrier maltodextrin), according to GLP and OECD Guideline 439 (2021). According to the results obtained, the test item would be classified as non-irritant to skin.

The *in vitro* eye irritation study (BCOP) was performed with *L. plantarum* DSM 19457 (carrier maltodextrin) according to GLP and OECD Guideline 437 (2020). According to the results obtained, the test item would be classified as non-irritant to the eyes.

No data were provided on the skin sensitisation potential of the additive.

Once an active agent has been authorised as a silage additive, different formulations can be placed on the market with reference to that authorisation. The applicant listed several cryoprotectants and carriers which would allow multiple formulations of the additive to be produced and, consequently, not all forms can be directly tested for user safety. However, for assessing the safety for the user of the additive, the active agent is the principal concern provided that other components do not introduce safety issues. For this specific product, the excipients used in the preparation of the final formulation do not introduce additional risks.

[15] Technical dossier/Supplementary information September 2022/Annex (ix) Skin irritation_Epiderm.
[16] Technical dossier/Supplementary information September 2022/Annex (iv) YM_LP1E10_027.

The applicant declares that no adverse effects on the health of workers have been observed in the production plant or during usage of the additive since its authorisation.[17]

3.2.1. Conclusions on safety

The FEEDAP Panel concludes that there is no new evidence to lead it to reconsider the previous conclusions that *L. plantarum* DSM 19457 is safe for the target species, consumers and the environment under the authorised conditions of use. Regarding user safety, *L. plantarum* DSM 19457 is not irritant to skin or eyes, but owing to its proteinaceous nature, it is assumed to be a respiratory sensitiser. In the absence of data, no conclusions can be drawn on the skin sensitisation potential.

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 *Lactiplantibacillus plantarum* DSM 19457 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. In the absence of data, 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.

5. Documentation provided to EFSA/chronology

Date	Event
28/05/2021	Dossier received by EFSA. Lactiplantibacillus plantarum DSM 19457 for all animal species. Submitted by Biomin GmbH
15/09/2021	Reception mandate from the European Commission
21/12/2021	Application validated by EFSA – Start of the scientific assessment
21/03/2022	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 and safety for the user*
21/09/2022	Reception of supplementary information from the applicant – Scientific assessment re-started
24/03/2022	Comments received from Member States
22/11/2022	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012b. Scientific Opinion on the safety and efficacy of 18 strains of Lactobacillus plantarum (DSM 23375, CNCM I-3235, DSM 19457, DSM 16568, LMG 21295, DSM 16565, VTT E-78076, CNCM MA 18/5U, NCIMB 30238, ATTC PTA-6139, DSM 18112, ATCC 55058, DSM 18113, DSM 18114, ATCC 55942, ATCC 55943, ATCC 55944 and NCIMB 30094) as silage additives for all species. EFSA Journal 2012;10(6):2732, 36 pp. https://doi.org/10.2903/j.efsa.2012.2732

[17] Technical dossier/Section III/Annex II_01.

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2013. Guidance on the renewal of the authorisation of feed additives. EFSA Journal 2013;11(10):3431, 8 pp. https://doi.org/10.2903/j.efsa.2013.3431

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Abbreviations

CFU	colony-forming unit
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
MIC	minimum inhibitory concentration
WGS	whole genome sequence