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SCIENTIFIC OPINION

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Assessment of the feed additive copper bilysinate for all animal species for the renewal of its authorisation (Senzyme GmbH)

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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 copper bilysinate as nutritional feed additive for all species and categories. The additive is currently authorised for use in all animal species (3b411). The applicant has provided evidence that the additive, in powder or granule forms, complies with the conditions of the authorisation. The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) confirms that the use of copper bilysinate under the current authorised conditions of use is safe for the target species, consumers and the environment. Regarding user safety, both forms of the additive are not irritant to the skin, but the powder product is an eye irritant. Both forms of the additive should be considered skin and respiratory sensitisers. Inhalation and dermal exposure are considered a risk. There is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

KEYWORDS

copper bilysinate, efficacy, functional group: Compounds of trace elements; nutritional additives, safety

CONTENTS

1 | INTRODUCTION

1.1 | Background and Terms of Reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 14(1) of that Regulation lays down that an application for renewal shall be sent to the Commission at the latest 1 year before the expiry date of the authorisation.

The European Commission received a request from Senzyme GmbH[2] for the renewal of the authorisation of the additive consisting of copper bilysinate, when used as a feed additive for all animal species (category: nutritional additives; functional group: compounds of trace elements).

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 14(1) (renewal of the authorisation). The dossier was received on 20 December 2023 and the general information and supporting documentation are available at https://open.efsa.europa.eu/questions/EFSA-Q-2023-00901. The particulars and documents in support of the application were considered valid by EFSA as of 5 March 2024.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the feed additive consisting of copper bilysinate, when used under the proposed conditions of use (see **Section 3.1.2**).

1.2 | Additional information

The additive copper bilysinate is currently authorised for use in feed for all animal species (3b411).[3] EFSA issued an opinion on the safety and efficacy of this additive for all animal species (EFSA FEEDAP Panel, 2014).

2 | DATA AND METHODOLOGIES

2.1 | Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[4] in support of the authorisation request for the use of copper bilysinate as a feed additive.

The confidential version of the technical dossier was subject to a target consultation of the interested Member States from 8 March 2024 to 8 June 2024; the comments received were considered for the assessment.

In accordance with Article 38 of the Regulation (EC) No 178/2002[5] 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,[6] 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 31 July to 21 August 2024 for which no comments were received.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers, other scientific reports and experts' (elicitation) knowledge, to deliver the present output.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment regarding the methods used for the control of the copper bilysinate in animal feed/marker residue in tissues are valid and applicable for the current application.[7]

[1]Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2]Senzyme GmbH, Gierlichsstraße 6, 53840 Troisdorf, Germany.
[3]Commission implementing regulation (EU) No 1230/2014 of 17 November 2014 concerning the authorisation of copper bilysinate as a feed additive for all animal species.
[4]Dossier reference: FEED-2023-015591.
[5]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, pp. 1–48.
[6]Decision available at: https://www.efsa.europa.eu/en/corporate-pubs/transparency-regulation-practical-arrangements.
[7]Evaluation report 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.

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of copper bilysinate is in line with the principles laid down in Regulation (EC) No 429/2008[8] and the relevant guidance documents: Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2021).

3 | ASSESSMENT

Copper bilysinate is currently authorised for use as a nutritional additive (functional group: compounds of trace elements) in feed for all animal species. The current application regards the renewal of this authorisation.

3.1 | Characterisation

3.1.1 | Characterisation of the additive

The additive copper bilysinate is authorised in powder and granulate forms with a minimum content of 14.5% copper and 84% lysine-HCl.[9] The applicant stated that other constituents are limited in both forms of the additive (powder and granulate) to [redacted] and it is reported to be mainly bound potassium, zinc, calcium and sodium. The granulated form contains a binding agent at approximately 0.5% (e.g. carboxymethylcellulose).

The applicant stated that the manufacturing process or the composition of the additive have not been modified since the original authorisation.[10]

Data on the batch-to-batch variation of the active substance in the additive for five batches[11] of each form of the additive, and three for impurities[12] (Table 1) were made available.

TABLE 1 Data on the batch-to-batch variation, impurities and physical properties of the two forms of copper bilysinate. The data presented are average values and (range) for batch-to-batch variation and ranges for impurities. The number of batches analysed for each group of parameters are indicated in [].

	Powder	Granulate
Specifications[1]		
Copper (%)	≥ 14.5	≥ 14.5
Lysine-HCl (%)	≥ 84.0	≥ 84.0
Batch-to-batch variation	[5]	[5]
Copper (%)	14.6 (14.4–14.7)	14.6 (14.5–14.8)
Lysine-HCl (%)	85.0 (84.9–85.2)	85.0 (84.8–85.2)
Impurities	[3]	[3]
Lead (mg/kg)	7.9 (7.8–8.0)	8.1 (8.0–8.2)
Mercury (mg/kg)	< 0.1	< 0.1
Cadmium (mg/kg)	1.9 (1.8–1.9)	1.5(1.4–1.5)
Arsenic (mg/kg)	1.6 (1.6–1.6)	1.7 (1.7–1.7)
Dioxins and PCBs (upper bound)[2]		
PCDD/Fs (ng WHO_{2005}-TEQ/kg)	0.08–0.09	0.09–0.10
PCDD/Fs + PCBs (ng WHO_{2005}-TEQ/kg)	0.09–0.10	0.1–0.11

Note: <: means below the limit of quantification.

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

[1]Specifications set in Regulation (EU) No 1230/2014.

[2]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.

[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.

[9]Detailed identification_confid.

[10]ADR received November 2024: Manufacturing_RFI_confid.

[11]Annex II 1_2 and Annex II 1_3.

[12]Annex II 1_4; Annex II 1_5.

The data provided by the applicant showed compliance with the specifications set in the authorising regulation for copper bilysinate in terms of copper and lysine content, except from one batch from the powder form for which the copper values were slightly below the specification. The FEEDAP Panel considers that the levels of impurities do not raise safety concerns.

No new data were provided on the physico-chemical properties (dusting potential, particle size). The additive (both forms) is specified to be soluble at 1 g/L at 20°C, however no analytical evidence was provided. Considering that the manufacturing process and the composition of the additive have not been modified since the previous authorisation, the Panel considers that the data on physico-chemical properties assessed in the previous opinion (EFSA FEEDAP Panel, 2014) apply to the current assessment.

3.1.2 | Conditions of use

The additive is currently authorised[13] for use in feed for all animal species up to the following maximum authorised total copper content in complete feeds (mg/kg complete feed):

Animal species/categories	Maximum authorised total copper content (mg/kg complete feed)
Bovines before the start of rumination	15
Other bovines	30
Ovines	15
Caprines	35
Suckling and weaned piglets up to 4 weeks after weaning	150
Piglets from 5th week after weaning up to 8 weeks after weaning	100
Crustaceans	50
Other animals	25

Under other provisions it is stated:

1. The additive shall be incorporated into the feed in the form of a premixture.
2. For user safety: breathing protection, safety glasses and gloves should be worn during handling.
3. The following words shall be included in the labelling:

- For feed for sheep if the level of copper in the feed exceeds 10 mg/kg: 'The level of copper in this feed may cause poisoning in certain breeds of sheep.'
- For feed for bovines after the start of rumination if the level of copper in the feed is less than 20 mg/kg: 'The level of copper in this feed may cause copper deficiencies in cattle grazing pastures with high contents of molybdenum or sulfur'.
- 'The lysine content of the additive should be considered when formulating feed'.

The applicant did not request any change in the currently authorised conditions of use.

3.2 | Safety

In its previous assessment, the FEEDAP Panel concluded that the additive is safe for all animal species, provided the maximum authorised copper levels in feed are not exceeded. This conclusion was based on tolerance studies conducted with chickens for fattening and weaned piglets (EFSA FEEDAP, 2014).

It was also concluded that the additive was safe for the consumers and for the environment. Regarding user safety, the Panel concluded that the powder form should be considered as a risk by inhalation. Neither form of the additive is a dermal irritant, but the powder form is an eye irritant. In the absence of data, both forms were considered as potential skin sensitisers.

The applicant provided a statement[14] that no adverse effects have been reported for the target species, consumers, users and the environment since the first authorisation of copper bilysinate. Moreover, the applicant provided also a literature search and new data on the safety for the user and the environment.

[13]Conditions of use.

[14]Annex III 1_1.

3.2.1 | Extensive literature search

The applicant submitted an extensive literature search (ELS)[15] to support that the additive remains safe for the target species, consumer, user and the environment. The search covered the period from 2013 to 2023. A search in the following databases: Agricola, Agris, Basenet, Google Scholar, Ingenta, Europe PMC, PubMed, Science Direct, World Cat Library was performed. The search terms and the inclusion/exclusion criteria were provided. A total of 47 publications were retrieved of which six publications were considered relevant. The FEEDAP Panel assessed all the papers and concluded that none of them identified new information that would lead to reconsider its previous conclusions.

3.2.2 | Safety for the target species

Considering the fact that the manufacturing process and the composition of the additive have not been modified since the previous authorisation and that no new information has been found that would indicate a safety concern in the ELS, the FEEDAP Panel concludes that the additive remains safe for the target species under the current conditions of the authorisation.

3.2.3 | Safety for the consumer

Copper bilysinate is expected to be dissociated in the target animal, so only copper is considered of concern for the consumers. The amount of L-lysine released from the additive will be limited by the maximum authorised copper level in animal feed. L-lysine will be used in protein synthesis and/or metabolised to urea and carbon dioxide without any modification of edible tissues/products. It is expected that copper from the additive would not result in a different/higher copper deposition in edible tissue/products than the standard inorganic source copper(II) sulphate pentahydrate when supplemented to feed up to the maximum authorised copper level in the EU (EFSA FEEDAP Panel, 2014).

In the current dossier, no specific studies to demonstrate the safety of the additive for the consumer were submitted. The applicant submitted an ELS (see above) that covered the safety of the additive for the consumer.

The literature search carried out by the applicant did not identify any new information relative to copper deposition in animal tissues that would indicate concern for the consumer from the use of the additive in animal nutrition.

The toxicology of copper compounds has been previously reviewed by the FEEDAP Panel, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) and the Scientific Committee (EFSA FEEDAP Panel, 2015, 2016; EFSA NDA Panel, 2015; EFSA Scientific Committee, 2023) and by Ellingsen et al. (2015). To the knowledge of the FEEDAP Panel, there are no new relevant toxicological studies on copper that would modify the latest review (EFSA Scientific Committee, 2023). Under normal circumstances, copper homoeostasis ensures that copper overload in humans does not occur. An excess of copper has been recorded and shown to cause problems only under certain specific conditions, notably genetic disorders such as Wilson disease (EFSA NDA Panel, 2015).

The FEEDAP Panel in 2016 reported that 'The main food group contributing to copper intake in adults is grains and grain-based products'. 'The food group meat and meat products are also an important contributor to copper intake, with an average contribution up to 19% in males and up to 16% in females'.

'Dietary upper levels (ULs) for copper have already been established by the Scientific Committee on Food (SCF) for different population classes (EC, 2003). The SCF derived a tolerable upper intake level (UL) of 5 mg Cu/day for adults and extrapolated UL for toddlers, children and adolescents (e.g. UL of 1 mg/day for toddlers). More recently, the EFSA Scientific Committee re-evaluated the existing health-based guidance values for copper and exposure assessment from all sources and established an acceptable daily intake (ADI) for copper (EFSA Scientific Committee, 2023). In establishing this ADI, the EFSA Scientific Committee placed emphasis on hepatic copper retention as an early marker of potential adverse effects. The EFSA Scientific Committee concluded that no hepatic retention of copper is expected to occur with an intake of 5 mg Cu/day (for a 70 kg adult) and established an ADI of 0.07 mg/kg body weight (bw). Dietary exposure to total copper does not exceed the health-based guidance values (HBGV) in adolescents, adults, elderly and the very elderly. The FEEDAP Panel notes that this ADI is established for the general population and that ULs for all age groups will be established by the NDA Panel in line with the NDA Panel Guidance on establishing and applying tolerable upper intake levels for vitamins and essential minerals (EFSA NDA Panel, 2022).

In re-assessing the consumer exposure and safety of the additive, the FEEDAP Panel considered the following:

- No new data were made available on possible copper deposition in animal tissues following the administration of the additive under assessment;
- there is no evidence that would indicate that the different organic and inorganic sources of copper have different bioavailability leading to different deposition of copper in animal food products;

[15]Annex_III_1_2.

– the toxicological profile of copper is well known and copper overload in healthy humans does not occur under usual dietary exposure conditions. An excess of copper has been recorded and shown to cause problems only under certain specific conditions, notably genetic disorders such as Wilson disease (EFSA NDA Panel, 2015);
– the conclusion of the EFSA Scientific Committee (EFSA Scientific Committee, 2023) indicates that current maximum authorised levels for copper in feed do not cause concern with regard to the consumer exposure to copper.

In the light of the above, the FEEDAP Panel considers that an update of the consumer exposure is not necessary and concludes that the additive remains safe for the consumers under the current authorised conditions of use in feed.

3.2.4 | Safety for the user

The highest dusting potential measured for the powder and the granulated forms of the additive was 5100 and 50 mg/m^3, respectively (FEEDAP Panel, 2014). Therefore, the exposure by inhalation is considered likely.

The FEEDAP Panel notes that the additive contains copper (≥ 14.5%). An occupational exposure limit (OEL) of 0.01 mg/m^3 for the respirable fraction is established (European Commission, 2014). Therefore, to reduce the risk, the FEEDAP Panel considers that the exposure of the users should be minimised.

The skin sensitisation potential of copper bilysinate powder was tested in two studies performed according to Organisation for Economic Co-operation and Development (OECD) testing guidelines (TGs) 442D and 442E, which showed that the additive is a skin sensitiser.[16]

3.2.4.1 | *Conclusions on safety for the user*

Considering all the information submitted for the previous and the current assessments, the FEEDAP Panel concludes that both forms of the additive are not skin irritant but the powder product is an eye irritant. Copper bilysinate powder should be considered a skin and respiratory sensitiser. Inhalation and dermal exposure are considered a risk. This conclusion would also apply to copper bilysinate granulate.

3.2.5 | Safety for the environment

In its previous opinion the FEEDAP Panel concluded that the additive will not further increase the environmental burden of copper (EFSA FEEDAP Panel, 2014).

For the current application, the safety of the additive for the environment is evaluated in line with the current requirements of the FEEDAP Panel (EFSA FEEDAP Panel, 2019).[17]

The environmental risk assessment is made assuming that the whole amount of the additive ingested by the animals is excreted and is focused on copper.

As regards the use of the additive in terrestrial farm animals, the piglet was considered as the worst-case scenario. The applicant noted that the production cycle of piglets was of 7 weeks and that the maximum authorised dose of 150 mg/kg feed was only applicable to the first 4 weeks, being the concentration of the last 3 weeks of 100 mg/kg feed maximum. With these assumptions and considering an average feed intake of 11 kg/piglet during the first 4 weeks and of 29 kg/piglet during the last 3 weeks, the average concentration of copper in feed for piglets during the 7 weeks production cycle is 114 mg/kg feed, that results in a PEC_{soil} of 1.9 mg Cu/kg soil dry weight. Compared with the 10% of the natural background concentration of copper in soil (90th percentile of the distribution of copper in natural land in Europe), corresponding to 3.4 mg Cu/kg soil dry weight[18], the calculated predicted environmental concentration in soil (PEC_{soil}) is below this value. Therefore, no concerns are expected for the terrestrial compartment at the authorised conditions of use.

Considering the use of the additive in aquaculture, the highest PEC in surface water (land-based aquaculture) for sea bass/sea bream is of 0.063 µg Cu/L. Compared with the natural background concentration of copper in water (10% of the 90th percentile reported for water, FOREGS, 2005) of 0.245 µg Cu/L, no safety concerns are expected from the use of the additive in land-based aquaculture at the authorised conditions of use.

When the additive is used in marine aquaculture (sea cages), the PEC for marine sediment is 55 mg Cu/kg sediment dry weight. The applicant provided information from the Oslo and Paris Conventions (OSPAR) commission (2014) indicating that copper has a background concentration in marine sediment of 20 mg/kg sediment dry weight, which is lower than the estimated concentration in marine sediments. The applicant, in addition, referred to the copper predicted no effect concentration in sediment ($PNEC_{sed}$) of 338 mg Cu/kg dw (Monteiro et al., 2010), derived using the equilibrium partitioning approach. The FEEDAP Panel notes that, although the calculated PEC_{sed} exceeds the reported median copper level in

[16]ADR reply November 2024: Annex_III_3_12_Sens_442D; ADR reply November 2024: Annex_III_3_11_Sens_442E.
[18]Based on the data available in FORGES database http://weppi.gtk.fi/publ/foregsatlas/ForegsData.php. Geochemical Atlas of Europe; copyright © 2005 the Association of the Geological Surveys of The European Union (EuroGeoSurveys)/the Geological Survey of Finland.
[17]https://www.efsa.europa.eu/sites/default/files/2024-01/wg-environment-2018-2024.pdf.

marine sediment (EFSA FEEDAP Panel, 2023; OSPAR Commission, 2014), the ratio PEC/PNEC is lower than 1, indicating no safety concerns for marine sediment.

Considering the above, the FEEDAP Panel concludes that the use of the additive under the approved conditions remains safe for the environment.

3.3 | Efficacy

The present application for renewal of the authorisation does not include a proposal for amending or supplementing the conditions of the original authorisation that would have an impact on the efficacy of the additive. Therefore, there is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

3.4 | Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation[19] and Good Manufacturing Practice.

4 | CONCLUSIONS

The applicant provided evidence that the additive currently on the market complies with the conditions of the authorisation.

The use of copper bilysinate in animal nutrition remains safe for the target species, the consumers and the environment under the approved conditions of use.

Regarding user safety, both forms of the additive are not irritant to the skin but the powder product is an eye irritant. Both forms of the additive should be considered skin and respiratory sensitisers. Inhalation and dermal exposure are considered a risk.

There is no need to assess the efficacy of the additive in the context of the renewal of the authorisation.

5 | RECOMMENDATIONS

The Panel notes that some breeds of dog are particularly sensitive to copper toxicity (EFSA FEEDAP Panel, 2016). It is recommended that this is indicated in the label of the feed supplemented with copper.

ABBREVIATIONS

ADI	acceptable daily intake
BW	body weight
ECHA	European Chemicals Agency
ELS	extensive literature search
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
HBGV	health-based guidance values
LOQ	limit of quantification
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo *p*-dioxins
PCDFs	polychlorinated dibenzofurans
PEC	predicted environmental concentration
$PNEC_{sed}$	predicted no effect concentration in sediment
SC	EFSA Scientific Committee
SCF	Scientific Committee on Food
TG	Testing Guideline
UF	uncertainty factor
WHO	World Health Organization

[19]Regulation (EC) No 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

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European Commission

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