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SCIENTIFIC OPINION

Safety and efficacy of a feed additive consisting of L-lysine sulfate produced with *Corynebacterium glutamicum* CGMCC 23982 for all animal species (Eppen Europa SAS)

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) | **Roberto Edoardo Villa** | **Giovanna Azimonti** | **Eleftherios Bonos** | **Henrik Christensen** | **Mojca Durjava** | **Birgit Dusemund** | **Ronette Gehring** | **Boet Glandorf** | **Maryline Kouba** | **Marta López-Alonso** | **Francesca Marcon** | **Carlo Nebbia** | **Alena Pechová** | **Miguel Prieto-Maradona** | **Ilen Röhe** | **Katerina Theodoridou** | **Montserrat Anguita** | **Matteo L. Innocenti** | **Nicole Bozzi Cionci** | **Elisa Pettenati** | **Jordi Tarrés-Call**

Correspondence: feedap@efsa.europa.eu

The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts

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 L-lysine sulfate produced by fermentation with a non-genetically modified strain of *Corynebacterium glutamicum* (CGMCC 23982) when used as a nutritional additive in feed for all animal species. The active substance is L-lysine. The FEEDAP Panel concluded that the production strain qualifies for the qualified presumption of safety (QPS) approach to safety assessment; therefore, L-lysine sulfate produced with *C. glutamicum* CGMCC 23982 does not pose any safety concern associated with the production strain. L-Lysine sulfate produced with *C. glutamicum* CGMCC 23982 is considered safe for the target species when administered via feed. When using L-lysine sulfate, the background sulfur/sulfate content in the compound feed should be taken into account when formulating diets. The FEEDAP Panel has concerns on the use of L-lysine sulfate in water for drinking. L-Lysine sulfate produced with *C. glutamicum* CGMCC 23982 is safe for the consumer and for the environment. With regard to user safety, the additive should be considered irritant to skin, eyes and the respiratory tract. Any exposure to the additive is a risk. L-lysine sulfate is considered as an efficacious source of the essential amino acid L-lysine for non-ruminant animal species. For the supplemental L-lysine to be as efficacious in ruminants as in non-ruminant species, it would require protection against degradation in the rumen.

KEYWORDS

amino acid, CGMCC 23982, *Corynebacterium glutamicum*, efficacy, lysine sulfate, nutritional additive, safety

CONTENTS

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 feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from Eppen Europa SAS[2] for the authorisation of the additive consisting of L-lysine sulfate produced by fermentation with a non-genetically modified strain of *Corynebacterium glutamicum* (CGMCC 23982), when used as a feed additive for all animal species (category: nutritional additives; functional group: amino acids, their salts and analogues).

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). The dossier was received on 31 October 2023 and the general information and supporting documentation are available at https://open.efsa.europa.eu/questions/EFSA-Q-2023-00712. The particulars and documents in support of the application were considered valid by EFSA as of 19 February 2024.

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 L-lysine sulfate produced by fermentation with *C. glutamicum* CGMCC 23982, when used under the proposed conditions of use (see **Section 3.1.6**).

1.2 | Additional information

L-Lysine sulfate (minimum 55% lysine) produced by fermentation with *C. glutamicum* CGMCC 23982 is currently not authorised in the European Union (EU). L-Lysine produced by fermentation with different microbial strains is currently authorised for its use in all animal species as nutritional additive and as sensory additive.[3]

The Scientific Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) has published several opinions on the safety and efficacy of L-lysine and/or its salts produced by fermentation with different production strains for all animal species.[4]

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[5] in support of the authorisation request for the use of L-lysine sulfate produced by fermentation with *C. glutamicum* CGMCC 23982 as a feed additive.

In accordance with Article 38 of the Regulation (EC) No 178/2002[6] 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,[7] a non-confidential version of the dossier has been published on Open.EFSA.

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, EFSA carried out a public consultation on the non-confidential version of the technical dossier from 20 May to 10 June 2024, for which no comments were received.

The confidential version of the technical dossier was subject to a target consultation of the interested Member States from 20 February 2024 to 20 May 2024; the comments received were considered for the assessment.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA, peer-reviewed scientific papers and experts' knowledge, to deliver the present output.

[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]Eppen Europa SAS, 10 Rue de la Paix, 75002 Paris, France.
[3]See the European Union Register of Feed Additives, available online https://ec.europa.eu/food/system/files/2021-12/animal-feed_additives_eu-register_1831-03.pdf.
[4]Available online at EFSA Journal: https://efsa.onlinelibrary.wiley.com/journal/18314732.
[5]Dossier reference: FEED-2023-19630.
[6]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, p. 1–48.
[7]Decision available at: https://www.efsa.europa.eu/en/corporate-pubs/transparency-regulation-practical-arrangements.

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of L-lysine sulfate produced by fermentation with *C. glutamicum* CGMCC 23982 in animal feed.[8]

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and efficacy of L-lysine sulfate produced by fermentation with *C. glutamicum* CGMCC 23982 is in line with the principles laid down in Regulation (EC) No 429/2008[9] and the relevant guidance documents: Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017a), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEEDAP Panel, 2017b), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017c), Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019), Guidance on the assessment of the safety of feed additives for the users (EFSA FEEDAP Panel, 2023) and Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2024).

3 | ASSESSMENT

The additive L-lysine sulfate produced with *C. glutamicum* CGMCC 23982 is intended to be used as a nutritional additive (functional group: amino acids, their salts and analogues) in feed and water for drinking for all animal species.

3.1 | Characterisation

3.1.1 | Characterisation of the production microorganism

The active substance L-lysine is produced with a non-genetically modified strain of *C. glutamicum* which is deposited at the China General Microbiological Culture Collection Center (CGMCC) with the accession number CGMCC 23982.[10] The production strain was obtained [redacted] by conventional mutagenesis [redacted].[11]

The taxonomic identification of the production strain, CGMCC 23982, was confirmed [redacted].[12] [redacted].[13]

The antimicrobial susceptibility of the strain *C. glutamicum* CGMCC 23982 was tested [redacted] against the battery of antibiotics recommended by the EFSA FEEDAP Panel (EFSA FEEDAP Panel, 2018).[14] All the minimum inhibitory concentration (MIC) values fell below the corresponding cut-off values for '*Corynebacterium* and other Gram-positive' (EFSA FEEDAP Panel, 2018). Therefore, the strain is considered susceptible to the relevant antibiotics.

The [redacted] production strain were searched for the presence of antimicrobial resistance (AMR) genes [redacted].[15] [redacted], therefore, the strain [redacted] raises no concern.

3.1.2 | Manufacturing process

The active substance is produced by fermentation with *C. glutamicum* CGMCC 23982. [redacted]

[8]Evaluation report received on 16/05/2024 and available on the EU Science Hub https://joint-research-centre.ec.europa.eu/eurl-fa-eurl-feed-additives/eurl-fa-authorisation/eurl-fa-evaluation-reports_en.

[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]Other supporting document – 2.2.1.2.a Certificate of deposition CGMC23982.

[11]Other supporting document – 2.2.1.2.b Development strain.

[12]Study report – 2.2.1.2.c Bioinformatic T1481R1647_2023.

[13]Study report – 2.2.1.2.c Bioinformatic T1481R1647_2023.

[14]Study report – 2.2.2.2 MIC antimicrobial sensitivity T1481R1473.

[15]Study report – 2.2.1.2.c Bioinformatic T1481R1647_2023.

[redacted].

The applicant declared that no antibiotics are used during the manufacturing process.[16]

3.1.3 | Characterisation of the active substance/additive

L-Lysine sulfate (CAS No 60343-69-3) has a molecular weight of 390.38 g/mol. The molecular formula is $C_{12}H_{28}N_4O_4 \cdot H_2SO_4$ and the molecular structure is given in Figure 1. The theoretical content of lysine in lysine sulfate is 75%.

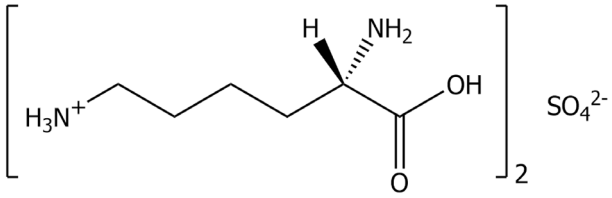

FIGURE 1 Molecular structure of L-lysine sulfate.

The specifications of the feed additive are ≥ 55% L-lysine on a dry matter (DM) basis, ≥ 10% 'other amino acids' on a DM basis[17] and ≤ 3% water.

Analytical data to confirm the specifications were provided for five batches of the additive, showing the following average values: 55.4% lysine (range: 55.0%–56.2%)[18] on DM basis; 19.9% sulfate (range: 19.3%–20.3%) on DM basis; 1.9% water (range: 1.3%–2.7%). Total free amino acids other than lysine represent 0.7%, and calculated protein ranged 9.6%–10% on DM (measured from nitrogen *6.25 (assuming that proteins have 16% N), N ranged from 1.5% to1.6%, only three batches analysed).[19]

Other compositional data reported included total sugar (1.1%–1.3%), ammonia (1.12%–1.13%), crude ash (0.6%–1.7%), lactic acid (0.28%–0.31%), cadaverine (939–955 mg/kg) and tyramine (43–45 mg/kg).

The average of the identified material of the additive was 96.4% (range: 94.6%–97.9%) on DM basis.[20]

Three batches of the additive were analysed for impurities.[21] Cadmium concentrations ranged from below the limit of detection (LOD) of the analytical method to 0.0025 mg/kg. Lead ranged from 0.039 to 0.042 mg/kg. Mercury ranged from 0.003 to 0.004 mg/kg, and the concentration of arsenic was 0.16 mg/kg in all three batches.

The calculated upper bound (UB) concentrations for the sum of PCDD/Fs ranged between 0.154 and 0.158 ng WHO 2005-TEQ/kg, and between 0.272 and 0.276 ng WHO 2005-TEQ/kg for the sum of PCDD/Fs and DL-PCBs. The UB for the sum of non DL-PCBs was below 3 µg/kg (all values are expressed based on 88% dry matter).[22] The antifoaming agent used in the manufacture of the product was not detected in three batches.[23]

As regards the presence of mycotoxins, analytical concentrations of aflatoxins (not further specified) ranged from < LOD to 1.12 µg/kg, concentrations of ochratoxin A ranged from 11.4 to 16.5 µg/kg, deoxynivalenol ranged from 221 to 351 µg/kg, citrinin ranged from 21.7 to 25.7 µg/kg, zearalenone and fumonisins B1 + B2 + B3 showed values below the LOD.[24]

Microbiological contamination was analysed by determination of *Enterobacteriaceae*, *Salmonella* spp., yeasts, moulds and *Escherichia coli* in 25 g samples (except for *Enterobacteriaceae* where 10 g samples were tested). No microbial contamination was detected.[25]

The FEEDAP Panel considers that the amounts of the detected impurities do not raise safety concerns.

The presence of viable cells of the production strain in the final product was analysed in three batches of the additive L-lysine sulfate analysed in triplicate.[26] [redacted]

[16] Annex 2.3.1.b.

[17] Section 2.1–2.2 Consolidated 250228. "Other amino acids" are derived from residual protein and other free amino acids.

[18] Annex 2.1.3.b Other substances, dust. Sect_2.6 Consolidated 250228. Analytical method to determine concentration of lysine in the additive was EN ISO 17180:2013.

[19] Annex 2.1.3.b1 Statement concentration real protein consolidated 250214. N measured by Kjeldahl method in precipitated protein and N concentration was multiplied by the nitrogen to protein conversion factor of 6.25.

[20] Study Report 2.1.3.b Other substances, dust.

[21] Study report - 2.1.3.a BtB impurities 133465. LOD in mg/kg was 0.002 for cadmium.

[22] Study report - 2.1.4.a Dioxins PCBs. Upper bound concentrations are calculated on the assumption that all values of the different congeners below the limit of quantification are equal to the limit of quantification. TEQ = toxic equivalency factors for PCDD/Fs and DL-PCBs established by WHO in 2005 (van den Berg et al., 2006).

[23] Annexes 2.1.4.d Impurities AF; 2.3.1.g1 Information on methods of analysis POG; 2.3.1.g2 Lab information on methods of analysis POG; and 2.3.1g3 Interpretation results residues. Limit of quantification stated to be 0.001%.

[24] Study report - 2.1.3.a BtB impurities 133465. LOD in µg/kg was 0.05 for aflatoxins (unspecified), 17 for zearalenone and 25 for fumonisins B1 + B2 + B3.

[25] Study report - 2.1.3.a BtB impurities 133465, and Sect_2.6.

[26] Study report – 2.1.4.b Absence of viable cells T1481R1535.1.

[redacted]. Therefore, it can be concluded that the final product does not contain viable cells of the production strain.

3.1.4 | Physical properties of the additive

The bulk density is reported to be 550–650 kg/m^3.[27] The solubility in water is reported to be 360 g/L at 30°C.

The dusting potential of three batches of the additive was determined using the Stauber-Heubach method and showed values of 100 mg/m^3 in all three batches.[28]

3.1.5 | Stability and homogeneity

The applicant referred to data on the shelf-life, stability (including water for drinking) and homogeneity from an L-lysine sulfate that shows a similar composition to the one under assessment, manufactured by the same producer but with a different *C. glutamicum* production strain (CGMCC 7.266). Those data were evaluated by the EFSA FEEDAP Panel (2020). The FEEDAP Panel considers that the results of the shelf-life, stability and capacity to distribute homogeneously in feed of the previous scientific opinion are applicable for the product under assessment.

3.1.6 | Conditions of use

L-Lysine sulfate is intended to be used directly in feedingstuffs/complementary feedingstuffs or via premixture and in water for drinking for all animal species. No inclusion levels are proposed, as the optimal daily allowance in quantitative terms depends on the nutrient composition, in particular the amino acid composition of the unsupplemented diet, the species, the animal's age, the physiological state of the animal, the performance level of the animal and the environmental conditions.

3.2 | Safety

3.2.1 | Safety for the target species, consumers and the environment

Safety concerns on the use of the additive would not derive from the L-lysine, which is considered safe, but they may arise from residues of the fermentation process/production strain remaining in the final product. The final product contains on average 96.4% identified material on a DM basis. The production strain belongs to a species, *Corynebacterium glutamicum*, that qualifies for the qualified presumption of safety (QPS) approach to safety assessment when used for production purposes (EFSA BIOHAZ Panel, 2024). The production strain was unambiguously identified as *C. glutamicum* and was shown not to harbour acquired AMR determinants for antibiotics of human and veterinary importance, and the final product does not contain viable cells of the production strain, thus meeting the QPS requirements. The ingredients used in the fermentation medium do not raise safety concerns. Consequently, no safety concerns for target animals, consumers and the environment are expected from the additive concerning the production strain and/or potential fermentation residues that may be present in the final additive.

L-Lysine requirements of different non-ruminant species and animal categories, the absorption and metabolic fate of L-lysine, the tolerance to L-lysine excess and the lysine to arginine antagonism are well known and described in the literature. The Panel considers that no safety concerns for ruminants would arise from ruminal lysine metabolism. The use of the amino acid 'per se' will not raise safety concerns for the target animals provided it is supplemented in appropriate amounts to the diets. With regard to the high intrinsic content of sulfate in L-lysine sulfate, the FEEDAP Panel considers that the formulation of the complete feed should carefully take into account the maximum tolerable level of total sulfur (S), as established by NRC (2005) and set in ruminant diets at 3 g S/kg DM (diet rich in concentrate) or 5 g S/kg DM (diet rich in roughage); and in non-ruminant diets at 4 g S/kg DM. Also, the contribution of sulfur/sulfate present in water for drinking to the total sulfur intake should be considered. Consequently, no negative effects are to be expected for the target species provided that the total sulfur intake complies with the recommendations established by scientific bodies. Finally, due to the risk of nutritional imbalances and hygienic reasons, associated with the use of amino acids via water for drinking (EFSA FEEDAP Panel, 2010), the FEEDAP Panel has concerns on the safety of the use of the amino acid via water for drinking.

The absorption, distribution, metabolism and excretion of L-lysine are well known and well described in the scientific literature. The use of the additive in animal nutrition is considered safe for consumers.

The amino acid L-lysine is a physiological and natural component of animals and plants. It is not excreted as such (but as urea/uric acid and carbon dioxide). The use of amino acids in water for drinking, when given in addition to complete diets

[27]Technical dossier text - Sections 2.1–2.2 Consolidated 250228.

[28]Study Report 2.1.3.b Other substances, dust.

with a well-balanced amino acid profile, would disturb the nitrogen balance and increase nitrogen excretion via urine. The use of L-lysine in animal nutrition would not lead to any localised increase in the concentration of L-lysine or its metabolites in the environment. Moreover, sulfate is widely present in the terrestrial and aquatic environments (Forum of the European Geological Surveys [FOREGS] database, 2005).[29] It is a macronutrient in the marine environment, and the use of the additive will not significantly increase the natural background concentrations of sulfate in the environment.

3.2.1.1 | *Conclusions on safety for the target species, consumers and the environment*

L-Lysine sulfate produced with *C. glutamicum* CGMCC 23982 is safe for the target species, consumers and for the environment when administered via feed. The FEEDAP Panel has concerns on the use of L-lysine sulfate in water for drinking.

3.2.2 | Safety for the user

No studies were submitted to support the safety of the additive for the user.

Based on the dusting potential measured (100 mg/m^3), the FEEDAP Panel considers that the exposure of users through inhalation is likely.

According to the safety data sheet,[30] the additive may cause skin and eye irritation, and irritation of the respiratory tract. Therefore, the Panel concludes that the additive should be considered irritant to skin, eyes and the respiratory tract, and therefore, any exposure is a risk.

3.3 | Efficacy

Efficacy studies are not required for amino acids naturally occurring in proteins of plants and animals. The nutritional role of the amino acid L-lysine is well established in the scientific literature. In general, L-lysine sulfate is considered as an efficacious source of the essential amino acid L-lysine for non-ruminant animal species. For the supplemental L-lysine to be as efficacious in ruminants as in non-ruminant species, it would require protection against degradation in the rumen.

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[31] and good manufacturing practice.

4 | CONCLUSIONS

L-Lysine sulfate produced by fermentation with *C. glutamicum* CGMCC 23982 does not pose any safety concerns associated with the production strain.

L-Lysine sulfate produced with *C. glutamicum* CGMCC 23982 is considered safe for the target species when administered via feed. When using L-lysine sulfate, the background sulfur/sulfate content in the compound feed should be taken into account when formulating diets. The FEEDAP Panel has concerns on the use of L-lysine sulfate in water for drinking.

L-Lysine sulfate produced by fermentation with *C. glutamicum* CGMCC 23982 is safe for the consumers and the environment.

With regard to user safety, the additive should be considered an irritant to skin, eyes and the respiratory tract. Any exposure to the additive is a risk.

The additive L-lysine sulfate is considered as an efficacious source of the essential amino acid L-lysine for non-ruminant animal species. For the supplemental L-lysine to be as efficacious in ruminants as in non-ruminant species, it would require protection against degradation in the rumen.

ABBREVIATIONS

CAS	Chemical Abstracts Service
CFU	colony forming unit
DM	dry matter
EINECS	European Inventory of Existing Chemical Substances
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed

[29] FOREGS database (2005) available online: http://weppi.gtk.fi/publ/foregsatlas/article.php?id=15.

[30] 2.5.2 MSDS L-lysine sulfate.

[31] 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.

IUPAC	International Union of Pure and Applied Chemistry
LOD	limit of detection
MIC	minimum inhibitory concentration
OECD	Organisation for Economic Co-operation and Development
WHO	World Health Organization

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REQUESTOR

European Commission

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PANEL MEMBERS

Roberto Edoardo Villa, Giovanna Azimonti, Eleftherios Bonos, Henrik Christensen, Mojca Durjava, Birgit Dusemund, Ronette Gehring, Boet Glandorf, Maryline Kouba, Marta López-Alonso, Francesca Marcon, Carlo Nebbia, Alena Pechová, Miguel Prieto-Maradona, Ilen Röhe, and Katerina Theodoridou.

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