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SCIENTIFIC OPINION

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Safety and efficacy of a feed additive consisting of L-lysine monohydrochloride produced with *Corynebacterium glutamicum* CGMCC 7.453 for all animal species (Eppen Europa 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, EFSA was asked to deliver a scientific opinion on the safety and efficacy of L-lysine monohydrochloride produced by fermentation with a genetically modified strain of *Corynebacterium glutamicum* (CGMCC 7.453) as nutritional feed additive for all animal species. Neither viable cells nor recombinant DNA of the production strain were detected in the final product. Therefore, the FEEDAP Panel concluded that the additive does not pose any safety concern regarding the production strain. The FEEDAP Panel concluded that the use of L-lysine HCl produced by fermentation with the strain *C. glutamicum* CGMCC 7.453 is safe for the target species when administered via feed. However, the FEEDAP Panel expressed concerns on the use of L-lysine HCl in water for drinking. The Panel concluded that the use of L-lysine HCl produced by fermentation with *C. glutamicum* CGMCC 7.453 in animal nutrition is considered safe for the consumers and for the environment. With regards 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 HCl is considered as 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, *Corynebacterium glutamicum* CGMCC 7.453, efficacy, lysine monohydrochloride, 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 Europe SAS[2] for the authorisation of the additive consisting of L-lysine monohydrochloride 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 14 November 2023 and the general information and supporting documentation are available at https://open.efsa.europa.eu/questions/EFSA-Q-2023-00723. The particulars and documents in support of the application were considered valid by EFSA as of 29 January 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 monohydrochloride produced by fermentation with *Corynebacterium glutamicum* CGMCC 7.453, when used under the proposed conditions of use (see **Section 3.1.6**).

1.2 | Additional information

L-Lysine monohydrochloride (minimum 78% 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 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 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 monohydrochloride produced by fermentation with *C. glutamicum* CGMCC 7.453 as a feed additive.

The confidential version of the technical dossier was subject to a target consultation of the interested Member States from 30 January 2024 to 30 April 2024; the comments received were considered for the assessment.

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 30 May to 20 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 or other expert bodies, peer-reviewed scientific papers, other scientific reports 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 Europe SAS, 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 in EFSA Journal: https://efsa.onlinelibrary.wiley.com/journal/18314732.
[5]Dossier reference: FEED-2023-19953.
[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 the L-lysine monohydrochloride in animal feed.[8]

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of L-lysine monohydrochloride 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 FEEDAP 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) and Guidance on the assessment of the safety of feed additives for the users (EFSA FEEDAP Panel, 2023), EFSA statement on the requirements for whole genome sequence analysis of microorganisms intentionally used in the food chain (EFSA, 2024) and Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2024).

3 | ASSESSMENT

The additive L-lysine monohydrochloride (L-lysine HCl) produced 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 production strain is a genetically modified strain of *C. glutamicum* that is deposited in the China General Microbiological Culture Collection Centre (CGMCC) with accession number CGMCC 7.453.[10]

The taxonomic identification of the production strain CGMCC 7.453 as *C. glutamicum* was confirmed by [redacted] whole genome sequence (WGS) data, [redacted].[11] [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 the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, , 2018).[12] All the minimum inhibitory concentration (MIC) values were below or equal to the corresponding cut-off specified in this guidance. Therefore, the production strain is considered susceptible to all relevant antibiotics.

The WGS data of the production strain were interrogated for the presence of antimicrobial resistance (AMR) genes [redacted].[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 2/4/2024 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 CGMCC 7.453.

[11]2.2.1.2.c1 Bioinformatics P1807R205824 Consolidated.pdf.

[12]2.2.2.2 MIC antimicrobial sensitivity T1497R1650.

[13]2.2.1.2.c1 Bioinformatics P1807R205824 Consolidated.

3.1.1.1 | *Information regarding the genetically modified microorganism*[14]

[redacted]

Description of the genetic modification

[redacted][15][redacted]. No safety concerns were identified in the production strain.

3.1.2 | Manufacturing process

L-Lysine HCl is produced by fermentation with *C. glutamicum* CGMCC 7.453. [redacted][16]

The applicant states that no antibiotics are used in the manufacturing process.[17]

3.1.3 | Characterisation of the active substance/additive

L-Lysine monohydrochloride (IUPAC name: (2S)-2,6-diaminohexanoic acid monohydrochloride, synonym L-lysine hydrochloride, a compound identified with the CAS No. 657-27-2 and the EC number 211-519-9), has a molecular weight of 182.65 g/mol. The theoretical content of lysine in lysine monohydrochloride is 80%. The molecular formula is $C_6H_{14}N_2O_2 \cdot HCl$ and the molecular structure is given in Figure 1.

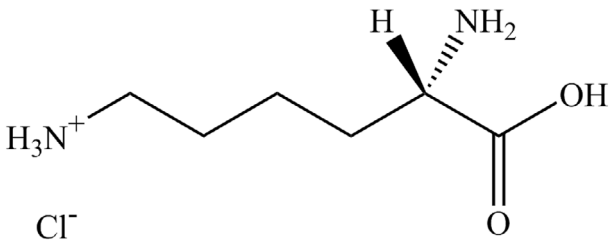

FIGURE 1 Molecular structure of L-lysine monohydrochloride.

[14] 2.2.1.2.b Development production strain CGMCC7.453 and 2.2.1.2.c1 Bioinformatics P1807R205824 Consolidated.
[15] 2.2.1.2.c4 P1807_Annex2.
[16] Annex 2.3.1.a manufacturing flow chart & medium 20230927.
[17] Annex 2.3.1.b CGMCC7.453-statement of no use of antibiotics.

The product is specified to contain ≥ 78% L-lysine on a dry matter (DM) basis, and maximum 1% moisture. Compliance with the specification was shown in five batches in which lysine was on average 79.1% (78.8%–79.3%) on as is basis.[18] The average water content was 0.44% (0.38%–0.51%).[19] The average content of lysine on DM basis corresponds to 79.5% (79.2%–79.7%). The average content of chloride was on average 19.3% (19.2%–19.4%).[20] The amount of identified material on DM basis was on average 98.7% (98.5%–98.9%).

The specific optical rotation of five batches of L-lysine HCl was analysed (United States Pharmacopoeia [USP] method) and ranged from +20.4 to +20.7°,[21] which is within the USP reference range of +20.3 to +21.5°, confirming the presence of the L-enantiomer.

Three batches of the additive were analysed for impurities and the concentrations of arsenic, cadmium and lead were below the limit of detection (LOD) of the analytical methods. Mercury concentrations ranged below the LOD to 0.0023 mg/kg.[22] Polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and dioxin-like polychlorinated biphenyls (DL-PCBs) were analysed in three batches. The calculated upper bound (UB) concentrations for the sum of PCDD/Fs were below 0.50 ng world health organisation (WHO) (PCDD/F)-TEQ 88% DM/kg, and between 0.55 and 0.62 ng WHO (PCDD/F/PCB)-TEQ 88% DM/kg the sum of PCDD/Fs and DL-PCBs. The UB for the sum of non-DL-PCBs was 3 µg/kg.[23]

The analysis of mycotoxins, including aflatoxins (not specified), zearalenone, ochratoxin A, fumonisins (B1 + B2 + B3), deoxynivalenol and citrinin showed values below the LOD except for total aflatoxins (1.5–3 µg/kg), fumonisins (58.7–61.2 µg/kg) and citrinin (34.4–90.7 µg/kg).[24]

Microbiological contamination was analysed by determination of *Enterobacteriaceae*, *Salmonella* spp., yeasts and moulds and *Escherichia coli* with no detection in 25 g samples.[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 was tested in three batches of the final product L-lysine HCl, each batch tested in triplicate.[26] [redacted] No viable cells of the production strain were found in the samples tested.

The presence of recombinant DNA from the production strain was analysed [redacted].[27] [redacted] No DNA from the production strain was detected.

3.1.4 | Physical properties of the additive

Solubility in water is reported to be 649.5 g/L.[28]

The dusting potential of 3 batches of the additive was determined using the Stauber-Heubach method and showed values in the range 3400–3700 mg/m^3.

3.1.5 | Stability and homogeneity

No information is available on the shelf-life, stability and capacity of the additive to distribute homogeneously in feed. The applicant provided information on the shelf-life, stability in premixtures, feed and water for drinking, and on the capacity to distribute homogeneously in feed of a L-lysine HCl of the same characteristics produced by fermentation with a different production strain (EFSA FEEDAP Panel, 2020). The producer of both L-lysine HCl products and the manufacturing process is the same. The FEEDAP Panel considers that the outcome of the shelf-life, stability and homogeneity studies of the L-lysine HCl reported in the previous opinion are applicable to the shelf-life, stability and capacity to distribute homogeneously of the product under assessment.

[18]Annex 2.1.3 BtB impurities 133928 and 2.1.3.a Method 1522009. Analytical method in accordance with the EU Regulation 152/2009, Appendix III, G and F.

[19]Study report – 2.1.3.b Dry matter CoAs.

[20]Annex 2.1.3.c Chloride-20241112.

[21]Annex 2.1.5.c Specific Rotation-20241112.

[22]Annex 2.1.3 BtB impurities 133928. LOD in mg/kg were 0.002 for cadmium and mercury, and 0.01 for arsenic and cadmium.

[23]Annex 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]Annex 2.1.3 BtB impurities 133928. LOD in µg/kg was 5 for ochratoxin A, 17 for zearalenone and 134 for deoxynivalenol.

[25]Annex 2.1.3 Btb impurities 133928. LOD one colony forming unit (CFU)/25 g sample.

[26]Annex 2.1.4.b Absence cells production strain T1497R1726.

[27]Annex 2.1.4.c Absence DNA T1497R720.

[28]Annex 2.5.2 MSDS L-Lysine monohydrochloride.

3.1.6 | Conditions of use

The additive is intended to be used in feed for all species and can be added directly in compound feed, through complementary feed or via premixtures. It is also intended for use in water for drinking in all animal species. No proposed inclusion levels are provided, 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 organism

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, 2023). The taxonomic identification of the production strain was unequivocally established, it does not carry acquired AMR genes and the genetic modification does not raise safety concerns. The production strain and its DNA were not detected in the final product. Therefore, the final product does not pose any safety concern as regards the genetically modified production strain.

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 is highly purified (≥ 78% lysine and an average of 98.7% identified material on a DM basis). The additive is produced by fermentation using a strain identified as *C. glutamicum* which qualifies for the QPS safety assessment approach and no safety concerns were identified for the production strain (see Section 3.2.1), the fermentation process and its residues/metabolites. The ingredients of 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 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. However, due to the risk of nutritional imbalances and hygienic reasons, associated to 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 described in the scientific literature. The use of the additive under assessment 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 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.

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

The FEEDAP Panel concludes that L-lysine HCl produced by fermentation with *C. glutamicum* CGMCC 7.453 is safe for the target species, for the consumer and the environment. The FEEDAP Panel has concerns on the use of L-lysine HCl in water for drinking.

3.2.3 | Safety for the user

No specific studies were submitted to support the safety for the user.

Based on the highest dusting potential measured value (3700 mg/m^3), the FEEDAP Panel considers that the exposure of users through inhalation is likely.

Based on the information present in the safety data sheet,[29] the additive is to be considered as an irritant to the skin, eyes and the respiratory tract, and therefore, any exposure is a risk.

[29] 2.5.2 MSDS L-Lysine monohydrochloride.

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, the product L-lysine HCl 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[30] 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 HCl produced with *C. glutamicum* CGMCC 7.453 is considered safe for the target species when administered via feed. FEEDAP Panel has concerns on the use of L-lysine HCl in water for drinking.

The use of L-lysine HCl produced by fermentation with *C. glutamicum* CGMCC 7.453 in animal nutrition is considered safe for the consumers and for the environment.

With regards 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 HCl 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.

ABBREVIATIONS

AMR	antimicrobial resistance
ANI	average nucleotide identity
CAS	Chemical Abstracts Service
CFU	colony forming unit
CV	coefficient of variation
DM	dry matter
DL-PCBs	dioxin-like polychlorinated biphenyls
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
IUPAC	International Union of Pure and Applied Chemistry
LOD	limit of detection
LOQ	limit of quantification
MCE	mixed cellulose esters
MIC	minimum inhibitory concentration
OECD	Organisation for Economic Co-operation and Development
PCDDs	polychlorinated dibenzo-p-dioxins
PCDFs	polychlorinated dibenzofurans
QPS	qualified presumption of safety
UB	upper bound
USP	United States Pharmacopoeia
WGS	whole genome sequence

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[30]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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