Assessment : Assessment of the application for renewal of authorisation of zinc chelate of hydroxy analogue of methionine (Novus Europe SA/NV) for all animal species

Reference Number RP1388

Risk Assessment Unit
Science, Evidence and Research Division, FSA

Risk Assessment Team
Science Division, FSS

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Contents

1.Executive summary

The Food Standards Agency (FSA) and Food Standards Scotland (FSS) have undertaken an assessment of application RP1388 for the renewal of zinc chelate of hydroxy analogue of methionine (≥17% zinc and ≥79% 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 zinc 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 2020;18(12):6337,11 pp.) and confirm that it is adequate and relevant for GB risk analysis and used this to form the basis of GB opinion.

The FSA/FSS risk assessors concluded that the EFSA opinion is adequate and relevant for GB risk analysis. Therefore, the use of zinc 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 2020;18(12):6337 **Question number**: EFSA-Q-2019-00360

In accordance with Retained EU Regulation 1831/2003 on feed additives, the application RP1388 for the renewal of zinc 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. Zinc 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**) 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 containing 17.5-18% zinc, 81% (2-hydroxy-4-methylthio)butanoic acid (DL-methionine hydroxy analogue, HMTBa) and up to a maximum of 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 ≥17% zinc and ≥79% HMTBa. The additive no longer contains mineral oil. Three recent batches of the additive were analysed; the zinc content ranged from 18.2% to 18.6% and the content of HMTBa ranged from 80.0% to 80.4%.

Three 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, 4.1-5.5 mg Pb/kg additive, 0.22-0.34 mg Cd/kg additive, 0.02 to 0.03 mg Hg/kg additive, 0.087-0.236 ng WHO-PCDD/F-TEQ/kg dioxins and 0.089-0.244 ng WHO-PCDD/F-PCB-TEQ/kg for the sum of dioxins and dioxin-like PCBs. 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), 2020. Scientific Opinion on the assessment of the application for renewal of authorisation of zinc chelate of hydroxy analogue of methionine for all animal species. EFSA Journal 2020;18(12):6337,11 pp. https://doi.org/10.2903/j.efsa.2020.6337

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

Nickel was analysed in three batches of the additive and ranged from 1.54 to 1.64 mg/kg. EFSA evaluated the risks of nickel to the target species (see section 3.6, Toxicology data, below.)

The additive is a grey tan powder or granules. The dusting potential, determined by the Stauber-Heubach method, was measured in three samples of the additive and ranged from 165 to 3500 mg/m^3. The particle size distribution of the dust was measured in two batches (it was attempted in three but the applicant reported that it could not be assessed in one batch as the amount of dust was too low) and averaged 10.7% (range 10.5%-11.0%) of particles <1 µm and 83.9% (range 80.1%-87.8%) of particles <10 µm.

New shelf-life studies were conducted on three batches of the additive, which were stored for at least 5.5 years. A total of 97.0% of the initial zinc and a total of 99.0% 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 26.0% and 25.3%, respectively, were tested. For each formulation, samples from 9 bags were analysed for zinc content. The coefficients of variation were 2.9% for Premix-1 and 2.5% for Premix-2.

3.5 Exposure assessment

EFSA concluded in a previous evaluation, based on data submitted on the deposition of zinc from the use of this additive in the tissues/products of pigs (muscle, liver, kidney and skin/fat), laying hens (eggs) and cows (milk), that there was no indication that the use of this additive would lead to any higher zinc concentration in the tissues/products compared to the use of inorganic zinc (EFSA, 2009). Therefore, EFSA concluded that consumer exposure to zinc would not be increased by the use of this particular form of zinc. For this renewal application the applicant conducted a literature search from 2008 to April 2019. This did not identify any studies reporting different tissue levels to those previously considered by EFSA.

3.6 Toxicological data

EFSA previously concluded that the additive is safe for all species up to the maximum authorised levels of zinc in feed (EFSA, 2009). From the applicant's literature search, a total of nine new studies were identified relevant to the safety of target species. The studies were conducted in pigs, chickens for fattening, laying hens, dairy cows, heifers, fish and shrimp. No adverse effects were reported. However, the levels of zinc tested were below the maximum authorised concentrations in feed, with the exception of the study in shrimp which tested approximately 1.4 times the maximum authorised level for zinc.

Because the additive contains nickel as an impurity, EFSA assessed the safety of this for target species. Considering the highest maximum total zinc authorised in feed of 200 mg/kg (dogs and cats), nickel would be incorporated into the diet at concentrations up to 0.4 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 for adverse effects of the additive, there were three reports of safety-related incidents in users of the product. In two cases this was attributed to the additive being handled without following the measures stated in the safety data sheet. In the other case, two users from the same employer developed skin irritation despite wearing gloves and a face mask. The applicant sent additive from that batch to an external laboratory for acute dermal irritation/corrosion testing, and the results were that the additive was not a skin irritant. No complaints were received from other customers using the same batch. EFSA concluded that this adverse event report was a chance effect.

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 >1.04 mg/L in both male and female rats.

Based on the highest dusting potential of the additive being 3.5 g/m^3 and the maximum zinc concentration of the dust being 164.3 mg/kg, EFSA estimated that a maximum zinc concentration of 575 mg/m^3 could be released when handling the additive. The respirable fraction of the dust is up to 87.8% and therefore the respirable zinc from the dust is up to 505 mg/m^3. This exceeds a threshold limit value for zinc of 2 mg/m^3 (ACGIH, 2015) by two orders of magnitude. Therefore, handling of the additive poses a risk to users by inhalation. EFSA considered the risks from inhaling nickel as an impurity in the additive. Considering the highest dusting potential of the product of 3.5 g/m^3, and the highest concentration of nickel measured of 1.64 mg/kg, the estimated exposure is 0.006 µg Ni/m^3. This is below the occupational exposure limit for nickel proposed (European Commission, 2011) of 0.01 mg Ni/m^3. However, due to the established sensitising properties of nickel the additive should be considered a respiratory sensitiser.

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. 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 non-irritant to skin.

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 non-irritant to eyes (UN GHS: no category).

Considering the nickel content of the additive of up to 1.64 mg/kg, and that nickel 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 any relevant studies on the safety of the additive for the environment. Thus, there is no new evidence that would require a modification of the conclusion previously drawn by EFSA that the use of this additive would not pose risks to the environment compared to other sources of zinc (EFSA, 2008).

4. EFSA assessment and conclusions

A revised specification is proposed for the additive. The additive complies with the revised specification (≥17% zinc and ≥79% (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.

Due to the zinc and nickel contents, the additive poses a risk to users by inhalation. The additive is not considered a skin or eye irritant. Due to the nickel content, it is considered a skin sensitiser.

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 (including EFSA, 2009).

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.

[4] The report linked to the previous dossier (related to EFSA-Q-2007-098) is available on the EURL website: https://joint-research-centre.ec.europa.eu/system/files/2013-02/FinRep-FAD-2007-0010.pdf

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 zinc 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.

8. References

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