Assessment : Assessment of the safety of the feed additive consisting of copper chelate of hydroxy analogue of methionine (Novus Europe SA/NV) for all animal species for the renewal of its authorisation

Reference Number RP1386

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1.Executive summary

The Food Standards Agency (FSA) and Food Standards Scotland (FSS) have undertaken an assessment of application RP1386 for the renewal of copper chelate of hydroxy analogue of methionine (≥16% copper and ≥78% DL-methionine hydroxy analogue, (HMTBa)[1]) for use in all species, from Novus Europe S.A./N.V., Woluwe Atrium - 5th Floor, Rue Neveldstraat 101-103, BE-1200, Brussels, Belgium (category: nutritional additives; functional group: compounds of trace elements, as a source of copper and the essential amino acid methionine in the feed).

A feed additive application has been received by Great Britain (GB) where EFSA, prior to the end of the transition period, evaluated an application for the product. FSA/FSS have reviewed the EFSA opinion (EFSA Journal 2021;19(5):6618, 16 pp.) and confirm that it is adequate and relevant for GB risk analysis and used this to form the basis of the GB opinion.

The FSA/FSS risk assessors concluded that the EFSA opinion is adequate and relevant for GB risk analysis. Therefore, the use of copper chelate of hydroxy analogue of methionine, as described in this application, is safe and is not liable to have an adverse effect on the target species, worker safety, environmental safety and human health at the intended concentrations of use.

There are no specific conditions or restrictions in relation to labelling, post-market monitoring requirements and use of this additive as described in this application. Maximum Residue Limits (MRLs) are not required for this additive. For user safety, breathing protection, safety glasses and gloves should be worn during handling.

2.Background and purpose of review

EFSA Journal 2021;19(5):6618 **Question number**: EFSA-Q-2019-00358

In accordance with Retained EU Regulation 1831/2003 on feed additives, the application RP1386 for the renewal of copper chelate of hydoxy analogue of methionine as a feed additive for all species, from Novus Europe S.A./N.V. has been submitted for authorisation in GB.

Whilst it was a Member State of the EU, UK accepted the assessments of EFSA in respect of authorisations for regulated food and feed products. Since the end of the transition period, FSA/FSS has adopted equivalent technical guidance and quality assurance processes to be able to undertake GB risk assessments for regulated product applications.

Where EFSA, prior to the end of the transition period, evaluated an application for the product for which an application is now made to GB, FSA/FSS has decided to make use of the EFSA risk assessment, where this is appropriate, in forming its

[1] The determination of HMTBa was by potentiometric titration with bromide/bromate. Copper analysis was by Inductively Coupled Plasma Optical Emission spectroscopy (ICP-OES) as described in EN 15510:2017.

opinion. Therefore, FSA/FSS risk assessors have reviewed the EFSA opinion[2] for the application below in the context of intended GB use and have concluded that the intended uses are safe.

In reviewing the output of the EFSA risk assessment the reviewers have verified that the standard approach as outlined in the relevant guidance[3] has been followed and the arguments made are consistent with the data summarised in the opinion. Consideration has been given to the processes undertaken to ensure the opinion is robust and whether there are any aspects that would require further review such as specific issues for the countries of GB. The result of the assessment is that the EFSA scientific opinion is adequate also for GB risk analysis. Therefore, a full risk assessment has not been performed by FSA/FSS.

3.Details of the EFSA assessment

3.1 Methodology applied in the EFSA opinion

EFSA FEEDAP guidance: Guidance on the renewal of the authorisation of feed additives (**2013**), Guidance on the assessment of the safety of feed additives for the consumer (**2017**) and principles in Regulation (EC) No. 429/2008.

3.2 Source/organism

Not relevant.

3.3 Genetic modification step

Not relevant.

3.4 Specification

The additive is currently authorised with a specification of containing 18% copper, 79.5-81% (2-hydroxy-4-methylthio)butanoic acid (DL-methionine hydroxy analogue, HMTBa) and 1% mineral oil. Some modifications have subsequently been made in the production process (the information on these modifications is redacted by EFSA), which have resulted in a small difference to the composition of the additive. The applicant proposed that the new specification is ≥16% copper and ≥78% HMTBa. Four recent batches of the additive were analysed; the copper content ranged from 16.8% to 19.1% and the content of HMTBa ranged from 80.0% to 81.3%.

Five recent batches of the additive were analysed for arsenic, lead, cadmium, mercury, dioxins and the sum of dioxins and dioxin-like PCBs. The results were <0.8 mg As/kg additive, 4-15 mg Pb/kg additive, <0.2 mg Cd/kg additive, <0.01 to 0.02 mg Hg/kg additive, 0.123 ng WHO-PCDD/F-TEQ/kg dioxins (one batch) and 0.124 ng WHO-PCDD/F-PCB-TEQ/kg for the sum of dioxins and dioxin-like PCBs (one batch). These results were not considered a concern by EFSA.

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[2] EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2021. Scientific Opinion on the 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.). EFSA Journal 2021;19(5):6618, 16 pp. https://doi.org/10.2903/j.efsa.2021.6618

[3] See reference list for the full set of guidance applied.

Nickel was analysed in three batches of the additive and ranged from 3.13 to 4.23 mg/kg. EFSA evaluated the risks of nickel to the target species (see section 3.6, Toxicology data, below).

The additive is a granular coarse powder. The particle size distribution, determined by laser diffraction, and dusting potential, determined by the Stauber-Heubach method, were measured in three samples of the additive. The particle size distributions were between 306 and 1,472 µm. The dusting potential ranged from dust-free (one batch) to 0.235 g/m^3.

New shelf-life studies were conducted on three batches of the additive, which were stored at ambient conditions (approximately 25°C, 60% relative humidity) for at least five years. A total of 98.1% of the initial copper and a total of 98.7% of the initial HMTBa, were recovered at the end of the study period.

Data were provided to support the homogeneous distribution of the additive in premixtures. One lot each of two premix formulations, Premix-1 and Premix-2, in which the inclusion rates of the additive were 14% and 14.75%, respectively, were tested. For each formulation, samples from 9 bags were analysed for copper content. The coefficients of variation were 3.99% for Premix-1 and 2.61% for Premix-2.

3.5 Exposure assessment

From the applicant's literature search, EFSA identified three studies reporting on the tissue distribution of copper. One, in piglets, had already been taken into account by EFSA in a previous opinion (EFSA, 2009). The other two, in fish and shrimps, respectively, could not be taken into account due to limitations in design.

EFSA updated their assessment of consumer exposure to copper from use of the additive from previous evaluations (EFSA, 2008, 2009) using the latest approach in their most recent guidance on the assessment of risks to the consumer (EFSA, 2017). Residue concentrations in birds liver, mammals meat, mammals liver, mammals offal, mammals fat, eggs and milk were taken from the previous opinions (EFSA, 2008, 2009) and consumption data derived from the EFSA Comprehensive European Food Consumption Database were used in EFSA's Feed Additive Consumer Exposure (FACE) tool to estimate intakes for high percentile consumers in different European countries and age groups. The highest intakes estimated for toddlers and adults were compared to tolerable upper intake levels (ULs) for copper established by the Scientific Committee on Food of 1 mg/day and 5 mg/day, respectively (EC, 2003). The estimated intake for toddlers was 28.7% of its UL; the highest intake for adults was 21.8% of its UL.

FSA/FSS notes that consumption data for UK consumers were included in the EFSA Comprehensive European Food Consumption Database and in the FACE tool at the time of EFSA's assessment, and therefore the EFSA assessment took account of UK consumers.

FSA/FSS also notes that the consumer exposure assessment was based on use of the additive in compliance with the maximum permitted levels for total copper in complete animal feed, which are as shown in Table 1, below:

Table 1: Maximum permitted levels for copper in complete feed established in Commission Implementing Regulation (EU) 2018/1039

Animal species/category	Maximum total copper content in complete feed with a moisture level of 12 % (mg/kg)
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

*Including poultry

3.6 Toxicological data

From the applicant's monitoring programme of adverse effects, one complaint was received from one country of diarrhoea, low feed intake and gastritis in piglets. The same batches of the additive had been distributed to other farms in the country and to another country without any reports of adverse effects. EFSA concluded that this was an isolated incident, not linked to the additive.

From the applicant's literature search, covering the period 2008 to April 2019, the applicant identified 10 studies supporting the use of the additive in various species. In five of the studies, while no adverse effects were reported, the levels of copper in the diets were considerably below the maximum authorised level in feed for the relevant species. Another study involved concomitant supplementation with other substances and was not considered. EFSA considered the remaining four studies (two in pigs, one in fish, one in shrimp). There were no adverse effects reported at or below the maximum use levels for this additive.

Because nickel was measured in the additive as an impurity at concentrations up to 4.23 mg/kg, EFSA assessed the safety of this for the target species. Considering the highest maximum total copper authorised in feed of 150 mg/kg (suckling piglets and weaned piglets up to four weeks after weaning), nickel would be incorporated into the diet at concentrations up to 3.9 µg/kg feed. According to NRC (2005), fish and horses are the species most sensitive to nickel, with a maximum tolerable level of 50 mg/kg feed. Based on a background concentration of nickel in feed of about 4 mg/kg dry (dry matter basis), the total concentration of nickel in feed would be well below the maximum tolerable level and the contribution of this additive to nickel in the feed would be negligible.

According to the applicant's monitoring programme covering the period May 2010 to February 2019, there were three reports of safety-related incidents in users of the product in 2012 and 2014. In two cases this was due to the additive being handled

without following the measures stated in the safety data sheet. In the other case, irritation of the armpits of workers was possibly related to unusually high moisture and warm weather.

The applicant's literature search did not identify any papers related to user safety.

The applicant provided new studies on effects on the respiratory system and on skin and eyes. The study on effects on the respiratory system was an acute inhalation toxicity study, which followed OECD Test Guideline (TG) 403 and was conducted in accordance with good laboratory practice (GLP). The inhalation LC_{50} was estimated to be >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 larger than 356 µm in diameter. Therefore, EFSA concluded that the exposure to users by inhalation is very unlikely and the handling of the additive does not pose a risk to users by inhalation. EFSA considered the risks from inhaling nickel as an impurity in the additive. The highest dusting potential of the product was 0.235 g/m^3, which, based on the highest concentration of nickel measured of 4.23 mg/kg is equivalent to approximately 0.99 µg Ni/m^3. This is below the occupational exposure limit for nickel proposed by ECHA (2018) of 0.03 mg Ni/m^3 and therefore was not of concern.

An acute dermal toxicity test was performed in rats under GLP and following OECD TG 402. The acute dermal LD_{50} was estimated to be >2,000 mg/kg of body weight in male and female rats. The skin irritancy potential of the additive was tested in a GLP *in vitro* study performed according to the OECD TG 439. The additive was concluded to be irritant to skin (UN GHS: Category 2). 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). The additive was concluded to not be expected to cause skin corrosion.

The potential eye irritancy of the additive was tested in a GLP *in vitro* study performed according to OECD TG 437 (Bovine Corneal Opacity and Permeability test method). The results were inconclusive. Therefore, a second test to assess the potential eye irritancy of the additive was performed, the *in vitro* EpiOcular eye irritation test (OECD TG 492), under GLP. The additive was concluded to be irritant to eyes (UN GHS Category 2).

Considering the nickel content of the additive of up to 4.23 mg/kg, which is a well-established skin sensitiser, EFSA concluded the additive is considered to be a skin sensitiser.

The applicant's literature search did not identify relevant studies on the safety of the additive for the environment. Therefore, there was no new evidence that would require a modification of the previous conclusion by EFSA that the additive does not represent additional risks to the environment compared to other sources of copper (EFSA, 2008).

4. EFSA assessment and conclusions

A revised specification is proposed for the additive. The additive complies with the revised specification (≥16% copper and ≥78% (2-hydroxy-4-methylthio)butanoic acid

(DL-methionine hydroxy analogue, HMTBa). The additive is still considered safe for use for all animal species, food consumers and the environment under its current authorised conditions of use.

The additive is considered a skin and eye irritant and a skin sensitiser. The risk of respiratory sensitisation is considered low.

5. Caveats and uncertainties

There are no further caveats or uncertainties to highlight.

6. FSA Conclusion on reliability and applicability

The application has been assessed in line with the applicable guidance. The conclusions for this renewal are partly based on previous evaluations (EFSA, 2008 and 2009). EFSA has reassessed consumer exposures to copper from use of the additive using the latest approach in their most recent guidance on the assessment of risks to the consumer. This used consumption data which were included in the EFSA Comprehensive European Food Consumption Database at the time of the EFSA evaluation, which included UK consumption data and therefore EFSA's conclusions are applicable to UK consumers.

6.1 Analytical Method Review

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. FSA/FSS accepts the EURL analytical method evaluation report[4]. FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

7. Outcome of assessment

FSA/FSS has reviewed the EFSA opinion and consider it adequate and relevant for GB risk analysis. Therefore, the opinion was used to form the basis of the GB opinion.

FSA/FSS had access to all supporting documentation that was provided to the EFSA Panel by the applicant, and subsequently used to form the EFSA opinion. FSA/FSS agree with the safety conclusions outlined in the EFSA opinion.

The FSA/FSS opinion is that copper chelate of hydroxy analogue of methionine (Novus Europe SA/NV) for use as a feed additive for all animal species, as described in this application, is safe and is not liable to have an adverse effect on the target species, worker safety, environmental safety and human health at the intended concentrations of use.

[4] The report linked to the previous dossier (related to EFSA-Q-2007-097) is available on the EURL website: https://joint-research-centre.ec.europa.eu/system/files/2013-02/FinRep-FAD-2007-0012.pdf

8. References

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