REGULATED PRODUCTS SAFETY ASSESSMENT

Assessment on the Safety and Efficacy of a Modification of the Terms of Authorisation Regarding the Feed Additive Consisting of Liquid L-lysine Base Produced With Corynebacterium Glutamicum NRRL B-67439 or NRRL B-67535 for All Animal Species (ADM Specialty Ingredients (Europe) B.V.) (RP2109)

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FSA Research and Evidence

An application was submitted to the Food Standards Agency in July 2023 from ADM specialty ingredients (Europe) B.V. ("the applicant") for the modification of the terms of authorisation consisting of liquid *L*-lysine base produced with *Corynebacterium glutamicum* NRRL B-67439 or NRRL B-67535 under the category 'nutritional feed additive', functional group 'amino acids, their salts and analogues' for all animal species.

Under Assimilated Regulation (EU) No 2020/997 the liquid *L*-lysine base produced with *C. glutamicum* NRRL B-67535 or NRRL B-67439 is currently authorised for use as a nutritional additive in complete feed and water for drinking for all animal species. This application requested a modification to the current authorisation to include *C. glutamicum* NRRL B-68248 as a production strain.

The new production strain qualifies for the qualified presumption of safety (QPS) approach for production purposes as it was clearly identified as *C. glutamicum*. In addition, the strain was shown to lack acquired antimicrobial resistance determinants relevant for antibiotics of human and veterinary importance. All genetic modifications were deemed safe, with no viable cells or DNA from strain NRRL B-68248 detected in the final product. Therefore, *L*-lysine base produced using *C. glutamicum* NRRL B-68248 poses no safety concerns for target species, consumers, or the environment. The additive is not an eye or skin irritant and is not a skin sensitiser.

Using *C. glutamicum* NRRL B-68248 as a production strain produces an *L*-lysine base that is considered an efficacious source of the essential amino acid *L*-lysine for non-ruminant animals. To achieve similar efficacy in ruminants, protection against degradation in the rumen would be required.

The FSA/FSS has reviewed the applicant's modification of the terms of authorisation application, supporting documentation, and other regulators' risk assessments, most notably the EFSA risk assessment opinion and considers that sufficient evidence has been demonstrated to conclude without the need for further questions or risk assessment.

This is a joint FSA and FSS publication.

1. Introduction

The FSA and FSS have undertaken an assessment of a feed additive submitted by ADM specialty ingredients (Europe) B.V. (Kingsfordweg 83, GP Amsterdam, Netherlands, 1043) consisting of liquid *L*-lysine base produced with *C. glutamicum* NRRL B-67439 or NRRL B-67535 under Assimilated Regulation (EC) No 1831/2003 (EC, 2003) in each nation of Great Britain (GB). Under Assimilated Regulation (EU) No 2020/997 (EC, 2020), the additive produced with *C. glutamicum* NRRL B-67535 or NRRL B-67439 is currently authorised for use as a nutritional additive in complete feed and drinking water for all animal species. This application requested a modification to the current authorisation to include *C. glutamicum* NRRL B-68248 as a production strain.

In line with Article 8 of Assimilated Regulation No 1831/2003 (EC, 2003), the assessment has considered and concluded that the feed additive complies with the conditions laid down in Article 5, including: safety considerations for human, animal and environmental health; efficacy of the additive for its intended effect; potential impairment of the distinctive features of animal products. This, and the guidance put in place by the European Food Safety Authority (EFSA) for the evaluation of feed additive applications, has formed the basis and structure for the assessment.

To ensure regulatory systems of the FSA/FSS are risk proportionate and resources are used effectively, the FSA and FSS have used the evidence submitted by the applicant and other information in the public domain, including the EFSA risk assessment opinion, to provide a summary assessment of the evidence of safety presented in this report.

In 2024, EFSA published a risk assessment opinion on the modification of the terms of authorisation regarding the additive consisting of liquid *L*-lysine base produced with *C. glutamicum* NRRL B-67439 or NRRL B-67535 for all animal species (EFSA, 2024). This opinion has been reviewed by FSA/FSS risk assessors. It has been verified that the standard approach, when compared to the relevant guidance applied in GB, has been followed and the conclusions made are consistent with the data summarised in the opinion.

The result of the assessment is that there is sufficient evidence of safety and efficacy for the UK to conclude this assessment at this time. This assessment represents the opinion of the FSA and FSS.

Table 1. Table showing products included in this assessment.

Title	Product type	Intended use/s	Intended dose/intake
L-lysine base	Feed additive	Nutritional additive / amino acids their salts and analogues	no specified minimum or maximum limits

2. Assessment

2.1. Details of other regulators opinions

2.1.1. Other regulators opinions and current authorisation

The EFSA FEEDAP Panel previously issued two opinions on the safety and efficacy of monohydrochloride, and concentrated liquid *L*-lysine (base) produced by fermentation using *C. glutamicum* strains NRRL B-67439, NRRL B-67535, and NRRL B-50775 as a nutritional feed additive for all animal species (EFSA Panel, 2019c, 2019b).

The production strains *C. glutamicum* NRRL B-67439, NRRL B-67535, and NRRL B-50775 as well as their recombinant DNA were not detected in the respective final products, so no safety concerns of final products are associated with their genetic modifications. *L*-lysine HCl and concentrated liquid *L*-lysine (base) produced with these strains are deemed safe for target species, consumers, and the environment. Using amino acids in drinking water alongside balanced diets may pose risks for target species,

potentially causing nutritional imbalances, hygiene issues, and increased nitrogen excretion through urine (EFSA, 2010). Therefore, the FEEDAP Panel had safety concerns regarding lysine additives in drinking water.

L-lysine HCl produced with strains NRRL B-67439, NRRL B-67535, or NRRL B-50775 is not an irritant to eyes or skin and is not a skin sensitiser. The FEEDAP Panel, however, could not conclude on the inhalation toxicity of *L*-lysine HCl due to limited data. In contrast, concentrated liquid *L*-lysine (base) from these strains, with high pH values (10.7 to 11), was anticipated to be corrosive to skin and eyes and poses an inhalation risk.

Both *L*-lysine HCl and concentrated liquid *L*-lysine (base) produced by these strains are efficacious as sources of the essential amino acid *L*-lysine for non-ruminant species. To be equally effective for ruminants, the supplemental *L*-lysine requires protection against degradation in rumen.

The additive produced with *C. glutamicum* NRRL B-67535 or NRRL B-67439 is currently authorised for use as a nutritional additive in complete feed and water for drinking for all animal species under Assimilated Regulation (EU) No 2020/997 (EC, 2020) in the European Union (EU) as well as GB.

2.1.2. Methodology applied in the EFSA opinion

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) assessed the safety and the efficacy of liquid *L*-lysine base produced with *C. glutamicum* strain NRRL B-68248 in accordance with guidance documents:

- Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEEDAP Panel, 2017c);
- Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018a);
- Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018b);
- Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017a);
- Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b);
- Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019a);
- 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, 2021);

and principles in Regulation (EC) No 429/2008 (EC, 2008).

These guidance documents, with exception of Guidance on the assessment of the safety of feed additives for the users (EFSA FEEDAP Panel, 2023), were developed and implemented prior to the UK's exit from the EU and were also adopted by the FSA and FSS on exit.

2.2. Section II: Identity, characterisation and condition of use

2.2.1. Characterisation of the production organism

The *L*-lysine base is produced via fermentation using a genetically modified strain of *C. glutamicum*, deposited as NRRL B-68248 in the US Agricultural Research Culture Collection. This strain shares the same parental strain as the currently authorised strain NRRL B-67535 (EFSA, 2019c). Whole genome sequencing (WGS) confirmed NRRL B-68248 as *C. glutamicum*, with an average nucleotide identity of 98.3% with the type strain ATCC 13032^{T}. Phylogenetic analysis, based on the alignment of 146 genes, confirmed that the production strain belongs to the *C. glutamicum* species. The production strain was tested for susceptibility to a range of antibiotics as recommended by the FEEDAP Panel (EFSA Panel, 2018b). All minimum inhibitory concentration values were below the established thresholds for Gram-positive bacteria, confirming the strain's susceptibility to each antibiotic tested. Additionally, no antimicrobial resistance genes of concern were detected in the WGS data analysis of NRRL B-68248 using the ResFinder and the NCBI Bacterial Antimicrobial Resistance Reference Gene databases.

The recipient strain *C. glutamicum* was obtained by classical mutagenesis. The applicant provided list of genetic modifications to production strain *C. glutamicum* NRRL B- 68248. WGS confirmed the absence of transiently introduced antimicrobial resistance genes during the genetic modification.

The FSA and FSS agree with the conclusions reached on the characterisation of the production organism, which is supported by the guidance that is also applicable in GB.

2.2.2. Manufacturing process

The applicant states that the manufacturing process remains unchanged from the previously assessed version, aside from the change in the production strain. No antimicrobials, including antibiotics, are employed in the manufacturing processes according to the applicant.

The manufacturing process of the additive has not been changed by the current application made to the FSA and FSS and as such has not been subject to further assessment. The data was reviewed by EFSA in 2019, prior to the UK's exit from the EU; thus, this opinion is applicable to GB. The data formed was used in the assessment leading to the current authorisation of the additive in GB.

2.2.3. Characterisation of the active substance and the additive

L-lysine, also known as (2S)-2,6-diaminohexanoic acid (CAS No. 56-87-1, EINECS No. 200-294-2), has a molecular weight of 146.2 g/mol and the molecular formula NH_2-$(CH_2)_4$-$CH(NH_2)$-COOH. The liquid *L*-lysine base additive, authorised as an aqueous solution containing a minimum of 50% *L*-lysine, averaged 50.4% (50.0–51.0%) and 42.6% water (42.0–43.0%) across eight batches, with additional constituents: 1.3% sulfate, 0.4% ash, 0.4% crude fat, 0.4% organic acids, 0.3% amino acids other

than lysine, 0.3% protein (hydrolysed amino acids minus free amino acids other than lysine), 0.09% cadaverine, 0.04% sugars, 0.01% ammonia, 0.01% water soluble vitamins and 2.3% of other identified compounds.

Tests of 8 batches confirmed levels of heavy metals (arsenic, cadmium, lead and mercury) below the limit of quantification (LOQ) of the method. Three batches were further analysed, showing concentrations of dioxins and the sum of dioxins plus dioxin-like PCBs ranging from 0.05 to 0.10 ng WHO-PCDD/F-TEQ/kg and 0.05 to 0.10 ng WHO-PCDD/F-PCB-TEQ/kg, respectively. Mycotoxin analysis included aflatoxins (B1, G1, B2, G2), fumonisins (B1, B2, B3), ochratoxin A, 3-acetyl-deoxynivalenol, deoxynivalenol, HT-2 toxin, T2-toxin, zearalenone. All mycotoxin concentrations were below the LOQ of the analytical method, except for fumonisin B1, which ranged from 37 to 60 µg/kg. In addition, levels of aerobic plate count, Enterobacteriaceae, *Escherichia coli*, *Pseudomonas* spp., total coliforms, yeasts, and filamentous fungi were below 10 CFU/g based on the analysis of three batches, and no *Salmonella* spp. was detected in 25 g of these samples. The results of the microbiological analyses and the amounts of the detected impurities do not raise safety concerns according to the FEEDAP Panel.

Three production batches of the additive were analysed in triplicate for viable cells and DNA of the production strain, with no colonies and DNA detected in samples.

The additive is a water-soluble liquid with a pH of 10.1, viscosity between 56.0 and 57.9 cP (at 25°C), and density of 1150 kg/m^3 (at 20°C) in 3 batches. No particles smaller than 500 nm were observed in three batches using scanning electron microscopy. As the composition of the additive and manufacturing process are unchanged, previous outcomes on shelf life, stability, and homogeneity in feed remain applicable for the current assessment (EFSA, 2019c).

The FSA and FSS agree with the conclusions reached for the characterisation of the additive and active substance. The certificates of analysis were reviewed by the FSA and FSS and confirmed compliance with the specifications. The composition and the manufacturing process of the additive are not changed by the current application made to the FSA and FSS and as such have not been subject to further assessment. Therefore, the outcomes shelf life, stability, and homogeneity in feed remain applicable for the current assessment. This data was reviewed by EFSA in 2019, prior to the UK's exit from the EU; thus, this opinion is applicable to GB. This data formed part of the assessment leading to the current authorisation of the additive in GB.

2.2.4. Condition of use

Under current authorisation, the additive can be used as a feed additive for all animals, with no specified minimum or maximum limits.

Under other provisions:

- The lysine content shall be indicated on the labelling of the additive.
- *L*-lysine base, liquid, may be placed on the market and used as an additive consisting of a preparation.
- For users of the additive and premixtures, feed business operators shall establish operational procedures and organisational measures to address potential risks by inhalation and for the skin and eyes. Where those risks cannot be eliminated or reduced to a minimum by such procedures and measures, the additive and premixtures shall be used with personal protective equipment, including breathing, skin and eye protection.
- The additive may be also used via water for drinking.

- Declarations to be made on the labelling of the additive and premixtures: 'The supplementation with *L*-lysine, in particular via water for drinking, should take into account all essential and conditional essential amino acids in order to avoid imbalances.

Modification to the terms of the authorisation to use *C. glutamicum* NRRL B-68248 as a production strain and to allow the use of *L*-lysine base liquid produced with this strain in feed for all animal species, with no specified minimum or maximum content was requested by the applicant.

The applicant requested the same conditions of use as EFSA evaluated in their latest opinion (EFSA, 2024).

2.2.5. Conclusion on Section II: Identity, characterisation and condition of use

The production strain *C. glutamicum* NRRL B-68248 is genetically modified, and the FEEDAP Panel has concluded that this modification presents no safety concerns. No viable cells or DNA from the production strain were detected in the final product, indicating no safety concerns related to the production strain in the final product. The strain identity and susceptibility to tested antibiotics was confirmed and no antimicrobial resistance genes were detected in the WGS data analysis.

The formulation and manufacturing process remain the same as those previously evaluated by the FEEDAP Panel in 2019, therefore the data on shelf life, stability and homogeneous distribution in feed from that assessment apply to the current assessment (EFSA, 2019c). The FEEDAP Panel concluded that the amounts of the detected impurities, as well as microbial contamination, do not raise safety concerns.

The FSA and FSS agree with the conclusions reached for the characterisation of the production strain, additive and active agent. The FSA/FSS agree with the conditions of use proposed by the applicant.

2.3. Section III: Safety

2.3.1. Safety for the target species, consumer and the environment

The FEEDAP Panel previously assessed the safety of *L*-lysine base produced with *C. glutamicum* NRRL B-67535 (EFSA FEEDAP Panel, 2019c). Given that the manufacturing process and additive composition remain unchanged except for the production strain, the Panel considers the strain change to be the sole safety aspect requiring evaluation.

The production strain, *C. glutamicum*, qualifies for the qualified presumption of safety (QPS) approach for production use (EFSA BIOHAZ Panel, 2023). It was clearly identified as *C. glutamicum* and confirmed to lack acquired antimicrobial resistance genes for antibiotics significant to human and veterinary importance. All introduced genetic sequences or mutations are considered safe, with no viable cells or DNA of the production strain detected in three additive batches. Therefore, no safety concerns are anticipated for target animals, consumers, or the environment regarding the strain or any fermentation residues in the final additive. The FEEDAP Panel, therefore, upholds its previous conclusion that the additive is safe for target species, consumers, and the environment.

The FSA and FSS agree with the conclusions reached on the data and the use of qualified presumption of safety (QPS) approach, as this approach has been previously used in GB. The FSA and FSS agree that the identity and lack of acquired antimicrobial resistance genes for antibiotics significant to human and veterinary importance were confirmed and the introduced genetic sequences or mutations are considered safe.

2.3.2. Safety for the user

No specific studies were submitted to support the safety of the product for the user. However, the applicant provided an acute eye irritation study, an acute skin irritation study, and a skin sensitisation study conducted with a 50% liquid *L*-lysine solution produced with a different strain (*C. glutamicum* KCTC 12307BP), with a pH of 9.96.

The FEEDAP Panel considered that (i) both lysine products share the same physico-chemical properties (≥50% lysine, ≤48% water, density 1.12–1.17 g/mL); (ii) both products undergo a similar manufacturing process; and (iii) the pH of several batches of the lysine under assessment does not exceed 10.4, close to that of the tested product. Therefore, the FEEDAP Panel concludes that the studies are applicable to the product under assessment, which is not considered an irritant to eyes or skin nor a dermal sensitiser.

Based on these previously evaluated studies, the FEEDAP Panel concluded that the product was neither an irritant to eyes or skin nor a dermal sensitiser (EFSA Panel, 2019d). These conclusions are applicable to the current assessment.

The FSA and FSS agree with the conclusions reached for the safety of the user. The studies were reviewed by EFSA in 2019, prior to the UK's exit from the EU; thus, this opinion is applicable to GB. These studies formed part of the assessment leading to the current authorisation of the additive in GB. The FSA and FSS agrees with the EFSA's view that the studies are applicable for the current assessment.

2.3.3. Conclusion on Section III: Safety

The production strain qualifies for the QPS approach for production use, as it was clearly identified as *C. glutamicum* and shown to lack acquired antimicrobial resistance genes relevant to human and veterinary medicine. All introduced genetic sequences or mutations are deemed safe, with no viable cells or DNA of the production strain detected in three batches of the additive. No safety concerns are expected for target animals, consumers, or the environment regarding the strain or any fermentation residues in the final product. The FEEDAP Panel concludes that the additive was considered to be neither irritant to skin or the eyes, nor a dermal sensitiser.

The FSA and FSS agree with the conclusions reached for the safety for the target species, consumer, environment and user.

2.4. Section IV: Efficacy

The FEEDAP Panel concludes that changing the production strain will not affect the efficacy of the additive. Consequently, *L*-lysine base produced with *C. glutamicum* strain NRRL B-68248 is regarded as an efficacious source of the essential amino acid *L*-lysine for non-ruminant animal species. However, for supplemental *L*-lysine to be equally efficacious in ruminants, it must be protected from degradation in the rumen.

The FSA and FSS agree with the conclusions on efficacy and the EFSA's view that the change in the production strain would not have an impact on the efficacy of the additive. This demonstrates that the additive satisfies the nutritional needs of animals.

3. Analytical method evaluation

FSA/FSS evaluated the EURL analytical method evaluation, noting it was carried out in 2018, when the UK was still part of the EU and would have participated of their approval. No concerns are raised at this stage for the validity of the methods for UK/GB use, and therefore, the FSA/FSS accept the EURL analytical method evaluation report (EURL, 2018). FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

4. Conclusions

The FEEDAP Panel concludes that the genetic modification of the production strain *C. glutamicum* NRRL B-68248 does not raise any safety concerns. Viable cells or DNA of the production strain were not detected in the final product, indicating that it poses no safety risks related to

the strain. Furthermore, *L*-lysine base produced with *C. glutamicum* NRRL B-68248 is deemed safe for target species, consumers, and the environment.

Based on the submitted data, the additive is considered a non-irritant to eyes and skin and is not a dermal sensitiser. Additionally, *L*-lysine base from this strain is considered as an efficacious source of the essential amino acid *L*-lysine for non-ruminant animal species. To ensure equivalent efficacy in ruminants, the supplemental *L*-lysine must be protected from degradation in the rumen.

5. Caveats and uncertainties

Using amino acids in drinking water alongside balanced diets may pose risks for target species, potentially causing nutritional imbalances, hygiene issues, and increased nitrogen excretion through urine. According to Assimilated Regulation (EU) No 2020/997 (EC, 2020), it is appropriate to indicate on the label of the additive, and premixtures containing it, an alert to take into account the dietary supply with all the essential and conditionally essential amino acids, particularly in the case of supplementation with *L*-lysine as amino acid via water for drinking.

No conclusion was made on the possible risk by inhalation.

An acute eye irritation study, an acute skin irritation study, and a skin sensitisation study were conducted with a 50% liquid *L*-lysine solution produced with a different strain (*C. glutamicum* KCTC 12307BP), with a pH of 9.96.

6. FSA/FSS conclusions for GB risk analysis

The application has been assessed in line with the applicable guidance and is partially based on considerations of detailed proprietary information available to the Panel, which were also submitted to the FSA and FSS. The EFSA opinion identifies and characterises the hazards present from this proposed modification of the terms of authorisation and there is sufficient information to enable an assessment of exposure, which is also relevant to GB. The risk characterisation is unchanged from the 2019 opinion for most areas, and appropriate evidence was submitted to support the requested modification. The conclusions of the EFSA opinion have been reviewed in detail by the FSA and FSS and are considered appropriate and consistent, including the caveats and uncertainties identified in the opinion which are applicable to GB. Sufficient evidence has been demonstrated to conclude without further questions or risk assessment.

Abbreviations

Abbreviation	Definition
AMR	Antimicrobial resistance
ANI	Average nucleotide identity
CAS	Chemical Abstracts Service
CFU	Colony firming units
EC	European Commission
EU	European Union
EFSA	European Food Safety Authority
EURL	European Union Reference Laboratory
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
FSA	Food Standards Agency
FSS	Food Standards Scotland
GB	Great Britain
IUPAC	International Union of Pure and Applied Chemistry
LOQ	Limit of quantification
OECD	Organisation for Economic Co-operation and Development
QPS	Qualified Presumption of Safety
RP	Regulated Product
UK	United Kingdom
WGS	Whole genome sequence

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