Assessment of the safety and efficacy of Guanidinoacetic acid (Creamino®) as a feed additive for all animal species

Reference number RP1087

Regulated Products Risk Assessment Unit
Science, Evidence and Research Division, FSA

Risk Assessment Team
Science Division, FSS

Regulated Product Dossier Assessment
Assessment finalised: 15/03/2024

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Abbreviations

Acronym	Definition
ACAF	Advisory Committee on Animal Feedingstuffs
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
EURL	European Union Reference Laboratory
FSA	Food Standards Agency
FSS	Food Standards Scotland
GAA	Guanidinoacetic acid
HACCP	Hazard Analysis and Critical Control Points
HPLC-UV	High Performance Liquid Chromatography coupled to Ultraviolet feedingstuffs
IC-UV	Ion chromatography coupled with ultraviolet detection.
LOQ	Limit of Quantification
RSDr	Relative standard deviation for repeatability
RRec	Recovery rate

Summary

An application was submitted to the Food Standards Agency in May 2021 from AlzChem Trostberg GmbH ("the applicant") for the new use authorisation of an additive guanidinoacetic acid (Creamino®), under the category of 'nutritional additives" and functional group "amino acids, their salts, and analogues". The additive is proposed to be used in all animal species with a proposed level of inclusion in feed of 1.2 kg/ 1,000 kg (0.12 %) of complete feedingstuffs with a moisture content of 12%.

The Advisory Committee on Animal Feedingstuffs (ACAF) was asked to review the dossier and the supplementary information submitted by the Applicant, and to advise the Food Standards Agency and Food Standards Scotland (FSA/FSS) in evaluating the dossier.

The FSA/FSS concluded, based on the ACAF's advice, that the additive was correctly identified and characterised. No causes for concern were raised in this section of the dossier.

The additive can be considered safe for target species, consumers, and the environment. The additive is not irritant to eyes or skin and is not a dermal sensitiser or toxic through inhalation. It is advised that appropriate dusk masks are worn when handling the additive, due to its high dusting potential. No additional safety risks are to be expected if the additive were to be categorised as a "zootechnical additive".

The additive can be considered efficacious for growing pigs and poultry. No conclusion could be reached on efficacy for the other target species requested.

The views of ACAF have been taken into account in this safety assessment which represents the opinion of the FSA/FSS.

1. Introduction

The FSA/FSS have undertaken a risk assessment for a feed additive (guanidinoacetic acid - AlzChem Trostberg GmbH, Dr.-Albert-Frank-Str. 32, 83308 Trostberg, Germany) under Assimilated Regulation (EC) No 1831/2003[1] for a new authorisation (extension of use) under the category of "nutritional additives" and functional group "amino acids, their salts and analogues", for its use in all animal species. To support the safety assessment, the ACAF provided advice to the FSA/FSS outlined in this document.

The dossier was evaluated on behalf of the FSA/FSS by the ACAF. In line with Article 8 of 1831/2003, the assessment has considered whether 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.

With thanks to the members of the ACAF during the course of the assessment, who were: Professor Nicholas Jonsson, Martin Briggs, Professor Emily Burton, Professor Katrina Campbell, Susan MacDonald, Professor Matthew Fisher, Hannah Kane, Christine McAlinden, Dr. Donald Morrison, Derek Renshaw, Dr. Oonagh Markey, Dr. Michael Salter, Dr. Adam Smith, Dr. Helen Warren and Dr. Nick Wheelhouse.

The dossier was evaluated by the ACAF at their April 2023 and September 2023 meetings. Further information was provided by the applicant in August 2023, responding to queries by the FSA. The conclusions were reviewed and approved by the ACAF at their December 2023 meeting.

This document sets out the findings of the Committee's assessment on the safety and efficacy of the feed additive, on which the FSA/FSS have made their opinion for the request of a new authorisation.

2. Assessment

2.1. Section II: Identity, characterisation and conditions of use

The additive contains the active substance, guanidinoacetic acid (GAA) and is presented as a white crystalline powder with a minimum purity of 98%**.** The applicant provided data from several batches supporting the composition values outlined below (Table 1):

Table 1: Identity table guanidinoacetic acid

Composition		
Substance	**GAA (98 %)**	**Granulated preparation Creamino**
GAA	≥ 98 %	≥ 96 %
Dicyandiamide	≤ 0.5 %	-
Cyanamide	≤ 0.03 %	-
Water	-	≤ 1 %
Starch	-	Approx. 1%
Appearance		
White Crystalline Powder		
Chemical-physical properties		
Mean Dusting Potential	5.6 g/m^3	
Bulk Density	540 – 660 kg/m^3	
Tamped Apparent Density	690 kg/m^3	
Particle Size Distribution	Fraction (µm) < 63 < 100 < 200 < 315 < 500 < 710 < 850	Amount (%) 2.2 - 5.4 3.1 – 6.5 4.4 - 14.6 11.0 – 27.4 42.0 – 68.4 90.8 – 96.8 100.0
Purity		
Total Microbial Count	Max. 10 ^{5} cfu/g	
Coliform bacteria	Not Detectable in 10 g	
Yeasts	Max. 200 cfu/g	
Moulds	Max. 200 cfu/g	
Salmonella spp.	Not Detectable in 25g	
Clostridium spp.	Max. 10 cfu /g	
Bacillus cereus	Not tested	
Dicyandiamide	0.05 – 0.10 %	
Cyanamide	< 7 mg/kg (LOQ)	
Melamine	2.09 – 4.69 mg/kg	

In the first evaluation, the ACAF identified several pieces of information that the applicant would need to provide to inform the assessment of the product, including microbial purity certificates of analysis, HACCP details, component information, high dusting potential causes, homogeneity trial information, classification of GAA concentration inaccuracies and evidence of stability at 86°C for 6 minutes. These queries were successfully addressed by the applicant.

Members noted that the additive is very stable when exposed to a range of temperatures, pressures, and moisture contents for different durations. However, due to insufficient data, members were unable to conclude on the stability of the additive in breeder feed if processed at 86°C for 6 mins.

The proposed conditions of use are described in Table 2.

Table 2: Proposed conditions of use of guanidinoacetic acid

Proposed mode of use in animal nutrition					
Additive	Guanidinoacetic acid (GAA)				
Registration number/ EC No/No	3c.3.7.2				
Category(-ies) of additive	Nutritional additive				
Functional group(s) of additive	Amino acids, their salts, and analogues				
Description					
Description	**Chemical formula**	**Purity criteria**	**Method of analysis**		
Guanidinoacetic acid (CAS No 352-97-6) with a purity of at least of 98 % (on dry matter basis) produced by chemical synthesis	C3H7N3O2	≥ 98% GAA ≤ 0.5% dicyandiamide ≤ 0.03% cyanamide	Ion chromatography (IC) with UV detection (λ = 200 nm)		
Trade name (if appropriate)		Creamino® (granulated preparation with min. 96% GAA)			
Name of holder of authorisation (if appropriate)		N/A			
Conditions of use					
Species or category of animal	**Min-max Age**	**Min. content**	**Max. content**	**Withdrawal period**	
		mg/kg of complete feedingstuffs (12% moisture)			
All animal species	No maximum age or weight	600	1200	--	
		Drinking Water (mg /L)			

All animal species	No maximum age or weight	200	600	--
Specific conditions or restrictions of use	Store in original, closed packaging, in a dry place at ambient temperature (<25°C).			
Post market monitoring	As per EU feed hygiene regulation: traceability, HACCP, formal product/service complaints procedure and product recall capability.			
Specific conditions for use in complementary feedingstuffs	To supply 600 to 1200 mg GAA in the complete ration (12% moisture basis)			

2.1.1. Conclusions on Section II

The ACAF concluded that the additive was correctly identified and characterised. No evidence of stability when processed at 86°C for 6 minutes was provided.

No further concerns were raised for Section II of the dossier.

2.2. Section III: Safety

The applicant presented previous EFSA conclusions[2,3] and a literature review for the target species covering the period 1990 -2019 identifying 885 publications of which 70 were considered eligible. The ACAF concluded that the search was comprehensive and noted that no there were no concerns regarding tolerance studies, including no adverse effects on toxicological testing. The ACAF also concluded that based on the information provided the additive should be considered not irritant to eyes or skin, and to not be a dermal sensitiser. The applicant presented a new acute inhalation toxicity test in female rats, showing that the additive is not toxic through inhalation, however, due to the high dusting potential of the final formulation, it is advised that workers use appropriate dust protection masks when handling the additive.

2.2.1. Conclusions on safety

The Committee concluded that the additive can be considered safe for target species, consumers, and the environment. The additive is not irritant to eyes or skin and is not a dermal sensitiser or toxic through inhalation. It is advised that appropriate dusk masks are worn when handling the additive, due to its high dusting potential.

The ACAF was asked to consider any additional safety risks posed by potentially reclassifying the additive under the category “zootechnical additives”. It was concluded that no additional safety risks are expected.

2.3. Section IV: Efficacy

The efficacy of the additive had been previously assessed by EFSA through seven long term efficacy studies in chickens for fattening and one long term efficacy study in weaned piglets. The ACAF requested further efficacy data to allow for extrapolation to all animal species. Upon request for further data, the applicant did not provide further studies in other relevant species, therefore, no conclusion could be reached on efficacy for the other target species.

The ACAF concluded the additive to be efficacious in growing pigs and all growing poultry. No conclusion could be reached on efficacy for the other target species requested.

2.3.1 Conclusions on Efficacy

The ACAF concluded that the additive can be considered efficacious in growing pigs and all growing poultry. No conclusion could be reached on efficacy for the other target species requested.

3. Analytical methods evaluation

Conclusions on the analytical methods are presented here as an extract from the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of the Analysis for of guanidinoacetic acid (Creamino)[4].

> “For the determination of GAA in the feed additive and feedingstuffs the Applicant proposed a single laboratory validated and further verified method based on Ion Chromatography coupled to UltraViolet detection (IC-UV). The performance characteristics recalculated by EURL, based on the experimental data provided by the Applicant, are :

- a relative standard deviation for repeatability (RSDr) ranging from 0.11 to 4.2 %;

- a recovery rate (RRec) ranging from 96.4 to 99.1 %; and

- a limit of quantification (LOQ) in the feedingstuffs of 50 mg/kg.

For the determination of GAA in premixtures the Applicant proposed a single laboratory validated method based on High Performance Liquid Chromatography coupled to UltraViolet (HPLC-UV), which is very similar to the method applied for the feed additive and feedingstuffs. The Applicant reported RSDr values ranging from 0.6 to 1.4% and RRec values ranging from 96 to 108%.

Based on the performance characteristics presented, the EURL recommends for official control (1) the single laboratory validated and further verified method based on ion chromatography coupled to ultraviolet detection to determine guanidinoacetic acid in the feed additive and feedingstuffs and (2) the single laboratory validated to determine guanidinoacetic acid in the premixture."

FSA/FSS accepts the EURL analytical method evaluation reports. FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

4. Conclusions

The FSA/FSS have considered and agree with the conclusions reached by the ACAF on the safety and efficacy of the feed additive.

The ACAF concluded that the additive was correctly identified and characterised.

The Committee concluded that the additive can be considered safe for target species, consumers, and the environment. The additive is not irritant to eyes or skin and is not a dermal sensitiser or toxic through inhalation. It is advised that appropriate dusk masks are worn when handling the additive, due to its high dusting potential. The ACAF concluded that no additional safety risks are to be expected if the additive were to be categorised as a "zootechnical additive".

The ACAF concluded the additive to be efficacious in growing pigs and all growing poultry. No conclusion could be reached on efficacy for the other target species requested.

The FSA/FSS agree with the conclusions reached by the ACAF. FSA/FSS accepts the EURL analytical method evaluation reports. FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

5. References

1. EC (European Commission), 2003. Regulation No 1831/2003 of the European Parliament and of the Council on additives for use in animal nutrition. Available at Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition (Text with EEA relevance) (legislation.gov.uk)
2. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP); Scientific opinion on the safety and efficacy of guanidinoacetic acid as feed additive for chickens for fattening. EFSA Journal 2009;998:1-30. https://doi.org/10.2903/j.efsa.2009.988
3. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP); Scientific opinion on the safety and efficacy of guanidinoacetic acid as a feed additive for chickens for fattening, breeder hens and roosters, and pigs. EFSA Journal 2016;4394 https://doi.org/10.2903/j.efsa.2016.4394
4. EURL-FA (European Reference Laboratory for Feed Additives), 2022. Evaluation Report on the Analytical Methods submitted in connection with the Application for Authorisation of a Feed Additive according to Regulation (EC) No 1831/2003. Guanidinoacetic acid (3c372). Available at: FAD-2011-0043 - European Commission (europa.eu)

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