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

Reference Number RP1387

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1.Executive summary

The Food Standards Agency (FSA) and Food Standards Scotland (FSS) have undertaken an assessment of application RP1387 for the renewal of manganese chelate of hydroxy analogue of methionine (≥14% manganese and ≥76% 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 manganese 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(11):6281, 10 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 manganese 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(11):6281 **Question number**: EFSA-Q-2019-00362

In accordance with Retained EU Regulation 1831/2003 on feed additives, the application RP1387 for the renewal of manganese chelate of hydroxy 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. Manganese 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 of containing 15.5-17% manganese, 77-78% (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 ≥14% manganese and ≥76% HMTBa. Eight recent batches of the additive were analysed; the manganese content ranged from 14.2% to 17.0% and the content of HMTBa ranged from 76.9% to 77.8%. EFSA noted that around 5-8% of the additive remains unidentified.

Nine 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 6-14 mg As/kg additive, 6-29 mg Pb/kg additive, ≤0.2-2 mg Cd/kg additive and ≤0.1 mg Hg/kg additive. The results for the dioxins and the sum of dioxins and dioxin-like PCBs were reported as “conform” for eight batches, indicating that the specification was not exceeded (<1 ng WHO-PCDD/F-TEQ/kg and <1.5 ng WHO-PCDD/F-PCB-TEQ/kg additive, respectively) and for the ninth batch as 0.0057 ng WHO-PCDD/F-

[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 manganese chelate of hydroxy analogue of methionine for all animal species. EFSA Journal 2020;18(11):6281, 10 pp. https://doi.org/10.2903/j.efsa.2020.6281

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

TEQ/kg and 0.109 ng WHO-PCDD/F-PCB-TEQ/kg additive, respectively. These results were not considered a concern by EFSA.

Nickel was analysed in three batches of the additive and ranged from 165 to 168 mg/kg. EFSA evaluated the risks of nickel to the target species (see section 3.6, Toxicology data, below.)

The additive is marketed in the form of granules. The particle size distribution and dusting potential, determined by the Stauber-Heubach method, were measured in three samples of the additive. The particle sizes averaged 10.8% (range, 8.8-13.0%) of particles <1 µm and 74.1% (range 68.0-78.0%) <10 µm. The dusting potential ranged from 1.94 to 3.14 g/m^3. The manganese content of the dust averaged 125.8 g/kg dust (range 117.0-131.8 g/kg dust).

New shelf-life studies were conducted on three batches of the additive, which were stored for at least five and a half years. A total of 89.8% of the initial manganese and a total of 97.9% 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 31.6% and 31.3%, respectively, were tested. For each formulation, samples from 9 bags were analysed for manganese content. The coefficients of variation were 2.1% for Premix-1 and 4.1% for Premix-2.

3.5 Exposure assessment

EFSA previously evaluated the additive in 2009 and 2010. In 2009 it conducted a consumer exposure assessment of residues of manganese in chickens for fattening and concluded there was no concern for consumer safety (EFSA, 2009), and in 2010, it conducted a consumer exposure assessment based on data for piglets (muscle, liver, kidney and skin/fat), laying hens (eggs) and dairy cows (milk) fed the additive, and concluded that there was no indication that use of the additive would lead to any higher manganese concentration in tissues/ edible products than the use of inorganic manganese and there were no consumer safety concerns (EFSA, 2010).

For this renewal application, the applicant's literature search did not identify any studies that reported different tissue levels than those considered previously. EFSA concluded that there were no relevant additional data which would lead to a change in the conclusions previously reached and therefore use of the additive remains safe for consumers under the authorised conditions of use.

3.6 Toxicological data

EFSA previously evaluated the additive and concluded that it was safe for all species up to the maximum authorised magnesium content in feed (EFSA, 2010). The applicant's literature search identified a total of six studies relevant to safety in target species. These studies were in pigs, chickens for fattening, laying hens, dairy cows, heifers and shrimps. No adverse effects were reported. However, the manganese levels in feed in all these studies were below the maximum authorised levels.

Because nickel was measured in the additive as an impurity, EFSA assessed the safety of this for target species. Considering the highest concentration of nickel

measured, the minimum manganese concentration in the additive and the maximum total manganese authorised in feed of 150 mg/kg (piglet feed), nickel would be incorporated into the diet at concentrations up to 0.178 mg/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.

Monitoring for adverse effects was implemented as part of the quality assurance of the applicant. Two incidents were reported, which EFSA did not consider to be a safety issue.

The applicant's literature search did not identify any relevant 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 in rats, which followed OECD Test Guideline (TG) 403 and was conducted in accordance with good laboratory practice (GLP). Under the conditions of the study the inhalation LC_{50} was >5.16 mg/L (the highest concentration tested) in both male and female rats. Since the highest measured dusting potential of the additive was 3.14 g/m^3, and the maximum concentration of manganese in the dust was 131.8 g/kg, EFSA estimated that a maximum manganese concentration of 414 mg/m^3 could be released when handling the additive. The respirable fraction of the dust was up to 78%, and thus the respirable manganese from the dust is 323 mg/m^3. The threshold limit value for manganese is 0.02 mg/m^3 (ACGIH, 2015), and this is exceeded by more than four orders of magnitude. Therefore, the handling of this additive poses a risk to users by inhalation.

EFSA considered the risks from inhaling nickel as an impurity in the additive. The highest nickel content of the additive analysed was 168 mg/kg. Based on the dusting potential of the additive of up to 3.14 g/m^3, the exposure to nickel corresponds to 0.53 mg/m^3. This exceeds the occupational exposure limit (OEL) proposed for the inhalable fraction of water-soluble nickel of 0.01 mg/m^3 (EC, 2011). Therefore, due to the nickel content, the handling of the additive poses a risk to users by inhalation.

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 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. The additive was concluded to be non-irritant to eyes.

As the nickel content of the additive is up to 168 mg/kg, which has well-known skin sensitisation potential, and in the absence of skin sensitisation studies for the additive, 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. Thus, there was no new evidence that would require modification of the conclusion previously drawn by EFSA that this additive does not pose additional risks to the environment compared to other sources of manganese used as feed additives (EFSA, 2008).

4. EFSA assessment and conclusions

A revised specification is proposed for the additive. The additive complies with the revised specification (≥14% manganese and ≥76% (2-hydroxy-4-methylthio)butanoic acid (DL-methionine hydroxy analogue, HMTBa). Mineral oil is now not used in the manufacturing process.

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 both the manganese and nickel contents of the additive, the handling of the additive poses a risk to users by inhalation. The additive is not a skin or eye irritant but 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 (EFSA, 2009 and 2010).

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-2007-094) is available on the EURL website: https://joint-research-centre.ec.europa.eu/system/files/2013-02/FinRep-FAD-2007-0011.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 manganese 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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