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Safety and efficacy of L-cysteine monohydrochloride monohydrate produced by fermentation using *Escherichia coli* KCCM 80109 and *Escherichia coli* KCCM 80197 for all animal species

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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 the safety and efficacy of L-cysteine monohydrochloride monohydrate produced by fermentation using two non-genetically modified strains of *Escherichia coli* K12 (*E. coli* KCCM 80109 and *E. coli* KCCM 80197) as a flavouring additive for all animal species. No safety concerns are derived from the use of these strains as production strains of the additive. The FEEDAP Panel concludes that the use of L-cysteine hydrochloride monohydrate produced by *E. coli* KCCM 80109 and KCCM 80197 at concentrations up to 25 mg/kg complete feed is safe for the target species, for the consumer and for the environment. The product is proposed to be classified as respiratory irritant; however, exposure by inhalation is unlikely. Based on the results of the studies provided, it should be classified as skin irritant and that it causes serious eye damage. L-Cysteine hydrochloride monohydrate is not a dermal sensitiser. Since L-cysteine hydrochloride monohydrate is used in food as flavourings, it is to be expected that it can provide a similar function in feed and no further demonstration of efficacy is necessary when used at concentrations up to 25 mg/kg complete feed and the corresponding concentration in water.

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

The European Commission received a request from CJ Europe GmbH² for authorisation of the product L-cysteine monohydrochloride monohydrate produced by fermentation with *Escherichia coli* KCCM 80109 and *Escherichia coli* KCCM 80197 when used as a feed additive for all animals (category: sensory additives; functional group: flavourings compounds).

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 particulars and documents in support of the application were considered valid by EFSA as of 4 March 2019.

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 product L-cysteine monohydrochloride monohydrate produced by fermentation with *Escherichia coli* KCCM 80109 and *Escherichia coli* KCCM 80197, when used under the proposed conditions of use (see Section 3.1.2).

1.2. Additional information

L-Cysteine hydrochloride monohydrate has been assessed by the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) as a flavouring substance in pets only (EFSA FEEDAP Panel, 2013). The FEEDAP Panel also evaluated L-cysteine hydrochloride monohydrate in an opinion on the safety and efficacy of the use of amino acids (chemical group 34) when used as flavourings for all animal species (EFSA FEEDAP Panel, 2014). In both opinions, the FEEDAP Panel did not conclude on L-cysteine hydrochloride monohydrate produced by fermentation because no information on the production strains was submitted. In 2020, the FEEDAP Panel adopted an opinion on the safety and efficacy of L-cysteine hydrochloride monohydrate produced by fermentation using two genetically modified strains of *Escherichia coli* K12 (*Escherichia coli* KCCM 80180 and *Escherichia coli* KCCM 80181) as a flavouring additive for all animal species (EFSA FEEDAP Panel, 2020).

L-Cysteine hydrochloride monohydrate has not been assessed for use as food flavour.

L-Cysteine hydrochloride monohydrate is listed in the European Union Register of Feed Additives as feed flavourings.

L-Cysteine hydrochloride monohydrate produced by chemical synthesis or protein hydrolysis instead of using production strains is currently authorised as a sensory additive for use in all animal species except cats and dogs in accordance with Regulation (EU) 2018/249³ and L-cysteine hydrochloride monohydrate produced by hydrolysis of keratin from avian feathers is authorised in dogs and cats in accordance with Regulation (EU) 2015/2306.⁴

L-Cysteine hydrochloride [17.032], but not its monohydrate form, is listed in the European Union (EU) database of flavouring substances.⁵

¹ Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

² CJ Europe GmbH, Ober der Roeth, 4, 65824 – Schwalbach am Taunus, Germany.

³ Commission Implementing Regulation (EU) 2018/249 of 15 February 2018 concerning the authorisation of taurine, beta-alanine, L-alanine, L-arginine, L-aspartic acid, L-histidine, D,L-isoleucine, L-leucine, L-phenylalanine, L-proline, D,L-serine, L-tyrosine, L-methionine, L-valine, L-cysteine, glycine, monosodium glutamate and L-glutamic acid as feed additives for all animal species and L-cysteine hydrochloride monohydrate for all species except cats and dogs. OJ L 53, 23.2.2018, p. 134.

⁴ Commission Implementing Regulation (EU) 2015/2306 of 10 December 2015 concerning the authorisation of L-cysteine hydrochloride monohydrate as a feed additive for cats and dogs. OJ L 326, 11.12.2015, p. 46.

⁵ Commission Implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012, p. 1.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier⁶ in support of the authorisation request for the use of L-cysteine monohydrochloride monohydrate produced by fermentation with *Escherichia coli* KCCM 80109 and *Escherichia coli* KCCM 80197 as a feed additive.

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, 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 L-cysteine monohydrochloride monohydrate produced by fermentation with *Escherichia coli* KCCM 80109 and *Escherichia coli* KCCM 80197 in animal feed. The Executive Summary of the EURL report can be found in Annex A.⁷

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of L-cysteine monohydrochloride monohydrate produced by fermentation with *Escherichia coli* KCCM 80109 and *Escherichia coli* KCCM 80197 is in line with the principles laid down in Regulation (EC) No 429/2008⁸ and the relevant guidance documents: Guidance on the identity, characterisation and conditions of use of feed additives (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 consumer (EFSA FEEDAP Panel, 2017c), Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012), Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018), Guidance on the safety of feed additives for the environment (EFSA, 2008).

3. Assessment

The present opinion assesses the safety and efficacy of L-cysteine monohydrochloride monohydrate produced by fermentation with *Escherichia coli* KCCM 80109 and *Escherichia coli* KCCM 80197 as a sensory additive (functional group: flavouring compounds) for all animal species. The proposed inclusion level of the additive is 25 mg/kg feed for all animal species in accordance with Commission Implementing Regulation (EU) 2018/249.³

3.1. Characterisation

3.1.1. Characterisation of the production organism

The additive is produced by two non-genetically modified strains of *E. coli* K12 which are deposited in the Korean Culture Collection of Microorganisms (KCCM) with accession numbers KCCM 80109 and KCCM 80197.

The production strains *E. coli* KCCM 80109 and *E. coli* KCCM 80197 are generated

Both production strains were verified to be *E. coli*. The identity of *E. coli* KCCM 80109 and *E. coli* KCCM 80197 as *E. coli* K12 derivatives was confirmed by whole genome sequence (WGS)

⁶ FEED dossier reference: FAD-2018-0091.

⁷ The full report is available on the EURL website: <https://ec.europa.eu/jrc/sites/jrcsh/files/finrep-fad-2018-0091-cysteine.pdf>

⁸ 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.

¹² Technical dossier/Supplementary information February 2020/03_SIN_CJE.

The production strains were tested for their susceptibility to all relevant antibiotics listed for 'Enterobacteriaceae' in the Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018)

The WGS of both production strains was analysed for the presence of antimicrobial resistance genes and no relevant hits were found

3.1.2. Manufacturing process

3.1.3. Characterisation of the additive

L-Cysteine hydrochloride monohydrate (International Union of Pure and Applied Chemistry (IUPAC) name: (R)-2-Amino-3-mercaptopropionic acid hydrochloride monohydrate; synonym β -Mercaptoalanine hydrochloride monohydrate) is a compound identified with the Chemical Abstracts Service (CAS) No 7048-04-6. It has a molecular mass of 175.6 g/mol. The molecular formula of L-cysteine hydrochloride monohydrate is $C_3H_7NO_2S \text{ HCl H}_2O$. The structural formula is given in Figure 1.

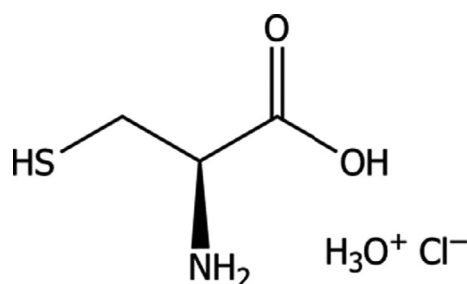


Figure 1: Molecular structure of L-cysteine hydrochloride monohydrate

The additive contains by specifications $\geq 98.5\%$ L-cysteine hydrochloride monohydrate (dry matter basis) with $\leq 12\%$ water.¹⁶ The analysis of five batches showed an average value of L-cysteine hydrochloride monohydrate of 99.3% (range 99.22–99.32%).¹⁷ Moisture average was 10.3% (range 10.32–10.37).¹⁷

Average cysteine content was 68.3% 'as is' (range 68.29–68.32%), and an average hydrochloride content of 20.6% (range 20.6–20.67%). Other components analysed were sulfate (0.2% in three batches and 0.1% in two batches), ammonium (detected in all five batches at 0.01%), and 0.15% free cysteine.¹⁷ The sum of the identified material on 'as is' basis was 99.46%.

Analytical data on specific optical rotation of three batches of L-cysteine hydrochloride monohydrate showed an average value of $+5.63^\circ$ (range $+5.60^\circ$ to $+5.67^\circ$), which is within the range described in the European Pharmacopoeia for this amino acid (5.5° – 7.0°)¹⁸ and confirms the presence of L-enantiomer (2017).

¹⁶ Technical dossier/Section II/Annex II.1.01.

¹⁷ Technical dossier/Section II/Annex II.1.03.

¹⁸ Technical dossier/Section II/Annex II.1.02.

3.1.3.1. Impurities

Three batches of the additive were analysed for impurities.¹⁹

Levels of heavy metals (cadmium, lead and mercury) and arsenic resulted in values below the limit of detection (LOD).²⁰ Dioxins, furans, pesticides and dioxin-like polychlorinated biphenyls (PCBs) were not detected in the same batches.²¹ In the same batches, total bacteria counts were < 1000 colony-forming units (CFU)/g, bacterial counts of *Salmonella* in 25 g and *E. coli* were negative; the determination of yeasts and moulds were < 50 CFU/g.

Aflatoxins (B1, B2, G1, G2) and ochratoxin A were not detected in the same batches (LOD 0.1 µg/kg). Zearalenone (LOD 1.5 µg/kg) and deoxynivalenol (LOD 0.5 µg/kg) were not detected as well.

The absence of viable cells of the production strains was confirmed

3.1.3.2. Physico-chemical characteristics

The additive is an off-white crystalline powder, with a bulk density of 600–800 kg/m³ and a solubility in water (at 25°C) of 50 g/L, pH 0.8–1.2 (100 g/L water).

The particle size distribution (three batches of the additive) was analysed

The dusting potential of three batches of the final product (Stauber-Heubach method) ranged from

3.1.4. Stability and homogeneity

No information on the shelf-life, stability (in premixtures, feedingstuffs and water for drinking) and capacity of the additive under assessment to distribute homogeneously in feed was provided. The applicant provided information on the shelf-life and stability in water for drinking with an L-cysteine hydrochloride monohydrate originating from different strains (*E. coli* KCCM 80180 and KCCM 80181) of the same producer. Such studies were described in a previous opinion (EFSA FEEDAP Panel, 2020). As the production process is the same and the product characteristics are very similar, the FEEDAP Panel considers that the results of those studies can be applicable to the product under assessment.

The shelf-life of the additive (three batches) was studied when stored in sealed brown glass containers at 25°C for 12 months or 40°C for 6 months. The losses of L-cysteine detected at the end of the respective storage periods ranged from 0.5 to 0.8% at 25°C and from 0.1 to 0.8% at 40°C.²⁶

The stability of the additive (three batches) was studied in water for drinking when used at a concentration of 0.05% (20 times the recommended dose in feed) and stored at 25 or 40 °C for 48 h.²⁷ Losses up to 5% and 33% were detected in samples stored at 25°C and 40°, respectively.

3.1.5. Physico-chemical incompatibilities

No physico-chemical incompatibilities in feed are expected with other additives, medicinal products or other feed materials.

3.1.6. Conditions of use

The applicant proposes the use of L-cysteine hydrochloride monohydrate as a flavouring compound in feed for all animal species at a level of 25 mg/kg complete feed. The applicant also proposes the use of L-cysteine hydrochloride monohydrate in water for drinking for all animal species, but no use level is proposed.

¹⁹ Technical dossier/Section II/Annex II.1.02 and II.1.04.

²⁰ LOD of cadmium, lead, mercury 1 µg/kg, LOD of mercury 5 µg/kg.

²¹ LOD for dioxin and furans 0.05 µg/kg, LOD for dioxin-like PCBs 0.13 µg/kg, LOD pesticides 0.5-8.0 µg/kg.

²⁶ Technical dossier/Section II/Annex II_4_01.

²⁷ Technical dossier/Section II/Annex II_4_03.

3.2. Safety

3.2.1. Safety for the target species, consumer and environment

The additive is highly purified with < 1% unidentified material and no bacterial endotoxin activity was measured in the additive. Concerns from the use of the additive would not derive from L-cysteine hydrochloride monohydrate, which is considered safe, but may arise from residues of the fermentation process/production strains remaining in the final product. Since the identity of the production strains has been established as *E. coli* K12 derivatives, they are susceptible to relevant antimicrobials used in human and veterinary medicine and no viable cells of the production strains are in the final product and the proposed use level (25 mg/kg complete feed) is well below the requirements, the use of L-cysteine hydrochloride monohydrate produced by *E. coli* KCCM 80109 and KCCM 80197 under the proposed conditions of use is considered safe for the target species. Due to the risk of nutritional imbalances and hygienic reasons, associated with the use of amino acids via water for drinking, the FEEDAP Panel has concerns on the safety of the simultaneous oral administration of L-cysteine hydrochloride monohydrate containing additives via feed and water for drinking.

The composition of edible tissues and products of animal origin will not be changed by the use of the additive; therefore, L-cysteine hydrochloride monohydrate produced by *E. coli* KCCM 80109 and KCCM 80197 is safe for the consumer.

L-Cysteine is a physiological and natural component of proteins in animals and plants. It is not excreted as such but as urea or uric acid, sulfate and CO₂. The use of L-cysteine in animal nutrition would not lead to any localised increase in its concentration in the environment. It is concluded that the use of this product as feed additive does not represent a risk to the environment.

The FEEDAP Panel concludes that the use of L-cysteine hydrochloride monohydrate, produced by *E. coli* KCCM 80109 and KCCM 80197 under the proposed conditions of use, is safe for the target species, for the consumer and for the environment.

3.2.2. Safety for the user

The applicant did not submit studies performed with the additive under assessment to assess the safety for the user. The applicant submitted an acute inhalation test performed according to OECD guideline 403,²⁸ a skin irritation test performed according to OECD guideline 439,²⁹ an eye irritation test performed according to OECD guideline 437,³⁰ and a skin sensitisation test following OECD guideline 429³¹ performed with of L-cysteine hydrochloride monohydrate produced by *E. coli* K12 KCCM 80180 and KCCM 80181. All studies were performed in compliance with good laboratory practices (GLP). Data from these tests were assessed in a previous opinion (EFSA FEEDAP Panel, 2020). As the composition, purity and physico-chemical characteristics of the active substance under assessment are the same as of that assessed in the above-mentioned opinion (including the low pH of the additive in aqueous solution and dusting potential) and the production process is the same (or very similar), the FEEDAP Panel considers that the results of the studies performed with L-cysteine hydrochloride monohydrate produced by *E. coli* K12 KCCM 80180 and KCCM 80181 can be used to support the safety for the user for the additive under assessment.

Based on the results with the other product, the FEEDAP Panels conclude that although users' exposure via inhalation is unlikely due to the low dusting potential, the product is proposed to be classified as respiratory irritant due to its low pH when in solution. In addition, based on the results of the studies provided, it should be classified as skin irritant and that it causes serious eye damage. L-cysteine hydrochloride monohydrate is not a dermal sensitiser.

3.3. Efficacy

Since L-cysteine hydrochloride monohydrate is used in food as flavouring, it is to be expected that it can provide a similar function in feed and no further demonstration of efficacy is necessary when used in feed and the corresponding concentration in water.

²⁸ Technical dossier/Section III/Annex III_3_02.

²⁹ Technical dossier/Section III/Annex III_3_04.

³⁰ Technical dossier/Section III/Annex III_3_03.

³¹ Technical dossier/Section III/Annex III_3_05.

4. Conclusions

The additive is produced by two non-genetically modified strains of *Escherichia coli* K12 (*E. coli* KCCM 80109 and KCCM 80197). No safety concerns are derived from the use of these strains as production strains of the additive.

The FEEDAP Panel concludes that the use of L-cysteine hydrochloride monohydrate produced by *E. coli* KCCM 80109 and KCCM 80197 at concentrations up to 25 mg/kg complete feed is safe for the target species, for the consumer and for the environment.

Based on the results with the other product, the FEEDAP Panels conclude that although users' exposure via inhalation is unlikely due to the low dusting potential, the product is proposed to be classified as respiratory irritant due to its low pH when in solution. In addition, based on the results of the studies provided, it should be classified as skin irritant and that it causes serious eye damage. L-cysteine hydrochloride monohydrate is not a dermal sensitiser.

Since L-cysteine hydrochloride monohydrate is used in food as flavourings, it is to be expected that it can provide a similar function in feed and no further demonstration of efficacy is necessary when used at concentrations up to 25 mg/kg complete feed and the corresponding concentration in water.

Documentation provided to EFSA/Chronology

Date	Event
29/01/2019	Dossier received by EFSA
21/01/2019	Reception mandate from the European Commission
04/03/2019	Application validated by EFSA – Start of the scientific assessment
30/04/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: characterisation.</i>
21/10/2019	Reception of supplementary information from the applicant - Scientific assessment re-started
28/10/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: characterisation</i>
19/12/2019	Reception of supplementary information from the applicant - Scientific assessment re-started
20/12/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: characterisation</i>
03/03/2020	Reception of supplementary information from the applicant - Scientific assessment re-started
04/06/2019	Comments received from Member States
15/05/2019	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives
19/03/2020	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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Abbreviation

CFU	Colony-forming units
EURL	European Union Reference Laboratory
FEEDAP	the Panel on Additives and Products or Substances used in Animal Feed
GLP	Good laboratory practices
KCCM	Korean Culture Collection of Microorganisms
LOD	Limit of detection
PCBs	polychlorinated biphenyls
WGS	Whole genome sequence

Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis for L-cysteine monohydrochloride monohydrate produced by fermentation with *Escherichia coli* KCCM 80109 and *Escherichia coli* KCCM 80197

In the current application, authorisation is sought under Article 4(1) for L-cysteine monohydrochloride monohydrate produced (L-cysteine HCl H₂O) by fermentation with *Escherichia coli* KCCM 80109 and *Escherichia coli* KCCM 80197, under the category/functional groups 2(b) 'sensory additives/flavouring compounds' according to Annex I of Regulation (EC) No 1831/2003. Authorisation is sought for all animal species.

According to the Applicant L-cysteine HCl H₂O has a minimum purity (mass fraction) of 98.5%. The feed additive is intended to be added directly into feedingstuffs or through premixtures and water for drinking. The Applicant proposed a maximum content of L-cysteine HCl H₂O of 25 mg/kg feedingstuffs.

For the quantification of L-cysteine HCl H₂O in the feed additive, the Applicant presented experimental data obtained when analysing the feed additive with the VDLUFA method 4.11.6 designed for the analysis of lysine, methionine and threonine in feed additives and concentrated premixtures and based on ion-exchange chromatography coupled with postcolumn derivatisation and optical detection (IEC-VIS/FD). The results presented are considered sufficient to demonstrate the suitability of the procedure for the determination of the amino acid in the feed additive. Furthermore, according to the experience of NRLs, the VDLUFA method and other ring-trial validated methods designed for the analysis of amino acids and based on a similar analytical procedure are fit for purpose. Hence, for official control, the EURL recommends this method (or equivalent) for the determination of L-cysteine HCl H₂O in the feed additive.

For the quantification of the L-cysteine HCl H₂O content in premixtures and feedingstuffs, the Applicant submitted the ring-trial validated Community method (Commission Regulation (EC) No 152/2009) based on IEC-VIS. This method, designed for the analysis of free (synthetic and natural) and of total (peptide-bound and free) amino acids (including cysteine) in premixtures and feedingstuffs, does not distinguish between the salts and the amino acid enantiomers. The Community method was further ring-trial validated by 23 laboratories for the determination of total cyst(e)ine (sum of cysteine and cystine, peptide bound and free) in feed and resulted in the equivalent standard method EN ISO 13903:2005. While the Applicant proposed a maximum content of L-cysteine HCl H₂O in feedingstuffs of 25 mg/kg, a higher limit of quantification of 350 mg/kg feedingstuffs was derived for total cyst(e)ine. Therefore, the EURL is unable to recommend the Community method for the official control of this product in feedingstuffs.

Nevertheless, based on the performance characteristics available, the EURL recommends for official control the ring-trial validated Community method based on IEC-VIS to quantify L-cysteine HCl H₂O in premixtures.

The Applicant did not submit any method for the official control of L-cysteine HCl H₂O in water. However, in the frame of the stability studies, the Applicant presented experimental data obtained when analysing the amino acid with the above-mentioned ring-trial validated method VDLUFA – Method 4.11.6. The results presented are considered sufficient to demonstrate the suitability of the procedure for the analysis of L-cysteine HCl H₂O in water. Hence, for official control, the EURL recommends this method (or equivalent) for the determination L-cysteine HCl H₂O in water.

In the frame of the authorised 'Chemical Defined flavouring Group 34 – amino acids' (FAD-2010-0107), for the identification of L-cysteine HCl H₂O in the feed additive, the EURL positively evaluated the European Pharmacopeia 2.2.56 (2009) method for amino acids based on IEC coupled with post-column derivatisation and photometric detection (visible – VIS). Furthermore, the EURL recommendation has been included in the corresponding authorising regulation. In order to foster the use of the same method for identical substances, the EURL recommends this European Pharmacopeia method for official control to identify L-cysteine HCl H₂O in the feed additive.

Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by Article 10 (Commission Regulation (EC) No 378/2005), as last amended by Regulation (EU) 2015/1761 is not considered necessary.