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SCIENTIFIC OPINION

Safety and efficacy of a feed additive consisting of L-lysine sulfate produced by fermentation with *Corynebacterium glutamicum* CGMCC 7.453 for all animal species (Eppen Europe SAS)

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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 genetically modified strain of *Corynebacterium glutamicum* (CGMCC 7.453) 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 7.453 does not pose any safety concern associated with the production strain. L-Lysine sulfate produced with *C. glutamicum* CGMCC 7.453 is considered safe for the target species. The FEEDAP Panel has concerns on the use of L-lysine sulfate in water for drinking. When using L-lysine sulfate, the background sulfur/sulfate content in the compound feed should be taken into account. L-Lysine sulfate produced with *C. glutamicum* CGMCC 7.453 is safe for the consumer and for the environment. Based on the information provided in the safety data sheet of the additive under assessment, the FEEDAP Panel concludes that the additive should be considered irritant to skin, eyes and the respiratory tract, and that any exposure to the additive is a risk. L-Lysine sulfate is considered 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 7.453, *Corynebacterium glutamicum*, efficacy, lysine sulfate, nutritional additive, safety

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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 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 *Corynebacterium glutamicum* CGMCC 7.453, 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 06 December 2023 and the general information and supporting documentation are available at https://open.efsa.europa.eu/questions/EFSA-Q-2023-00865. The particulars and documents in support of the application were considered valid by EFSA as of 06 March 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 7.453, when used under the proposed conditions of use (see **Section 3.1.6**).

1.2 | Additional information

L-Lysine sulfate (≥ 55% lysine) produced by fermentation with *C. glutamicum* CGMCC 7.453 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 animal species as a nutritional additive and as a 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 7.453 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 39–39e 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 26 July to 16 August 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 08 March to 08 June 2024, for which no comments were received.

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-2023-19872.
[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, pp. 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 the L-lysine sulfate produced by fermentation with *C. glutamicum* CGMCC 7.453 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 7.453 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), EFSA statement on the requirements for whole genome sequence analysis of microorganisms intentionally used in the food chain (EFSA, 2021), 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 by fermentation with *C. glutamicum* CGMCC 7.453 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 by fermentation with a genetically modified strain of *C. glutamicum*, which is deposited at the China General Microbiological Culture Collection Center (CGMCC) with the accession number CGMCC 7.453.[10]

The taxonomic identification of the production strain CGMCC 7.453 as *C. glutamicum* was confirmed [redacted]

The susceptibility of the production strain to relevant antibiotics was tested against the list of antimicrobials described for '*Corynebacterium* and other Gram-positive' in the Guidance on characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018). All measured minimum inhibitory concentration (MIC) values were equal or lower than the cut-off values specified in this guidance. Therefore, the strain is considered susceptible to the relevant antibiotics.[13]

[redacted] Therefore, the FEEDAP Panel concludes that the strain harbours no acquired AMR genes and raises no safety concerns.

[8]Evaluation report received on 07/06/2024 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]2.2.1.2.a Certificate of deposit CGMCC7.453.

[11]2.2.1.2.c Bioinformatic T1497R1678_2023.

[12]2.2.1.2.c1 Bioinformatics P1807R205824 Consolidated.

[13]2.2.2.2 MIC antimicrobial sensitivity T1497R1650.

[14]2.2.1.2.c1 Bioinformatics P1807R205824 Consolidated.

3.1.1.1 | *Information regarding the genetically modified microorganism*[15]

[redacted]

Description of the genetic modification

[redacted] Any genetic modification, including intended and unintended modifications, was reported, and no concerns were identified.[16] [redacted]

3.1.2 | Manufacturing process

The active substance is produced by fermentation with *C. glutamicum* CGMCC 7.453. [redacted][17]

The applicant declared that no antibiotics are used during the manufacturing process.[18]

3.1.3 | Characterisation of the active substance/additive

L-Lysine sulfate (International Union of Pure and Applied Chemistry (IUPAC name: (2S)-2,6-diaminohexanoic acid; sulfuric acid), a compound identified by Chemical Abstracts Service (CAS) No 60343-69-3, has a molecular weight of 390.4 g/mol; the molecular formula is $C_{12}H_{28}N_4O_4 \cdot H_2SO_4$ and its structural formula is given in Figure 1. The theoretical content of lysine in lysine sulfate is 75%.

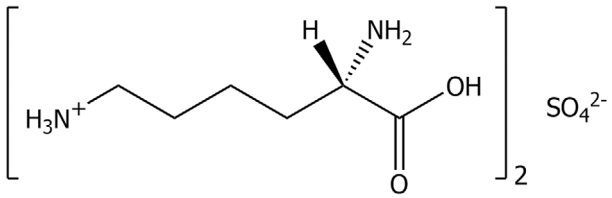

FIGURE 1 Molecular structure of L-lysine sulfate.

[15] 2.2.1.2.b Development production strain CGMCC7.453 and 2.2.1.2.c1 Bioinformatics P1807R205824 Consolidated.
[16] 2.2.1.2.c4 P1807_Annex2.
[17] 2.3.1.a Lysine production flow chart medium_Consolidated 240902.
[18] 2.3.1.b CGMCC7.453-statement of non use of antibiotics.

The specifications of the feed additive are ≥ 55% L-lysine on a dry matter (DM) basis and ≤ 3% moisture.

Analytical data to confirm the specifications were provided for five batches of the additive, showing the following average values: 55.9% L-lysine (55.5%–56.3%) on a DM basis, 19.3% sulfate (18.6%–20.0%) on a DM basis and 2.8% moisture (2.0%–3.5%).[19]

Other compositional data of three batches reported included 10.5% calculated protein on DM (measured from nitrogen ×6.25, N was 1.7%),[20] 1.9% crude ash, 1% ammonia, 0.24% lactic acid, 0.1% cadaverine, < 0.1% total sugar, and 40 mg/kg tyramine. Total free amino acids other than lysine represented 0.53%–0.57%.[21]

The average of the identified material of the additive ranged from 91.2% to 91.9% on a DM basis.

Three batches of the additive were analysed for impurities. Cadmium concentrations ranged from below the limit of quantification (LOQ) of the analytical method to 0.0043 mg/kg, lead ranged from 0.026 to 0.038 mg/kg, mercury ranged from 0.003 to 0.004 mg/kg and arsenic ranged from 0.12 to 0.16 mg/kg.[22]

The calculated upper bound (UB) concentrations for the sum of PCDD/Fs ranged between 0.138 and 0.150 ng WHO_{2005}-TEQ/kg, and the sum of PCDD/Fs and DL-PCBs was 0.269 ng WHO_{2005}-TEQ/kg in all three batches. The UB for the sum of non DL-PCBs was 3 µg/kg (all values are expressed based on 88% DM).[23]

As regards the presence of mycotoxins, analytical concentrations of aflatoxins (not further specified) ranged from < LOQ to 1.9 µg/kg. Ochratoxin A ranged from 17.8 to 25.5 µg/kg, deoxynivalenol ranged from 277 to 452 µg/kg, citrinin ranged from 17.7 to 41.1 µg/kg, fumonisins B1 + B2 + B3 ranged from 50.8 to 60.6 µg/kg and zearalenone showed values below the limit of detection (LOD).[24]

Microbiological contamination was analysed in three batches by determination of *Enterobacteriaceae*, *Salmonella* spp., yeasts, moulds and *Escherichia coli*. These microorganisms were not detected in 25 g samples.[25]

Three batches were analysed for the presence of the antifoaming agent (used in the manufacturing process) in the final product. Values were below the LOQ (0.001%).[26]

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

The presence of viable cells of the production strain was analysed in three batches of the additive L-lysine sulfate, in triplicate.[27] [redacted] A positive control was included in the analysis. No colonies were detected. Therefore, it can be concluded that the final product does not contain viable cells of the production strain.

The absence of DNA of the production strain in the final product was demonstrated in three batches of the final product tested in triplicate.[28] For each batch, three 1-g samples were taken. [redacted] The LOD of samples spiked with genomic DNA of the production strain was 10 ng/g of additive. DNA from the production strain was not detected in any of the samples tested.

3.1.4 | Physical properties of the additive

The additive appears as light yellow or brown granules. The density is 550–650 kg/m^3.[29] The solubility of the additive is 850 g/L.[30] The dusting potential of the additive was determined using the Stauber-Heubach method and showed values of 300 mg/m^3 in all three analysed batches.[31]

3.1.5 | Stability and homogeneity

The applicant referred to data on the shelf-life, stability and homogeneity from an L-lysine sulfate that shows similar composition to the one under assessment, but it is produced with a different *C. glutamicum* production strain (CGMCC 7.266). Those data were evaluated by the FEEDAP Panel in 2020(EFSA FEEDAP Panel, 2020). The FEEDAP Panel considers that the

[19]2.1.3.a BtB impurities 133927; EU-Verordnung 152/2009 VO (EG) 152/2009, Appendix III, G and F Method.

[20]Annex 2.1.3b Statement concentration real protein.

[21]2.1.3.b Impurities dust.

[22]2.1.3.a BtB impurities 133,927; LOQ for cadmium was 0.002 mg/kg.

[23]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).

[24]2.1.3.a BtB impurities 133927. LOQ for aflatoxins was: 0.05 µg/kg. LOD for zearalenone was: 17 µg/kg.

[25]2.1.3.a BtB impurities 133927.

[26]2.1.4.e Impurities AF.

[27]2.1.4.b Absence cells production strain T1498R1727; 2.1.4.d CoAs batches used in absence viable cells and DNA.

[28]2.1.4.c Absence DNA T1498R1722_2023; 2.1.4.d CoAs batches used in absence viable cells and DNA.

[29]2.1.3.c Measurement of density GBT 16913.

[30]2.1.5.a Solubility.

[31]2.1.3.b Impurities dust.

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 of the production microorganism

The production strain *C. glutamicum* CGMCC 7.453 is a genetically modified strain developed to increase the production of L-lysine. The production strain belongs to a species, *C. glutamicum*, that is suitable for the qualified presumption of safety (QPS) approach to safety assessment when used for production purposes (EFSA BIOHAZ panel, 2023b). The taxonomic identification of the production strain was unequivocally established, it does not carry acquired antimicrobial resistance genes, and the genetic modification does not raise safety concerns. No viable cells or DNA of the production strain were detected in the final product. Therefore, the FEEDAP Panel concludes that the additive does not pose any safety concern regarding the genetically modified *C. glutamicum* strain (CGMCC 7.453).

3.2.2 | 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 may arise from residues of the fermentation process/production strain remaining in the final product. The final product contains up to 92% identified material on a DM basis. The additive is produced by fermentation with a genetically modified *C. glutamicum* strain (CGMCC 7.453), and no safety concerns were identified for the production strain (see **Section 3.2.1**), the fermentation process and its residues/metabolites. Consequently, no safety concerns for target animals, consumers and the environment are expected from the additive concerning potential fermentation residues that may be present in the final additive.

The 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 and metabolic fate of L-lysine in the target animals is well known and well described in the scientific literature. The use of the amino acid L-lysine itself 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 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).[32] It is a macronutrient in the marine environment, and the use of the additive will not substantially increase the natural background concentrations of sulfate in the environment.

3.2.3 | Safety for the user

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

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

Based on the highest dusting potential measured value (300 mg/m^3), the FEEDAP Panel considers that the exposure of users through inhalation is likely.

According to the safety data sheet, the additive may cause irritation to the skin, eyes and respiratory tract.[33] Therefore, the Panel concludes that the additive should be considered an irritant to the 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[34] and good manufacturing practice.

4 | CONCLUSIONS

The production strain *C. glutamicum* CGMCC 7.453 does not pose any safety concern as regards the genetic modifications. No viable cells or DNA of the production strain were detected in the final product. Therefore, the FEEDAP Panel concludes that the additive does not pose any safety concern regarding the production strain.

L-Lysine sulfate produced with *C. glutamicum* CGMCC 7.453 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 considered. 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 7.453 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

BW	body weight
CAS	Chemical Abstracts Service
DM	dry matter
EURL	European Union Reference Laboratory
FAO	Food Agricultural Organization
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
IUPAC	International Union of Pure and Applied Chemistry
LOD	limit of detection
LOQ	limit of quantification
MIC	minimum inhibitory concentration
WHO	World Health Organization

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REQUESTOR

European Commission

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[33] 2.5.2 MSDS L-LYSINE SULFATE.

[34] 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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