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## Assessment of the feed additive consisting of *Lactococcus lactis* DSM 11037 for all animal species for the renewal of its authorisation (Chr. Hansen A/S)

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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 *Lactococcus lactis* DSM 11037, 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, consumer and the environment under the authorised conditions of use. Regarding user safety, the additive is not a skin and eye irritant but should be considered a respiratory sensitiser. In absence of data, the Panel cannot conclude 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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## 1. Introduction

### 1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003<sup>1</sup> 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 (Chr. Hansen A/S)<sup>2</sup> for the renewal of the authorisation of the additive consisting of *Lactococcus lactis* DSM 11037, 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 15 June 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 feed additive consisting of *Lactococcus lactis* DSM 11037, when used under the proposed conditions of use (see **Section 3.1.3**).

### 1.2. Additional information

The additive *Lactococcus lactis* DSM 11037 is currently authorised for use in feed for all animal species in the European Union (1k2081).<sup>3</sup>

EFSA issued one opinion on the safety and efficacy of this product when used in forages for all animal species (EFSA FEEDAP Panel, 2011).

## 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<sup>4</sup> in support of the authorisation request for the use of *Lactococcus lactis* DSM 11037 as a feed additive.

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.<sup>5</sup>

### 2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of active substance is in line with the principles laid down in Regulation (EC) No 429/2008<sup>6</sup> and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012), Guidance on the renewal of the authorisation of feed additives

<sup>1</sup> 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.

<sup>2</sup> Chr. Hansen A/S, 10 – 12 Boege Allé, DK 2970, Hoersholm, Denmark.

<sup>3</sup> Commission Implementing Regulation (EU) No 1263/2011 of 5 December 2011 concerning the authorisation of *Lactobacillus buchneri* (DSM 16774), *Lactobacillus buchneri* (DSM 12856), *Lactobacillus paracasei* (DSM 16245), *Lactobacillus paracasei* (DSM 16773), *Lactobacillus plantarum* (DSM 12836), *Lactobacillus plantarum* (DSM 12837), *Lactobacillus brevis* (DSM 12835), *Lactobacillus rhamnosus* (NCIMB 30121), *Lactococcus lactis* (DSM 11037), *Lactococcus lactis* (NCIMB 30160), *Pediococcus acidilactici* (DSM 16243) and *Pediococcus pentosaceus* (DSM 12834) as feed additives for all animal species OJ L 322, 6.12.2011, p. 3–8.

<sup>4</sup> FEED dossier reference: FAD-2020-0101.

<sup>5</sup> The full report is available on the EU Science Hub website: [https://joint-research-centre.ec.europa.eu/publications/20-fad-dossiers\\_en](https://joint-research-centre.ec.europa.eu/publications/20-fad-dossiers_en)

<sup>6</sup> 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.

(EFSA FEEDAP Panel, 2013) and Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018).

### 3. Assessment

The product consisting of viable cells of *L. lactis* DSM 11037 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 *L. lactis* DSM 11037 for the above-mentioned species.

#### 3.1. Characterisation

##### 3.1.1. Characterisation of the additive

The product consists of ~ 30% bulk (range 22–40%) containing the active agent and a cryoprotectant, 8% silica as an anticaking agent and 52–70% maltodextrin as a carrier. The information submitted regarding the manufacturing process lists the increase in the content of anticaking agent from 2% to 8% compared to the information submitted when the first authorisation was granted. The additive is currently authorised with a minimum content of the active agent *Lactococcus lactis* DSM 11037 of  $5 \times 10^{10}$  colony forming units (CFU) per gram of additive.

Analysis of five recent batches showed compliance with the specifications (mean:  $4.28 \times 10^{11}$  CFU/g additive, range  $3.8\text{--}4.7 \times 10^{11}$  CFU/g additive).<sup>7</sup>

Specifications are set for coliforms, yeasts and filamentous fungi (< 1,000 CFU/g), *Salmonella* spp. (no detection in 25 g) and *Escherichia coli* (< 10 CFU/g).<sup>8</sup> Analysis of the above-mentioned batches of the additive showed compliance with these limits<sup>7</sup> with the exception of *Salmonella* spp. detection for which the Panel notes that despite the specification, only data from analyses of 5 g instead of 25 g in three batches were provided.<sup>9</sup>

Three recent batches were tested for aflatoxin B1, mercury (Hg), lead (Pb), cadmium (Cd) and arsenic (As) concentrations. Results showed the following mean values: 0.0058 mg Hg/kg (range: 0.0040–0.0077 mg/kg), 0.024 mg Pb/kg (range: 0.022–0.026 mg/kg), 0.039 mg Cd/kg (range: 0.035–0.045 mg/kg) and 0.033 mg As/kg (range: 0.028–0.036 mg/kg).<sup>10</sup> Aflatoxin B1 in all batches was below the limit of quantification (0.46 µg aflatoxin B1/kg).<sup>10,11</sup>

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

In order to establish the impact of the change of the amount of anti-caking on the physico-chemical properties of the additive, the applicant has provided new data on dusting potential and particle size distribution. The dusting potential was measured in three recent batches (mean 1,178 mg/m<sup>3</sup>; range 1,010–1,300 mg/m<sup>3</sup>).<sup>12</sup> Results on the particle size distribution by laser diffraction showed that ~ 47% of the additive consists of particles with diameters below 100 µm, 32% below 50 µm and 8% below 10 µm.<sup>13</sup> No other new data were provided regarding the physico-chemical properties or stability of the additive. Since the changes introduced in the additive are not expected to have a significant effect on these characteristics, the data described in the previous opinion (EFSA FEEDAP Panel, 2011) still apply.

##### 3.1.2. Characterisation of the active agent

The active agent is deposited in the Deutsche Sammlung von Mikro-organismen und Zellkulturen (DSMZ) with accession number DSM 11037.<sup>14</sup>

The taxonomical identification was confirmed by [REDACTED]

<sup>7</sup> Technical dossier/Section II/Annex II.1.3a.

<sup>8</sup> Technical dossier/Section II/Sect\_II\_Identity.

<sup>9</sup> Technical dossier/Supplementary information December 2021/Annex\_Q2 and 1.Answers\_EFSA\_Qs\_DSM11037\_12.2021.

<sup>10</sup> Technical dossier/Section II/Annex II.1.4.2.

<sup>11</sup> Technical dossier/Supplementary information December 2021/1.Answers\_EFSA\_Qs\_DSM11037\_12.2021.

<sup>12</sup> Technical dossier/Section II/Annex II.1.5.b.

<sup>13</sup> Technical dossier/Section II/Annex II.1.5.a.

<sup>14</sup> Technical dossier/Section II/Annex II.2.1.2a.

<sup>15</sup> Technical dossier/Section II/Annex II 2.1.2.b.

<sup>16</sup> Technical dossier/Supplementary information December 2021/Annex\_Q4\_ID.Cert\_DSM11037.

The bacterial strain was subjected to antimicrobial susceptibility testing using broth microdilution method and including the set of antimicrobials recommended by EFSA (EFSA FEEDAP Panel, 2018).<sup>17</sup> All the minimum inhibitory concentration values were equal or below the corresponding EFSA cut-off values for *L. lactis*. Therefore, the strain is considered to be susceptible to all the relevant antimicrobials.

The WGS of the strain was interrogated for the presence of antimicrobial resistance genes

No hits of concern were identified.

### 3.1.3. Conditions of use

The additive is currently authorised for use in silage 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 microorganisms as silage additives:  $1 \times 10^8$  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.

## 3.2. Safety

### 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 was considered safe for target species, consumers and the environment (EFSA FEEDAP Panel, 2011). In the context of the current application, the identity of the strain as *Lactococcus lactis* was confirmed and evidence was provided that the strain does not show acquired antimicrobial determinants for antibiotics of human and veterinary importance. Consequently, the conclusions already reached are still valid and *Lactococcus lactis* DSM 11037 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, 2011), the Panel concluded regarding user safety: 'Given the proteinaceous nature of the active agent and in the absence of evidence to the contrary, the additive should be considered to have the potential to be a skin and respiratory sensitiser'.

The applicant submitted a total of four studies to address the safety for the user: three on skin irritation (two *in vitro* and one *in vivo*) and one on eye irritation.

The skin irritation potential of the additive was tested *in vitro* under GLP principles and according to OECD TG 439.<sup>20,21</sup> A first study did not allow to assign a definitive UN GHS category (Category 1 or Category 2).<sup>20</sup> A second study showed no skin irritation potential under the test conditions chosen (UN GHS Classification 'No Category').<sup>21</sup> The *in vivo* skin irritation potential of the additive was tested in a valid study performed according to OECD TG 404, which showed that it is not a skin irritant.<sup>22</sup>

<sup>17</sup> Technical dossier/Section II/ Annex II 2.2.2.b.

<sup>18</sup> Technical dossier/Section II/Annex II.2.2.2a.

<sup>19</sup> Technical dossier/Supplementary Information December 2021/Annex\_Q5.

<sup>20</sup> Technical dossier/Supplementary Information December 2021/Annex\_Q7.2\_OECD439a\_Skin.pdf.

<sup>21</sup> Technical dossier/Supplementary Information December 2021/Annex\_Q7.3\_OECD439b\_Skin.pdf.

<sup>22</sup> Technical dossier/Supplementary Information December 2021/Annex\_Q7.4\_OECD404\_InVivo\_skin.pdf.

The eye irritation potential of the additive was tested *in vitro* in a study under GLP principles performed according to OECD TG 492, which showed that is not an eye irritant (UN GHS Classification 'No Category').<sup>23</sup>

No information on skin sensitisation was provided; therefore, the FEEDAP Panel cannot draw conclusions on the skin sensitisation potential of the additive.

The applicant declares that no adverse effects on the health of manufacturing workers or users of the additive have been reported since the approval of the additive.<sup>24</sup>

### 3.2.3. Extensive Literature Search

The applicant performed a literature search to provide evidence that the additive remains safe under the approved conditions for target species, consumers, users and the environment.<sup>25</sup> The literature search was conducted in PubMed and EBSCO EDS (included the databases Academic Onefile, Food Science Source and AGRIS) and covered the period 2010–2020.<sup>26,27</sup> Search terms included the active agent and aspects related to the safety for animals, humans and the environment. The literature search retrieved a total of 26 results that were full text screened, from which three were further included in the review process but none considered relevant for the herein application because they referred either to other strain (two hits) or to biogenic amine production (one hit).

### 3.2.4. Conclusions on safety

The FEEDAP Panel concludes that there is no new evidence that would lead it to reconsider the previous conclusions that *Lactococcus lactis* DMS 11037 is safe for the target species, consumers and the environment under the authorised conditions of use. The additive is not a skin and eye irritant, but 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

Based on the QPS approach to safety assessment, *Lactococcus lactis* DSM 11037 is presumed safe for the target species, consumers and the environment.

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, consumer and the environment under the authorised conditions of use.

The additive is not an eye or skin irritant but should be considered a respiratory sensitiser. In absence of data, the FEEDAP Panel cannot draw conclusions 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
03/12/2020	Dossier received by EFSA. <i>Lactococcus lactis</i> DSM 11037. Submitted by Chr. Hansen A/S
18/12/2020	Reception mandate from the European Commission
15/06/2021	Application validated by EFSA – Start of the scientific assessment

<sup>23</sup> Technical dossier/Supplementary Information December 2021/Annex\_Q7.1\_OECD492\_Eye.pdf.

<sup>24</sup> Technical dossier/Section III and Section V\_Post\_Mark.

<sup>25</sup> Technical dossier/Section III/ Annex\_III\_1.1.

<sup>26</sup> Technical dossier/Section III/ Annex\_III\_1.1/3. Search\_Method\_Description.

<sup>27</sup> Technical dossier/Supplementary Information December 2021/Annex\_Q6.

Date	Event
<b>23/07/2021</b>	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: characterisation and safety</i>
<b>16/09/2021</b>	Comments received from Member States
<b>08/12/2021</b>	Reception of supplementary information from the applicant - Scientific assessment re-started
<b>23/03/2022</b>	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

## References

- EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2011. Scientific Opinion on the safety and efficacy of *Lactococcus lactis* (DSM 11037) as a silage additive for all species. EFSA Journal 2011;9(9):2374, 2 pp. <https://doi.org/10.2903/j.efsa.2011.2374>
- EFSA FEEDAP Panel, (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012. Guidance on studies concerning the safety of use of the additive for users/workers. EFSA Journal 2012;10(1):2539, 5 pp. <https://doi.org/10.2903/j.efsa.2012.2539>
- 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>
- EFSA Feedap Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Glandorf B, Herman L, Kärenlampi S, Aguilera J, Anguita M, Brozzi R and Galobart J, 2018. Guidance on the characterisation of microorganisms used as feed additives or as production organisms. EFSA Journal 2018;16(3):5206, 24 pp. <https://doi.org/10.2903/j.efsa.2018.5206>

## Abbreviations

CFU	colony forming unit
CV	coefficient of variation
DSMZ	Deutsche Sammlung von Mikro-organismen und Zellkulturen
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
LOD	limit of detection
LOQ	limit of quantification
OECD	Organisation for Economic Co-operation and Development
WGS	whole genome sequence