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Assessment of the feed additive consisting of copper chelate of hydroxy analogue of methionine for all animal species for the renewal of its authorisation (Novus Europe S.A./N.V.)

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Abstract

The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the application for renewal of authorisation of copper chelate of hydroxy analogue of methionine (Mintrex®Cu) for all animal species. The FEEDAP Panel has delivered two opinions (in 2008 and 2009) on the safety and efficacy of the additive. The additive was authorised in 2010 as 'Copper chelate of hydroxy analogue of methionine' containing 18% copper, 79.5−81% (2-hydroxy-4-methylthio)butanoic acid (DL-methionine hydroxy analogue, HMTBa) and 1% mineral oil. Following some modifications in the manufacturing process, the additive does not contain mineral oil and the applicant proposes the following specifications: ≥ 16% copper and ≥ 78% HMTBa. The data provided indicate that the additive complies with the new specifications. No new evidence was found that would make the FEEDAP Panel reconsidering its previous conclusions on the safety for target species, consumers and environment. The applicant provided new studies on the effects of the additive on the respiratory tract and on skin and eyes. Data on the characterisation of the additive and the new studies on skin/eyes led the Panel to reconsider the safety for the user. Mintrex®Cu is considered as a skin and eye irritant and a skin sensitiser; the risk of respiratory sensitisation is considered low. The present application did 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 was no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

Keywords: nutritional additive, compounds of trace elements, copper, copper chelate of hydroxy analogue of methionine, Mintrex®Cu, safety

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

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 one year before the expiry date of the authorisation.

The European Commission received a request from Novus Europe S.A./N.V[2] for renewal of the authorisation of copper chelate of hydroxy analogue of methionine, 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). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 9 July 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 copper chelate of hydroxy analogue of methionine, when used under the proposed conditions of use (see Section 3.1.4).

1.2. Additional information

The FEEDAP Panel has adopted two opinions on copper chelate of hydroxy analogue of methionine as feed additive for all animal species: a first one on the safety and efficacy of the additive (EFSA, 2008) and a second one on the safety for the target species and consumers (EFSA FEEDAP Panel, 2009).

Copper chelate of hydroxy analogue of methionine is authorised in the EU as a nutritional additive for all animal species (3b4.10).[3] This authorisation was further amended, regarding the maximum content of copper 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 dossier[5] in support of the authorisation request for the use of copper chelate of hydroxy analogue of methionine as a feed additive.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment are valid and applicable for the current application.[6]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of copper chelate of hydroxy analogue of methionine is in line with the principles laid down in Regulation (EC) No 429/2008[7] and the relevant guidance document: Guidance on the renewal of the authorisation of feed additives

[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] Novus Europe S.A./N.V. Woluwe Atrium - 5th Floor, Rue Nerveldstraat 101-103. BE-1200 Brussels.
[3] Commission Regulation (EU) No 349/2010 of 23 April 2010 concerning the authorisation of copper chelate of hydroxy analogue of methionine as a feed additive for all animal species. OJ L 104, 24.4.2010, p. 31.
[4] Commission Implementing Regulation (EU) 2018/1039 of 23 July 2018 concerning the authorisation of copper compounds. OJ L 186, 24.7.2018, p. 3.
[5] FEED dossier reference: FAD-2019-0033.
[6] The report linked to the previous dossier (related to EFSA-Q-2007-097) is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2007-0012.pdf
[7] 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.

(EFSA FEEDAP Panel, 2013) and Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017).

3. Assessment

The additive 'Copper chelate of hydroxy analogue of methionine' is authorised as nutritional additive (functional group: compounds of trace elements) as a source of copper for all animal species. The maximum content of copper authorised in animal feed, established in the Commission Implementing Regulation (EU) 2018/1039, ranges from 15 to 150 mg/kg complete feed depending on the animal species/categories (for more details see Section 3.1.4)

This assessment regards the renewal of the authorisation of the additive. From here onwards, the additive will be referred to as Mintrex®Cu, the trade name of the additive.

3.1. Characterisation

The additive is authorised as 'Copper chelate of hydroxy analogue of methionine' containing 18% copper, 79.5–81% (2-hydroxy-4-methylthio)butanoic acid (DL-methionine hydroxy analogue, HMTBa) and 1% mineral oil. The applicant declared that, since the additive was authorised, some modifications have been introduced in the manufacturing process: [redacted] These modifications have led to a slightly different additive composition; the applicant proposes the following specifications: ≥ 16% copper and ≥ 78% HMTBa, this representing a variation compared to the current authorisation.

3.1.1. Characterisation of the additive

The chemical name of the additive is copper bis(-2-hydroxy-4-methylthio)butanoate. The structural formula is $Cu(CH_3S(CH_2)_2\text{-}CH(OH)\text{-}COO)_2$ and the molecular weight 361.9 g/mol. The CAS number of the complexed compound is 292140–30–8. The theoretical contents of copper(II) and HMTBa are 17.5% and 82.5%, respectively.

Analytical data of four recent batches of the additive were provided by the applicant.[8] The copper content ranged from 16.8% to 19.1%; the content of HMTBa ranged from 80.0% to 81.3%. These data show compliance with the new specifications proposed by the applicant.

The measurement of undesirable substances (arsenic (As), lead (Pb), cadmium (Cd), mercury (Hg), dioxins and the sum of dioxins plus dioxin like PCBs) was done in five recent batches[9] of the additive. The results reported were the following: < 0.8 mg As/kg additive, 4–15 mg Pb/kg additive, < 0.2 mg Cd/kg additive, < 0.01–0.02 mg Hg/kg additive[10]; the dioxins and the sum of dioxins plus dioxin like PCBs (one batch) were 0.123 ng WHO-PCDD/F-TEQ/kg and 0.124 ng WHO-PCDD/F-PCB-TEQ/kg, respectively.[11] These values are below the thresholds set by Directive 2002/32 on undesirable substances[12] for compounds of trace elements, or if not mentioned in the Directive do not represent a concern.

The nickel content of the additive, analysed in three batches, ranged from 3.13 to 4.23 mg/kg.[13]

3.1.2. Physical characteristics of the product

The additive is marketed as a grey-green granular coarse powder. Its solubility in water is 0.05% at 20°C. The bulk and tap density of the additive were measured in three batches resulting in an average of 924 and 1,021 kg/m^3, respectively.[14]

Particle size distribution, determined by laser diffraction,[15] and dusting potential, determined by the Stauber-Heubach method,[16] were measured in the same three samples as density. The values for the

[8] Technical dossier/Section II/Annex_II_01_CoA. A total of 16 batches were submitted; however, 12 of these batches were not considered 'recent' according to the definition given in the Guidance of renewal of authorization of feed additives.
[9] Four batches coincident with those in which active substance was analysed, and one additional batch.
[10] Limits of quantification were reported as follows, in mg/kg: for As ≤ 0.8; for Cd ≤ 0.2, for Pb ≤ 0.2 and for Hg ≤ 0.01.
[11] Technical dossier/Section II/Annex_II_01_CoA and Annex_II_02_Impurities.
[12] Directive 2002/32/EC of the European Parliament and of the council of 7 May 2002 on undesirable substances in animal feed. OJ L 140, 30.5.2002, p. 10.
[13] Technical dossier/Supplementary Information/Appendix 1.
[14] Technical dossier/Section II/Annex_II_04_Bulk; Annex_II_05_Tap.
[15] Technical dossier/Section II/Annex_II_06_PSD.
[16] Technical dossier/Section II/Annex_II_03_Dusting.

particle size distribution were between 306 and 1,472 μm. The dusting potential ranged from dust-free (one batch) to 0.235 g/m^3.

3.1.3. Stability and homogeneity

The applicant has provided new data to support the shelf-life of the additive. Three batches of the additive were stored at ambient conditions (approximately 25°C, 60% RH) for at least Five years[17]; at the end of the experiment, a total of 98.1% and 98.7% of the initial copper and HMTBa, respectively, was recovered.

Data to support homogeneous distribution of the additive in premixtures were submitted.[18] The study was performed with two premix formulations, Premix-1 and Premix-2 (one lot from each), in which the inclusion of Mintrex®Cu was 14% and 14.75%, respectively. In both cases, samples from nine bags were taken and the copper content analysed. The coefficient of variation was 3.99 and 2.61% for Premix-1 and Premix-2, respectively.

3.1.4. Conditions of use

The additive is currently authorised for all animal species/categories up to the total copper content in complete feed established in the current legislation in force (Table 1).

Table 1: Maximum of copper in feed established in Commission Implementing Regulation (EU) 2018/1039

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

The current authorisation also includes the following *Other provisions*:

1) The additive shall be incorporated into 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 sulphur'.

3.2. Safety

The applicant provided data concerning the monitoring of adverse effects of the additive, a literature search and new studies on safety for the user.

The monitoring of adverse effects was implemented as part of the quality assurance programme of the company.[19] [redacted]

[17] Technical dossier/Section II/Annex_II_12_Stability.
[18] Technical dossier/Section II/Annex_II_13_Homogeneity.
[19] Technical dossier/Section II/Annex_III_1_Monitoring Report.

[redacted]

The applicant performed a structured literature search.[20] The sites consulted were LIVIVO and Ovid, 16 single databases (incl. PubMed and Web of Science), and eight publishers search facilities (incl. Elsevier, Ingenta, Springer, Wiley); the search period covered from 2008 to April 2019. The search terms used, relevant to Mintrex®Cu, comprised the active substances/additive and keywords related to the safety/toxicity. The search included also other keywords relevant for Mintrex®Zn and Mintrex®Mn. It resulted in a total of 394 hits.[21] In total, ten publications were considered relevant for the assessment of Mintrex®Cu; all of them aimed to support safety of target animals.

The relevant findings identified from the data above are described in the respective safety section below.

3.2.1. Safety for the target species

In its opinion of 2008, the FEEDAP Panel concluded that Mintrex®Cu was safe for chickens for fattening. However, considering the marked differences in copper sensitivity existing among species and even breeds and the fact that avian species are amongst the most tolerant, the FEEDAP Panel was unable to extend its conclusion from chickens for fattening to other animal species (EFSA, 2008). Following that opinion, the applicant submitted additional tolerance studies in piglets, laying hens and calves for rearing; based on those trials, and on the one already assessed in chickens for fattening, the FEEDAP Panel concluded that the additive was safe for all animal species up to the maximum copper content authorised in feed (EFSA FEEDAP Panel, 2009).

From the monitoring programme on adverse effects, one complaint was received from a non-EU country in 2016 reporting some adverse effects in piglets (diarrhoea, low feed intake and gastritis). The applicant reported that the same batches of Mintrex®Cu had been distributed in other farms of the same country and in another country without any report. Considering all facts, the FEEDAP Panel considers this as an isolated incident not linked to the use of the additive.

From the literature search, the applicant identified a total of ten studies to support the safety of Mintrex®Cu for the target animals. These studies were performed in pigs (Liu et al., 2014; Zhao et al., 2014; Ma et al., 2015), laying hens (Manangi et al., 2015), dairy cows (Nemec et al., 2012; Wang et al., 2012), heifers (Whitehurst et al., 2014), fish (Mohseni et al., 2012) and white shrimp (Bharadwaj et al., 2014; Katya et al., 2016).

The FEEDAP Panel revised these studies and found that in five of them (Nemec et al., 2012; Wang et al., 2012; Liu et al., 2014; Whitehurst et al., 2014; Manangi et al., 2015) the levels of copper tested in diet were (considerably) below the maximum authorised levels in feed for the relevant species; in none of these studies adverse effects were reported. The study of Katya et al. (2016) involved the concomitant supplementation with other Mintrex compounds, what would introduce uncertainties in the interpretation of the results obtained, and therefore was not considered. The other four studies— performed in pigs, fish and crustaceans– are described below.

Two studies were available with pigs. In the first one, Ma et al. (2015) conducted six experiments to evaluate the effect of different levels of copper from either Mintrex®Cu or copper sulfate on growth performance in nursery pigs; in only one experiment, levels of copper in feed higher than the maximum authorised (250 mg Cu from Mintrex®Cu/kg feed) were tested. Only performance was measured. No adverse effects were reported.

In the second study, Zhao et al. (2014) reported two experiments to investigate whether a chelated copper could replace copper sulfate in nursery pigs with the aim to enhance performance; the levels of copper tested ranged, as analysed values, from 150 to 208 mg Cu from Mintrex®Cu/kg feed. Performance and tissue deposition were measured. No adverse effects were reported.

Mohseni et al. (2012) conducted a 12-week study to determine the safe and toxic levels of dietary copper in juvenile olive flounder (*Paralichthys olivaceus*) fed copper from Mintrex®Cu. Several levels were tested: 0 (control), 5, 10, 20, 40, 80, 160, 320, 640 and 1,280 mg Cu from Mintrex®Cu/kg diet. Performance parameters, copper tissue (liver, intestine, kidney, gill and muscle) and whole-body copper concentration were measured; additionally, blood samples were taken and red blood cells, haemoglobin and haematocrit were measured. At the end of the study, some adverse effects on

[20] Technical dossier/Section II/Annex_III_2_Literature_search.

[21] The applicant explained that since the renewal of the three applications that he holds were all due for submission on May 2019, a joint literature search for the three additives (Mintrex®Cu, Mintrex®Mn and Mintrex®Zn) was considered to be adequate.

zootechnical parameters were observed at the intended copper level of 80 mg/kg feed (analysed value 82.1) and above. From the results of this study, it can be reasonably assumed that no adverse effects at the maximum authorised levels (25 mg Cu from Mintrex®Cu/kg feed) were observed.

Bharadwaj et al. (2014) conducted a study to evaluate the response of Pacific white shrimp (*Litopenaeus vannamei*) to inorganic or chelated sources of dietary copper. In this experiment, levels of copper in feed higher than the maximum authorised (52, 65 and 83 mg Cu from Mintrex®Cu/kg) were tested. Performance parameters and copper deposition in the whole body and hepatopancreas were measured. No adverse effects were reported.

Since the additive contains nickel as an impurity (levels measured up to 4.23 mg/kg), the FEEDAP Panel assessed the impact of nickel on the safety for the target species. If adding 150 mg Cu/kg (suckling and weaned up to 4 weeks after weaning) feed —the highest maximum total copper authorised in feed— from the compound under assessment, nickel would be incorporated at 3.9 µg/kg feed.[22] According to the National Research Council (NRC, 2005), fish and horses are the most sensitive animal species to nickel with a maximum tolerable level (MTL) of 50 mg/kg feed. Considering the background of nickel in feed (i.e. 4 mg/kg dry matter (DM) feed; Nicholson et al., 1999; Van Paemel et al., 2010), the contribution of the additive in the worst-case scenario would be negligible, and in total, the amount of nickel in feed would be well below the MTL.

3.2.1.1. Conclusions on the safety for the target animals

Based on the available data, the FEEDAP Panel concludes that Mintrex®Cu remains safe for the target species under the authorised conditions of use.

3.2.2. Safety for the consumers

In its Opinions of 2008 and 2009, the FEEDAP Panel concluded that, since exposure to copper from the consumption of animals' tissues and products would not lead to the tolerable upper intake level (UL; 5 mg/day for adults) being exceeded by consumers, no concerns for consumer safety would result from the use of Mintrex®Cu in feed at the maximum authorised copper levels (EFSA, 2008; EFSA FEEDAP Panel, 2009). The exposure assessment included a calculation with a 'worst-case scenario' based on the consumption model described in Regulation (EC) No 429/2008 which resulted in a copper daily exposure for adults of 3.70 mg. This calculation was followed by a refinement applying a more realistic model with the SCOOP food consumption data (European Commission, 2004); based on the latter, the daily copper intake for adults was 1.26 mg.

From the literature search, the FEEDAP Panel identified three studies in which tissue deposition was measured. The study of Zhao et al. (2014) in piglets reported data already assessed by the FEEDAP Panel in a previous opinion (EFSA FEEDAP Panel, 2009); the other two studies in fish (Mohseni et al., 2012) and in shrimps (Bharadwaj et al., 2014) could not be considered due to limitations in design.

The Panel updated the estimate of the consumer exposure to copper from the use of Mintrex®Cu, following the methodology described in the Guidance for assessment of consumer safety (EFSA FEEDAP Panel, 2017) (Appendix A); data from the studies already assessed in the previous FEEDAP Opinions on Mintrex®Cu (EFSA, 2008; EFSA FEEDAP Panel, 2009) were used as input data for the calculation (Table 2). The results of the chronic exposure of consumers to copper, and comparison against the UL, are reported in Table 3.

Table 2: Input data on copper content in food of animal origin used for the consumer exposure assessment

Animal products	mg/kg wet tissue	Reference
Birds liver	4.52*	EFSA (2008)
Mammals meat	0.5	EFSA FEEDAP Panel (2009)
Mammals liver	30.5	
Mammals offals	4.6	

[22] These calculations follow a worst-case scenario by (i) considering that all the copper in the feed comes from the additive, (ii) the minimum content of copper for the additive and (iii) taking into consideration the maximum nickel content reported for the additive under assessment.

Animal products	mg/kg wet tissue	Reference
Mammals fat**	0.7	
Eggs	1.21***	EFSA FEEDAP Panel (2009)
Milk	0.050	EFSA FEEDAP Panel (2009)

*: Calculated from the DM value (13.7), considering a 67% moisture in raw chicken liver.
**: The original value (1.4) was divided by 2 to take into consideration the proportion skin/fat.
***: Corresponded to the Limit of quantification of the analytical method.

Table 3: Chronic dietary exposure of consumers to copper based on residue data from several studies with Mintrex®Cu – Summary statistics across European dietary surveys. Comparison with the Tolerable upper intake limit (UL)

Population category	Maximum HRP(1) (mg/kg bw per day)	Default body weight (EFSA Scientific Committee, 2012)	Exposure (mg/day)	UL (mg/day) (European Commission, 2003)	% UL
Infants	0.0198	5	0.099		
Toddlers	0.0239	12	0.287	1	28.7
Other children	0.0178	23	0.409		
Adolescents	0.0116	52.4(2)	0.608		
Adults	0.0156	70	1.092	5	21.8
Elderly	0.0112	70	0.784		
Very elderly	0.0094	70	0.658		

(1): HRP: highest reliable percentile.
(2): Average of 43.4 and 61.3 kg.

In 2003, the Scientific Committee on Food established an UL for copper for adults as 5 mg/day and for toddlers (1–3 years of age) as 1 mg/day (European Commission, 2003). To compare the copper dietary exposure calculation to the UL, the FEEDAP Panel used the highest reliable percentile (HRP) for the different population categories and converted it from mg/kg bw per day into mg/person per day using the default body weight values (EFSA Scientific Committee, 2012). The contribution to the consumer exposure to copper from products of animals fed with the additive ranged from 21.8% to 28.7% of the ULs (Table 3). For the population groups infants, other children, adolescents, elderly and very elderly, no UL was established by the Scientific Committee on Food (SCF). However, the FEEDAP Panel assumes that the exposure would still be in the same relation to the UL as for the other population categories.

The FEEDAP Panel concludes that there is no safety concern for the consumer resulting from the intake of food from all animal species fed copper from Mintrex®Cu under the conditions of the existing authorisation.

3.2.2.1. Conclusions on the safety for the consumers

No additional data have become available that would lead to modify the previous conclusions on the safety of the additive for consumers. Therefore, the FEEDAP Panel concludes that Mintrex®Cu remains safe for the consumers under the authorised conditions of use.

3.2.3. Safety for user

In its Opinion of 2008, the FEEDAP Panel concluded that Mintrex®Cu was safe for the user provided that protective measures are taken (EFSA, 2008).

According to the monitoring report covering the period from May 2010 to February 2019, three customers reported safety-related incidents in 2012 and 2014. In two cases this was caused by handling of the additive without paying attentions to the measures as stated in the safety data sheet. In one case unusual high moisture and warm weather was identified as a possible cause for irritation of armpits of workers.

The literature search did not identify studies relevant to user safety.

The applicant provided new studies on the effects of the additive on the respiratory tract and on skin and eyes, which are described below.

3.2.3.1. Effects on the respiratory system

The applicant provided an acute inhalation toxicity test in rats.[23] The study was certified as good laboratory practice (GLP) and conducted according to OECD Test Guideline (TG) 403. Under the conditions of this study, the single exposure acute inhalation LC_{50} of the test substance is greater than 2.12 mg/L in female rats and between 1.07 and 2.12 mg/L in male rats.

Data on the product characterisation showed that the additive consists of particles higher than 356 μm of diameter. Thus, the exposure to users is very unlikely and the FEEDAP Panel considers that the handling of the additive does not pose a risk to users by inhalation.

The highest nickel content analysed in the additive was 4.23 mg/kg. The highest dusting potential of the product was 0.235 g/m^3, corresponding to about 0.99 μg Ni/m^3. Thus, according to that calculation, the exposure of users to nickel would not exceed the proposed occupational exposure limit (OEL) set at 0.03 mg Ni/m^3 (ECHA, 2018), and therefore would not constitute a hazard for the users by inhalation; the risk of respiratory sensitisation is considered low.

3.2.3.2. Effects on skin and eyes

An acute dermal toxicity test was conducted with rats to determine the potential for Mintrex®Cu to produce toxicity from a single topical application.[24] The study was certified as good laboratory practice (GLP) and was conducted according to OECD TG 402. Under the conditions of this study, the acute dermal LD_{50} of the test substance is greater than 2,000 mg/kg of body weight in male and female rats.

The potential of skin irritancy of the additive was tested in a GLP *in vitro* study performed according to the OECD TG 439.[25] Under the conditions of this study, Mintrex®Cu is considered irritant to skin (UN GHS: Category 2).

In the light of the positive results on skin irritancy, the potential of the additive for skin corrosion was subsequently evaluated in a GLP *in vitro* study performed according to the OECD TG 431 (EPIDERM™ Skin corrosion test).[26] Under the conditions of this study, Mintrex®Cu is not expected to cause skin corrosion.

The potential of eye irritancy of the additive was tested in a GLP *in vitro* study performed according to the OECD TG 437: Bovine Corneal Opacity and Permeability Test Method.[27] Under the conditions of this study, the results were considered inconclusive and based on the classification of UN GHS 'No Prediction can be made'. Thus, the applicant performed a second test to assess the potential eyes irritancy of the additive; the test selected was the *in vitro* EpiOcular™ eye irritation test (OECD TG 492: Reconstructed human Cornea-like Epithelium Test Method) and the study was done under GLP.[28] Under the conditions of this study, Mintrex®Cu is considered irritant to eyes (meets the requirement for UN GHS Category-Category 2).

The nickel content of the additive is up to 4.23 mg/kg; given its well-known sensitisation potential (European Commission, 2011a,b, ECHA, 2018), the additive is considered as a skin sensitiser.

3.2.3.3. Conclusions on the safety for the users

Mintrex®Cu is considered as a skin and eye irritant and a skin sensitiser; the risk of respiratory sensitisation is considered low.

3.2.4. Safety for the environment

In its Opinion of 2008, the FEEDAP Panel concluded that Mintrex®Cu did not represent additional risks to the environment compared to other sources of copper for which it would substitute (EFSA, 2008).

The literature search did not identify relevant studies on the safety of the additive for the environment. Thus, there is no new evidence that would lead to modify the Panel's previous conclusion. Therefore, the FEEDAP Panel reiterates that the use of Mintrex®Cu in feed does not pose an additional risk to the environment as long as the maximum authorised content in complete feed is not exceeded.

[23] Technical Dossier/Section III/Annex_III_5.
[24] Technical Dossier/Section III/Annex_III_4.
[25] Technical Dossier/Supplementary Information_December20/Appendix 1.
[26] Technical Dossier/Supplementary Information_December20/Appendix 2.
[27] Technical Dossier/Supplementary Information_December20/Appendix 3.
[28] Technical Dossier/Supplementary Information_December20/Appendix 4.

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[29] and Good Manufacturing Practice.

4. Conclusions

The additive complies with the new specifications proposed: ≥ 16% copper and ≥ 78% (2-hydroxy-4-methylthio)butanoic acid (DL-methionine hydroxy analogue, HMTBa). No mineral oil is used in the new proposed manufacturing process. These modifications represent a variation compared to the current authorisation.

The FEEDAP Panel concludes that the use of Mintrex®Cu under the current authorised conditions of use remains safe for all animal species, the consumers and the environment.

Mintrex®Cu is considered as a skin and eye irritant and a skin sensitiser; the risk of respiratory sensitisation is considered low.

There is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

5. Documentation as provided to EFSA/Chronology

Date	Event
08/05/2019	Dossier received by EFSA. Dossier Copper chelate of hydroxy analogue of methionine (MINTREX®Cu). Submitted by Novus Europe S.A./N.V.
23/05/2019	Reception mandate from the European Commission
09/07/2019	Application validated by EFSA – Start of the scientific assessment
20/09/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterisation*
09/10/2019	Comments received from Member States
14/11/2019	Reception of supplementary information from the applicant - Scientific assessment re-started
10/12/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. Issues: safety for the users
21/12/2020	Reception of supplementary information from the applicant - Scientific assessment re-started
05/05/2021	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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[29] 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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Abbreviations

DM	dry matter
EURL	European Union Reference Laboratory
GLP	good laboratory practice
MTL	maximum tolerable level
OEL	occupational exposure limit
SCF	Scientific Committee on Food
TG	Test Guideline
UL	upper intake level

Appendix A – Calculation of consumer exposure with FACE model

Methodology

As described in the Guidance on the safety of feed additives for consumers (EFSA FEEDAP Panel, 2017), consumption data of edible tissues and products as derived from the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) will be used to assess exposure to residues from the use of feed additives in different EU countries, age classes[30] and special population groups. For each EU country and age class, only the latest survey available in the Comprehensive Database will be used.

While the residue data reported for feed additives refer to organs and tissues (raw agricultural commodities, RAC), the Comprehensive Database includes consumption data for foods as consumed. In order to match those consumption data with the available residue data for feed additives, the consumption data reported in the Comprehensive Database have been converted into RAC equivalents. For assessing the exposure to copper from Mintrex®Cu from their use in the target species, the following list of commodities is considered: meat, liver and other offals (kidney). In the case of the additive under assessment, the FEEDAP Panel considered that only the chronic exposure assessment would be appropriate.

For chronic exposure assessments, the total relevant residues will be combined for each individual with the average daily consumptions of the corresponding food commodities, and the resulting exposures per food will be summed in order to obtain total chronic exposure at individual level (standardised by using the individual body weight). The mean and the higher percentile (usually the 95th percentile) of the individual exposures will be subsequently calculated for each dietary survey (country) and each age class separately.

Detailed results on chronic exposure calculation

Table A.1: Chronic dietary exposure per population class, country and survey (mg/kg body weight per day) to copper residues based on residue data from food of animal origin

Population class	Survey's country	Number of subjects	HRP(1)	HRP description
Infants	Bulgaria	523	0.0111515955	95th
Infants	Germany	142	0.0106137497	95th
Infants	Denmark	799	0.0197728045	95th
Infants	Finland	427	0.0051504918	95th
Infants	United Kingdom	1,251	0.0060823313	95th
Infants	Italy	9	0.0021545330	50th
Toddlers	Belgium	36	0.0111076102	90th
Toddlers	Bulgaria	428	0.0155799256	95th
Toddlers	Germany	348	0.0126573640	95th
Toddlers	Denmark	917	0.0238828184	95th
Toddlers	Spain	17	0.0108573240	75th
Toddlers	Finland	500	0.0097760594	95th
Toddlers	United Kingdom	1,314	0.0127425719	95th
Toddlers	United Kingdom	185	0.0186143417	95th
Toddlers	Italy	36	0.0077303429	90th
Toddlers	Netherlands	322	0.0232093131	95th
Other children	Austria	128	0.0160769335	95th
Other children	Belgium	625	0.0162575218	95th
Other children	Bulgaria	433	0.0165247506	95th
Other children	Czech Republic	389	0.0177608485	95th
Other children	Germany	293	0.0109159835	95th

[30] Infants: < 12 months old, toddlers: ≥ 12 months to < 36 months old, other children: ≥ 36 months to < 10 years old, adolescents: ≥ 10 years to < 18 years old, adults: ≥ 18 years to < 65 years old, elderly: ≥ 65 years to < 75 years old, and very elderly: ≥ 75 years old.

Population class	Survey's country	Number of subjects	HRP(1)	HRP description
Other children	Germany	835	0.0126036720	95th
Other children	Denmark	298	0.0150658797	95th
Other children	Spain	399	0.0124971314	95th
Other children	Spain	156	0.0153536347	95th
Other children	Finland	750	0.0162834666	95th
Other children	France	482	0.0123646323	95th
Other children	United Kingdom	651	0.0118123002	95th
Other children	Greece	838	0.0095482777	95th
Other children	Italy	193	0.0100829131	95th
Other children	Latvia	187	0.0137913335	95th
Other children	Netherlands	957	0.0177782243	95th
Other children	Netherlands	447	0.0113471056	95th
Other children	Sweden	1,473	0.0127225785	95th
Adolescents	Austria	237	0.0068763772	95th
Adolescents	Belgium	576	0.0052090823	95th
Adolescents	Cyprus	303	0.0035333432	95th
Adolescents	Czech Republic	298	0.0115699768	95th
Adolescents	Germany	393	0.0095272291	95th
Adolescents	Germany	1,011	0.0043004328	95th
Adolescents	Denmark	377	0.0070174584	95th
Adolescents	Spain	651	0.0074598876	95th
Adolescents	Spain	209	0.0078197573	95th
Adolescents	Spain	86	0.0056699928	95th
Adolescents	Finland	306	0.0046171737	95th
Adolescents	France	973	0.0071658384	95th
Adolescents	United Kingdom	666	0.0037221839	95th
Adolescents	Italy	247	0.0055256464	95th
Adolescents	Latvia	453	0.0081383042	95th
Adolescents	Netherlands	1,142	0.0065368137	95th
Adolescents	Sweden	1,018	0.0057624319	95th
Adults	Austria	308	0.0048647590	95th
Adults	Belgium	1,292	0.0049439938	95th
Adults	Czech Republic	1,666	0.0100926471	95th
Adults	Germany	10,419	0.0048379860	95th
Adults	Denmark	1,739	0.0058246932	95th
Adults	Spain	981	0.0052061270	95th
Adults	Spain	410	0.0049450737	95th
Adults	Finland	1,295	0.0051586378	95th
Adults	France	2,276	0.0079240106	95th
Adults	United Kingdom	1,265	0.0035916096	95th
Adults	Hungary	1,074	0.0155994248	95th
Adults	Ireland	1,274	0.0033938081	95th
Adults	Italy	2,313	0.0035805857	95th
Adults	Latvia	1,271	0.0067321646	95th
Adults	Netherlands	2,055	0.0047629727	95th
Adults	Romania	1,254	0.0081313013	95th
Adults	Sweden	1,430	0.0046643215	95th
Elderly	Austria	67	0.0091467402	95th
Elderly	Belgium	511	0.0060777037	95th
Elderly	Germany	2,006	0.0050132229	95th

Population class	Survey's country	Number of subjects	HRP(1)	HRP description
Elderly	Denmark	274	0.0070207592	95th
Elderly	Finland	413	0.0047700285	95th
Elderly	France	264	0.0093983243	95th
Elderly	United Kingdom	166	0.0041596823	95th
Elderly	Hungary	206	0.0111512483	95th
Elderly	Ireland	149	0.0048192363	95th
Elderly	Italy	289	0.0029754763	95th
Elderly	Netherlands	173	0.0041701823	95th
Elderly	Netherlands	289	0.0040937734	95th
Elderly	Romania	83	0.0058142310	95th
Elderly	Sweden	295	0.0058961338	95th
Very elderly	Austria	25	0.0026849949	75th
Very elderly	Belgium	704	0.0056269382	95th
Very elderly	Germany	490	0.0050719110	95th
Very elderly	Denmark	12	0.0033216947	75th
Very elderly	France	84	0.0094353300	95th
Very elderly	United Kingdom	139	0.0070357197	95th
Very elderly	Hungary	80	0.0081383161	95th
Very elderly	Ireland	77	0.0036657706	95th
Very elderly	Italy	228	0.0026526277	95th
Very elderly	Netherlands	450	0.0042266910	95th
Very elderly	Romania	45	0.0064241932	90th
Very elderly	Sweden	72	0.0086835758	95th

(1): HRP: highest reliable percentile, i.e. the highest percentile that is considered statistically robust for combinations of dietary survey, age class and possibly raw primary commodity, considering that a minimum of 5, 12, 30 and 61 observations are, respectively, required to derive 50th, 75th and 90th and 95th percentile estimates. Estimates with less than five observations were not included in this table.

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