

SCIENTIFIC OPINION

Safety and efficacy of a feed additive consisting of L-histidine monohydrochloride monohydrate produced with *Escherichia coli* CCTCC M 20241089 for all animal species (Anhui Huaheng Biotechnology Co., Ltd)

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) |

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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-histidine monohydrochloride monohydrate produced with a genetically modified strain of *Escherichia coli* (CCTCC M 20241089) as a nutritional additive in feed and water for drinking for all animal species and categories. L-Histidine monohydrochloride monohydrate manufactured by fermentation with *E. coli* CCTCC M 20241089 did not give rise to any safety concern regarding the genetic modifications of the production strain. No viable cells nor DNA of the production strain were detected in the final product. The use of L-histidine monohydrochloride monohydrate produced with *E. coli* CCTCC M 20241089 in feed is safe for the target species when supplemented in appropriate amounts to the diet according to their nutritional needs. The FEEDAP Panel had concerns on the use of L-histidine monohydrochloride monohydrate in water for drinking. The use of L-histidine monohydrochloride monohydrate produced by fermentation with *E. coli* CCTCC M 20241089 in animal nutrition was considered safe for the consumers of products from animals receiving the additive, and for the environment. The FEEDAP Panel could not conclude on the potential of the additive to be an irritant to skin and/or eyes and to be a potential skin sensitiser. The additive was regarded as an effective source of the amino acid L-histidine for all non-ruminant species. To be as efficacious in ruminants as in non-ruminants, it should be protected from ruminal degradation.

KEYWORDS

amino acid, efficacy, *Escherichia coli* CCTCC M 20241089, nutritional additive, safety

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1 | INTRODUCTION

1.1 | Background and Terms of Reference

Regulation (EC) No 1831/2003¹ 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 Anhui Huaheng Biotechnology Co., Ltd.² for the authorisation of the additive consisting of L-histidine monohydrochloride monohydrate produced with *Escherichia coli* CCTCC M 20241089, 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 10 April 2025 and the general information and supporting documentation are available at <https://open.efsa.europa.eu/questions/EFSA-Q-2025-00262>. The particulars and documents in support of the application were considered valid by EFSA as of 24 June 2025.

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-histidine monohydrochloride monohydrate produced with *E. coli* CCTCC M 20241089, when used under the proposed conditions of use (see **Section 3.1.4**).

1.2 | Additional information

The additive L-histidine monohydrochloride monohydrate produced with *E. coli* CCTCC M 20241089 has not been previously authorised as a feed additive in the European Union. L-Histidine monohydrochloride monohydrate produced by fermentation using different production strains is currently authorised for its use in all animal species as a nutritional and sensory additive.³

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) issued a series of scientific opinions on the safety and efficacy of L-histidine monohydrochloride monohydrate produced by fermentation using different production strains, when used as amino acid in feed.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 dossier⁵ in support of the authorisation request for the use of L-histidine monohydrochloride monohydrate produced with *E. coli* CCTCC M 20241089 as a feed additive.

In accordance with Article 38 of the Regulation (EC) No 178/2002⁶ 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 14 October to 4 November 2025 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 27 June 2025 to 27 September 2025 for which the received comments were considered for the assessment.

¹Regulation (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.

²Anhui Huaheng Biotechnology Co., Ltd., represented in the EU by Kempex Holland B.V., Zeelandsedijk 15, 5408 SL, Volkel (the Netherlands).

³See the European Union register of feed additives. Available online: <https://ec.europa.eu/food/feed-portal/screen/feed-additives/search>.

⁴Scientific opinions available online: <https://efsa.onlinelibrary.wiley.com/journal/18314732>.

⁵Dossier reference: FEED-2025-34496.

⁶Regulation (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.

⁷Decision available at: <https://www.efsa.europa.eu/en/corporate-pubs/transparency-regulation-practical-arrangements>.

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.

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the L-histidine monohydrochloride monohydrate in animal feed.⁸

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of L-histidine monohydrochloride monohydrate produced with *E. coli* CCTCC M 20241089 is in line with the principles laid down in Regulation (EC) No 429/2008⁹ 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), Guidance on the assessment of the safety of feed additives for the users (EFSA FEEDAP Panel, 2023), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2024) and EFSA statement on the requirements for whole genome sequence analysis of microorganisms intentionally used in the food chain (EFSA, 2024).

3 | ASSESSMENT

L-Histidine monohydrochloride monohydrate ($\geq 98\%$ L-histidine monohydrochloride monohydrate on a dry matter [DM] basis) produced by fermentation with a genetically modified strain of *E. coli* (CCTCC M 20241089) 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 and categories.¹⁰

3.1 | Characterisation

3.1.1 | Characterisation of the production microorganism

L-Histidine monohydrochloride monohydrate is produced with a genetically modified strain of *E. coli* K-12 which is deposited in the China Center for Type Culture Collection (CCTCC) with accession number CCTCC M 20241089.¹¹

The taxonomic identification of the production strain CCTCC M 20241089 as *E. coli* K-12, was confirmed by [REDACTED] based on the whole genome sequence (WGS) data.¹² The results of this analysis showed [REDACTED].¹³ The results were further confirmed by [REDACTED].

E. coli K-12 is well characterised, its safety (non-pathogenicity) has been documented (Gorbach, 1978; Kaper et al., 2004) and its ineffectiveness in colonising the human gut has been reported (Smith, 1975).

The antimicrobial susceptibility of the production strain was tested using a broth microdilution method (except for fosfomycin which was tested using an agar dilution method) against the battery of antibiotics recommended by the EFSA FEEDAP Panel (2018).¹⁴ All the minimum inhibitory concentration values fell below the corresponding cut-off values for 'Enterobacteriaceae' (EFSA FEEDAP Panel, 2018). Therefore, the production strain is considered susceptible to all relevant antibiotics.

The WGS data of the production strain was interrogated for the presence of antimicrobial resistance (AMR) genes against the [REDACTED].¹⁵ The search resulted in [REDACTED] (EFSA, 2024). [REDACTED] (EFSA BIOHAZ Panel, 2023) [REDACTED]. Therefore, the FEEDAP Panel concludes that the strain harbours no acquired AMR genes.

⁸Evaluation report received on 16/9/2025 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.

⁹Commission 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.

¹⁰Sect_2.1-2.2 Consolidated_250828.

¹¹2.2.1.2.a Deposition certificate.

¹²2.2.1.2.c1 Bioinformatics P1812R2112_Consolidated 250821.

¹³2.2.1.2.c1 Bioinformatics P1812R2112_Consolidated 250821.

¹⁴2.2.2.2 MIC P1812R2084.

¹⁵2.2.1.2.c1 Bioinformatics P1812R2112_Consolidated 250821.

The additive is specified to contain $\geq 98\%$ L-histidine monohydrochloride monohydrate on dry matter basis and $\leq 2\%$ moisture.

The data provided by the applicant on the batch-to-batch variation,²⁰ impurities²¹ and physicochemical and technological properties²² of the additive are reported in Table 1.

TABLE 1 Data on the batch-to-batch variation, impurities and physicochemical and technological properties of L-histidine monohydrochloride monohydrate. The data presented are average values and (range) for batch-to-batch variation, and ranges for all other parameters. The number of batches analysed per parameter or group of parameters are indicated in [].

Specifications	
L-Histidine monohydrochloride monohydrate (% DM) ⁽¹⁾	≥ 98
Chloride (% DM)	16.7–17.1
Moisture (% DM)	≤ 2
Specific optical rotation (°)	+ 9.2 to +10.6 ⁽²⁾
Sulfate (%)	≤ 0.02
Ammonium (%)	≤ 0.02
Iron (%)	≤ 0.001
Batch-to-batch variation	
L-Histidine monohydrochloride monohydrate (% DM)	[5]
L-Histidine (% 'as is' basis)	99.8 (99.6–100)
Chloride (% DM)	75.4 (74.6–76.1)
Moisture (%)	16.99 (16.95–17.04)
Ash (%)	0.006 (0.00–0.01)
Specific optical rotation (°)	0.07 (0.06–0.08)
Impurities	
Lead (mg/kg) ⁽³⁾	9.72 (9.2–10.2)
Mercury (mg/kg) ⁽³⁾	[3]
Cadmium (mg/kg) ⁽³⁾	< 0.01
Arsenic (mg/kg) ⁽³⁾	[3]
Sulfate (%)	< 0.02
Ammonium (%)	[3]
Iron (%)	< 0.01
Dioxins and furans (upper bound) ⁽⁴⁾	[3]
PCDD/Fs (ng WHO ₂₀₀₅ -TEQ/kg)	< 0.137
PCDD/Fs + PCBs (ng WHO ₂₀₀₅ -TEQ/kg)	< 0.269
nDL-PCBs (µg/kg)	< 3
Mycotoxins (µg/kg) ⁽³⁾	[3]
Aflatoxins	0.18–0.33
Ochratoxin A	5.4–6.1
Zearalenone	< 17
Fumonisin B1 + B2 + B3	< 250
Deoxynivalenol	334.8–374.3
Citrinin	< 15

²⁰Batch-to-batch: 2.1.3.a BtB Impurities stability 145293; 2.1.5.b Optical Rotation.

²¹Impurities: 2.1.3.a BtB Impurities stability 145293; 2.1.4.a Dioxins PCBs; 2.1.4.d Endotoxins.

²²Physicochemical and technological properties: 2.1.5.c Bulk density; 2.1.5.a Dust; 2.1.3.a BtB Impurities stability 145293; 2.4.1.b Stability in premix 145475; 2.4.1.d Stability feed homogeneity 145615.

TABLE 1 (Continued)

Microbial contamination	[3]
<i>Salmonella</i> spp. (per 25g)	Not detected
<i>Enterobacteriaceae</i> (per 25g)	Not detected
<i>E. coli</i> (per 25g)	Not detected
Yeasts and moulds (per 25g)	Not detected
Endotoxin activity (IU/g)	[3]
	< 300
Physical properties	
Physical form	Solid
Bulk density (g/cm ³)	0.701–0.702
Solubility (g/L at 20°C) ⁽⁵⁾	≥ 42
Dusting potential (Stauber Heubach) (mg/m ³)	[3]
	11–892
Stability (% loss)	
Shelf-life	[3]
Room temperature (RT), 5 months	0–1.5
Stability in premixtures	[3]
Vitamin-mineral premix, RT, 6 months	9.1–25.3
Stability in feed	[3]
Piglet feed (mash) RT, 3 months	0–3.8
Piglet feed (pelleted) feed, RT, 3 months	0
Pelleting, 78–80°C	0–1.3
Stability in water	[3]
8–10°C, 48h	1–47.7
Homogeneity (coefficient of variation, %)	[1]
Pelleted feed, free histidine	4.5

Abbreviations: DM, dry matter; nDL-PCBs, non-dioxin-like PCBs; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; TEQ, toxic equivalent factors for dioxins, furans and dioxin-like PCBs established by WHO in 2005 (Van den Berg et al., 2006); WHO, World Health Organization.

⁽¹⁾ Analytical method to determine L-histidine: EN ISO 17180:2013.

⁽²⁾ Reference range for specific optical rotation of L-histidine monohydrochloride monohydrate according to the European Pharmacopoeia, monograph 01/2017:0910. European Pharmacopoeia (2021), 10 Edition.

⁽³⁾ <: means below the limit of quantification.

⁽⁴⁾ 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. Values are expressed per kg of additive with 88% dry matter content.

⁽⁵⁾ As reported by the applicant. No experimental data provided.

The data provided showed compliance with the specifications set by the applicant. The FEEDAP Panel considers that the microbial contamination and the levels of impurities analysed are of no safety concerns. However, the Panel notes the high levels of deoxynivalenol (up to 374.3 µg/kg) which deserve attention/monitoring during the manufacturing process.

The presence of viable cells of the production strain was investigated in three batches of L-histidine monohydrochloride monohydrate analysed in triplicate (1 g per sample).²³ Methodology, incubation conditions and controls were performed according to the requirements set by the EFSA FEEDAP Panel (EFSA FEEDAP Panel, 2018). No viable cells of the production strain were found in any of the test samples.

The presence of DNA from the production strain was analysed by PCR in three batches of L-histidine monohydrochloride monohydrate in triplicate (1 g per sample).²⁴ The primers targeted a [REDACTED]. The limit of detection in samples spiked with total DNA of the production strain was 1 ng per gram of product. No DNA from the production strain was detected in any of the samples.

3.1.4 | Conditions of use

L-Histidine monohydrochloride monohydrate is intended to be used in feed for all animal species. It can be added via pre-mixture or directly into feedingstuffs (including complete feed and complementary feed), or to water for drinking, without

²³ 2.1.4.b Absence viable cells P1812R2105.

²⁴ 2.1.4.c Absence DNA P1812R2123.

maximum or minimum levels and without withdrawal period. No inclusion levels are proposed, as the requirements in quantitative terms depend on the species, the physiological state of the animal, its age, its performance level and the environmental conditions, as well as the amino acid composition of the unsupplemented diet.

3.2 | Safety

3.2.1 | Safety of the production microorganism

The parental strain is an *E. coli* K-12, which is considered to be safe. The genetic modifications performed to obtain the production strain CCTCC M 20241089 have the purpose to increase the production of L-histidine. The taxonomic identification of the production strain was unequivocally established, it does not carry acquired genes coding for resistance to therapeutic antimicrobials and the genetic modification does not raise safety concerns. No viable cells nor 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 production strain.

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

The L-histidine requirements of the target animal species and the safety of this essential amino acid in non-ruminant and ruminant nutrition are well known by feed formulators and available in general publications on animal nutrition.

Concerns on the use of the additive would not derive from the L-histidine monohydrochloride monohydrate, which is considered safe, but may arise from residues of the fermentation process/production strain remaining in the final product. The additive is produced by fermentation with a genetically modified *E. coli* K-12 derivative (CCTCC M 20241089), and no safety concerns were identified for the production strain (see **Section 3.2.1**), the fermentation process and its residues/metabolites. Moreover, the resulting product is highly purified ($\geq 98\%$ L-histidine monohydrochloride monohydrate and $> 99\%$ identified material on a DM basis). L-Histidine monohydrochloride monohydrate produced with *E. coli* CCTCC M 20241089 is safe for the target species when used to supplement the diet in appropriate amounts to satisfy the animal requirements.

The FEEDAP Panel reiterates its concerns on the use of amino acids in water for drinking (EFSA FEEDAP Panel, 2010), for hygienic reasons, and for the risk of nutritional imbalances when amino acids are administered simultaneously in feed and in water for drinking.

No endotoxin activity was found in the final additive. Considering the LOQ of 300 IU/g, the highest theoretical content would still be far below the levels commonly found in feedingstuffs (up to 1,000,000 IU/g) (Cort et al., 1990).

The absorption and metabolic fate of L-histidine in the animals is well known. The amino acid L-histidine, supplemented to feed, will be incorporated into proteins of tissues and/or products of animal origin and any of its potential excess will be metabolised and excreted. Therefore, the protein composition of tissues and products of animal origin will not be affected using L-histidine monohydrochloride monohydrate in animal nutrition. Therefore, the Panel considers that the use of the additive in animal nutrition is safe for the consumer.

The amino acid L-histidine is a physiological and natural component of animals and plants. The use of the product L-histidine monohydrochloride monohydrate in animal nutrition would not lead to any local increase in the concentration in the environment. The use of the additive 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. It is concluded that the use of L-histidine monohydrochloride monohydrate produced by fermentation with *E. coli* CCTCC M 20241089 as a feed additive does not represent a risk to the environment.

3.2.3 | Safety for the user

No specific information on the safety for the user was submitted.²⁵ In the absence of data, the FEEDAP Panel is not in the position to conclude on the potential of the additive to be irritant to skin or eyes, or on its potential to be a dermal sensitiser.

Users can suffer from occupational respiratory disease depending on the level of endotoxins in air and dust (Rylander et al., 1999; Thorn & Kerekes, 2001). Although no occupational exposure limits have been set in the EU for inhalable endotoxins, the Dutch Expert Committee on Occupational Safety recommended a health-based occupational exposure limit for inhalable endotoxins of 90 IU/m³ (8-h time-weighted average) (DECOS, 2010). To reduce the risk, the FEEDAP Panel considers that the exposure of the users to bacterial endotoxins potentially present in the additive should be minimised.

²⁵Sect_3.3_Consolidated 250822.

3.3 | Efficacy

Efficacy studies are not required for amino acids that occur naturally in plant and animal proteins. The nutritional role of the amino acid L-histidine is well established in the scientific literature. The additive L-histidine monohydrochloride monohydrate is regarded as an efficacious source of the essential amino acid L-histidine for non-ruminant nutrition. For the supplemental L-histidine 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 Regulation²⁶ and Good Manufacturing Practice.

4 | CONCLUSIONS

The production strain *E. coli* CCTCC M 20241089 does not raise safety concerns regarding the genetic modifications. No viable cells nor DNA of the production strain are detected in the final product. Therefore, the FEEDAP Panel concludes that the additive does not pose any safety concern regarding the production strain.

The use of L-histidine monohydrochloride monohydrate produced with *E. coli* CCTCC M 20241089 in feed is safe for the target species when supplemented in appropriate amounts to the diet according to their nutritional needs. The FEEDAP Panel has concerns on the use of amino acids in water for drinking.

The use of L-histidine monohydrochloride monohydrate produced by fermentation with *E. coli* CCTCC M 20241089 in animal nutrition is considered safe for the consumers and for the environment.

Regarding user safety, in the absence of data, the FEEDAP Panel cannot conclude on the potential of the additive to be irritant to skin and/or eyes or on its potential to be a dermal sensitiser.

The additive L-histidine monohydrochloride monohydrate produced by fermentation with *E. coli* CCTCC M 20241089 is regarded as an effective source of the amino acid L-histidine for all non-ruminant species. In order to be as efficacious in ruminants as in non-ruminants, it should be protected from ruminal degradation.

ABBREVIATIONS

AMR	antimicrobial resistance
ANI	average nucleotide identity
CAS	Chemical Abstracts Service
CV	coefficient of variation
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
FLAVIS	The EU Flavour Information System
HACCP	hazard analysis and critical control points
IUPAC	International Union of Pure and Applied Chemistry
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LOD	limit of detection
LOQ	limit of quantification
MIC	minimum inhibitory concentration
OECD	Organisation for Economic Co-operation and Development
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo-p-dioxins
PCDFs	polychlorinated dibenzofurans, nDL-PCBs: non-dioxin-like PCBs
SCAN	Scientific Committee on Animal Nutrition
TEQ	toxic equivalent factors for dioxins, furans and dioxin-like PCBs
WGS	whole genome sequence
WHO	World Health Organization

²⁶Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 laying down requirements for feed hygiene. OJ L 268, 24.9.2003, p. 1.

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REQUESTOR

European Commission

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