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Assessment of the application for renewal of authorisation of manganese chelate of hydroxy analogue of methionine for all animal species

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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 manganese chelate of hydroxy analogue of methionine (Mintrex[®]Mn) for all animal species. The FEEDAP Panel has delivered three opinions (in 2008, 2009 and 2010) on the safety and efficacy of the additive. The additive was authorised in 2010 as 'Manganese chelate of hydroxy analogue of methionine' containing 15.5–17 % manganese, 77–78 % (2-hydroxy-4-methylthio)butanoic acid (DL-Methionine Hydroxy Analogue, HMTBa) and maximum 1% mineral oil. Following some modifications in the manufacturing process the additive does not contain mineral oil and the applicant proposes the following specifications: ≥ 14 % manganese and ≥ 76 % 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. Owing to the manganese and nickel content of Mintrex[®]Mn, the handling of the additive poses a risk to users by inhalation; the additive is not a skin or eye irritant but is considered as a skin sensitiser. 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.

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1. Introduction

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

Regulation (EC) No 1831/2003¹ 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 manganese 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 manganese 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 three opinions on manganese chelate of hydroxy analogue of methionine as feed additive for all animal species: the first one on the safety and efficacy of the additive (EFSA, 2008), the other two opinions on the safety of the additive (EFSA FEEDAP Panel, 2009, 2010).

Manganese chelate of hydroxy analogue of methionine is authorised in the European Union as a nutritional additive for all animal species (3b5.10).³

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier⁴ in support of the authorisation request for the use of manganese 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.⁵

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of manganese chelate of hydroxy analogue of methionine is in line with the principles laid down in Regulation (EC) No 429/2008⁶ and the relevant guidance document: Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2013).

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 350/2010 of 23 April 2010 concerning the authorisation of manganese chelate of hydroxy analogue of methionine as a feed additive for all animal species. OJ L 104, 24.4.2010, p. 34.

⁴ FEED dossier reference: FAD-2019-0032.

⁵ The report linked to the previous dossier (related to EFSA-Q-2007-094) is available on the EURL website: <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2007-0011.pdf>

⁶ 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.

3. Assessment

The additive 'Manganese chelate of hydroxy analogue of methionine' is authorised as nutritional additive (functional group: compounds of trace elements), as a source of manganese for all animal species. The maximum content of manganese authorised in animal feed in the EU is 100 mg/kg complete feedingstuffs for fish and 150 mg/kg complete feedingstuffs for other animal species.

This assessment regards the renewal of the authorisation of the additive.

3.1. Characterisation

The additive is authorised as 'Manganese chelate of hydroxy analogue of methionine' containing 15.5–17 % manganese, 77–78 % (2-hydroxy-4-methylthio)butanoic acid (DL-methionine hydroxy analogue, HMTBa), and maximum 1% mineral oil. The applicant declared that, since the additive was authorised, some modifications have been introduced in the manufacturing process: [REDACTED]

[REDACTED] These modifications have led to a slightly different additive composition, and thus, the applicant proposes the following new specifications: ≥ 14 % manganese and ≥ 76 % HMTBa; this represents a variation compared to the current authorisation.

3.1.1. Characterisation of the additive

The chemical name of the additive is manganese bis(-2-hydroxy-4-methylthio)butanoate. The molecular formula is $\text{Mn}(\text{CH}_3\text{S}(\text{CH}_2)_2\text{-CH}(\text{OH})\text{-COO})_2$ and the molecular weight 353.3 Da. The CAS number of the complexed compound is 292140–32–0. The theoretical contents of manganese (as Mn(II)) and HMTBa are 15.5 % and 84.5 %, respectively.

Analytical data of eight recent batches were provided by the applicant.⁷ The manganese content ranged from 14.2% to 17.0%; the content of HMTBa ranged from 76.9% to 77.8%. These data show compliance with the new specifications proposed by the applicant. The FEEDAP Panel notes that ca. 5–8% of the additive remains unidentified.

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 nine recent batches⁸ of the additive. The results reported were the following: 6–14 mg As/kg additive, 6–29 mg Pb/kg additive, ≤ 0.2 –2 mg Cd/kg additive, ≤ 0.1 mg Hg/kg additive; dioxins and the sum of dioxins plus dioxin like PCBs were reported as 'Conform' in eight batches (indicating that the specification is not exceeded: < 1 ng WHO-PCDD/F-TEQ/kg and < 1.5 ng WHO-PCDD/F-PCB-TEQ/kg additive) and as 0.0057 ng WHO-PCDD/F-TEQ/kg and 0.109 ng WHO-PCDD/F-PCB-TEQ/kg additive, respectively, in the ninth batch.⁹ These values are below the threshold set by Directive 2002/32 on undesirable substances¹⁰ 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 165 to 168 mg/kg.¹¹

3.1.2. Physical characteristics of the product

The additive is marketed in the form of light to dark grey or dark brown granules. Its solubility in water is 7.1% at 20°C. The bulk and tap density of the additive were measured in three batches resulting on an average of 852 kg/m³ and 0.945 g/cm³, respectively.¹²

The dusting potential of the additive – measured in the same three batches as density – determined by the Stauber–Heubach method was in the range of 1.94 to 3.14 g/m³.¹³ Analysis of particle size distribution of the dust from three additive's batches resulted on average in 10.8 % (range

⁷ Technical dossier/Section II/Annex_II_01_CoA. A total of 16 batches were submitted, however eight of these batches were not considered 'recent' according to the definition given in the Guidance of renewal of authorization of feed additives.

⁸ Eight batches coincident with those in which the active substance was analysed and one additional batch.

⁹ Technical dossier/Section II/Annex_II_02_Impurities.pdf.

¹⁰ 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.

¹¹ Technical Dossier/Supplementary Information_November19/Appendix 1.

¹² Technical dossier/Section II/Annex_II_04_Bulk; Annex_II_05_Tap.

¹³ Technical dossier/Section II/Annex_II_03_Dusting.

8.8–13.0) of particles < 1 µm and 74.1% (range 68.0–78.0) < 10 µm. The manganese content of the dust from the same three batches resulted in an average of 125.8 g/kg dust (range 117.0–131.8).¹⁴

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 for at least 5.5 years¹⁵; at the end of the experiment a total of 89.8 and 97.9 % of the initial manganese and HMTBa, respectively, was recovered.

Data to support homogeneous distribution of the additive in premixtures were submitted.¹⁶ The study was performed with two premix formulations, Premix-1 and Premix-2 (one lot from each), in which the inclusion of Mintrex[®]Mn was 31.6% and 31.3%, respectively. In both cases, samples from nine bags per lot were taken and the manganese content analysed. The coefficients of variation were calculated as 2.1 and 4.1% for the Premix-1 and Premix-2, respectively.

3.1.4. Conditions of use

The additive is authorised for all animal species up to the total manganese content in complete feed established in the current legislation, i.e. 100 mg/kg complete feedingstuffs for fish and 150 mg/kg complete feedingstuffs for other animal species.

The current authorisation 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.

The applicant does not propose a modification of the current conditions of use.

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 program of the company. [REDACTED]

[REDACTED] Two incidents were reported; the FEEDAP Panel did not consider them as a safety issue.

The applicant performed a structured literature search on the safety of the additive.¹⁸ 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 for Mintrex[®]Mn, comprised the active substances/additive and keywords related to the safety/toxicity. The search included also other keywords relevant for Mintrex[®]Cu and Mintrex[®]Zn. It resulted in a total of 394 hits.¹⁹ In total six publications were considered relevant for the assessment of Mintrex[®]Mn.

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

3.2.1. Safety for the target species

In its opinion of 2008, the FEEDAP Panel concluded, based on a tolerance study, that Mintrex[®]Mn was safe for chickens for fattening; however, the Panel could not extend the conclusion to other animal species (EFSA, 2008). Following that opinion, the applicant submitted new data in the form of tolerance studies in laying hens, piglets and calves; based on those trials, and in the one already

¹⁴ Technical Dossier/Supplementary Information_November19/Appendix 2–5.

¹⁵ Technical dossier/Section II/Annex_II_12_Stability.

¹⁶ Technical dossier/Section II/Annex_II_13_Homogeneity.

¹⁸ Technical dossier/Section II/Annex_III_2_Literature_search.

¹⁹ 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.

assessed in chickens for fattening, the FEEDAP Panel concluded that Mintrex[®]Mn was safe for all species up to the maximum authorised manganese content in feed (EFSA FEEDAP Panel, 2010).

From the literature search a total of six studies were identified. These studies were performed in pigs (Liu et al., 2014), chickens for fattening (Yuan et al., 2011), laying hens (Manangi et al., 2015), dairy cows (Nemec et al., 2012), heifers (Whitehurst et al., 2014) and shrimps (Katya et al., 2016). No adverse effects were reported; however the FEEDAP Panel notes that the manganese levels used in feed in all these studies were below the maximum authorised ones.

Since the additive contains nickel as a contaminant, the FEEDAP Panel assessed the impact of nickel on the safety for the target species. If adding 150 mg Mn/kg piglet feed – the highest maximum total manganese authorised in feed – from the compound under assessment, nickel would be incorporated with 0.178 mg per kilogram feed.²⁰ According to the National Research Council (NRC, 2005), fish and horses are the most sensitive animal species to nickel with maximum tolerable level (MTL) of 50 mg/kg feed. In the worst-case scenario, the nickel that would be added to the feed from the additive together with the background nickel in feed (i.e. 4 mg/kg dry matter (DM) feed; Nicholson et al., 1999; Van Paemel et al., 2010) would amount to about 4.2 mg Ni/kg feed; this concentration is well below the MTL.

Based on the assessment above the FEEDAP Panel concludes that Mintrex[®]Mn remains safe for the target species under the authorised conditions of use.

3.2.2. Safety for the consumers

In its opinion in 2009, the FEEDAP Panel concluded that no concerns for the consumer would be raised when consuming food derived from chickens for fattening fed the additive; this conclusion was based on consumer exposure assessment of residues of manganese in tissues of chickens for fattening (EFSA FEEDAP Panel, 2009). In a subsequent opinion, and based on consumer exposure assessment of data on tissues/products from piglets (muscle, liver, kidney, skin/fat), laying hens (eggs) and dairy cows (milk) fed Mintrex[®]Mn, the FEEDAP Panel noted that there was no indication that Mintrex[®]Mn would lead to any higher manganese concentration in tissues/products compared to inorganic manganese; overall, the FEEDAP Panel concluded that no specific concerns for consumer safety would arise from the use of Mintrex[®]Mn in feed for all animal species (EFSA FEEDAP Panel, 2010).

The literature search did not identify studies that report tissue levels different from those submitted and discussed previously.

In summary, no relevant 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[®]Mn 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 identified a risk by inhalation and concluded that Mintrex[®]Mn was safe for the user provided that protective measures are taken (EFSA, 2008). The authorising regulation establishes that 'breathing protection, safety glasses and gloves should be worn during handling' of the additive.

The literature search did not identify relevant studies on the safety of the additive for the users.

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

Effects on the respiratory system

The applicant provided an acute inhalation toxicity test in rats.²¹ The study aimed at determining the potential for Mintrex[®]Mn to produce toxicity from a single dose via inhalation route (nose-only exposure). The study was conducted under good laboratory practice (GLP) and according to OECD Guideline 403. Under the conditions of this study, the single exposure acute inhalation LC₅₀ of the test substance is greater than 5.16 mg/L (the highest concentrations tested) in male and female rats.

Data on the product characterisation was also used to derive inhalation exposure. The highest measured dusting potential of the additive was 3.14 g/m³, and the manganese maximum concentration in the dust was 131.8 g/kg (see Section 3.1.2). Thus, a maximum concentration of

²⁰ These calculations follow a worst-case scenario by i) considering that all the manganese in the feed comes from the additive, ii) the minimum content of manganese for the additive and iii) taking into consideration the maximum nickel content reported for the additive under assessment.

²¹ Technical Dossier/Section III/Annex_III_5.

414 mg Mn/m³ could be released when handling the additive. The respirable fraction of the dust is up to 78 %, thus the respirable manganese from the dust is 323 mg/m³. Considering a threshold limit value (TLV) for manganese of 0.02 mg/m³ (ACGIH, 2015) the TLV is exceeded by more than four orders of magnitude. Owing to the manganese content of the additive, the FEEDAP Panel considers that handling of the additive poses a risk to users by inhalation.

The highest nickel content analysed in the additive was 168 mg/kg. The dusting potential of the product mounted up to 3.14 g/m³, corresponding to about 0.53 mg Ni/m³,²² which is one order of magnitude higher than the occupational exposure limit (OEL) proposed for the inhalable fraction of water-soluble nickel (0.01 mg Ni/m³; EC, 2011). Owing to the nickel content of the additive, the FEEDAP Panel considers that handling of the additive poses a risk to users by inhalation.

Effects on skin and eyes

An acute dermal toxicity test was conducted with rats to determine the potential for Mintrex[®]Mn to produce toxicity from a single topical application.²³ The study was conducted under GLP and according to OECD Guideline 402. Under the conditions of this study, the single dose acute dermal LD₅₀ 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 Guideline 439.²⁴ Under the conditions of this study, Mintrex[®]Mn is considered a non-irritant to skin.

The potential of eye irritancy of the additive was tested in a GLP *in vitro* study performed according to the OECD Guideline 437.²⁵ Under the conditions of this study, Mintrex[®]Mn is considered a non-irritant to eyes.

The nickel content of the additive is up to 168 mg/kg; given its well-known sensitisation potential (EC, 2011) and in the absence of skin sensitisation studies the additive is classified as a skin sensitiser.

Conclusions on the safety for the users

Owing to the manganese and nickel content of Mintrex[®]Mn, the handling of the additive poses a risk to users by inhalation. The additive is not a skin or eye irritant but is considered as a skin sensitiser.

3.2.4. Safety for the environment

In its opinion of 2008, the FEEDAP Panel concluded that Mintrex[®]Mn did not represent additional risks to the environment compared to other sources of manganese 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[®]Mn in feed does not pose an additional risk to the environment providing that the maximum authorised content in complete feed is not exceeded.

3.3. Efficacy

The present application 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 Regulation²⁶ and Good Manufacturing Practice.

²² Assuming an equivalent distribution of nickel in the dust than that in the additive. (No information of the content of nickel in dust was available).

²³ Technical Dossier/Section III/Annex_III_4.

²⁴ Technical Dossier/Supplementary Information_July20/Appendix 1.

²⁵ Technical Dossier/Supplementary Information_July20/Appendix 2.

²⁶ Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

4. Conclusions

The applicant has provided data demonstrating that the additive complies with the new specifications proposed of $\geq 14\%$ Manganese and $\geq 76\%$ HMTBa. No mineral oil is used in the manufacturing process. These modifications represent a variation compared to the current authorisation.

The FEEDAP Panel confirms that the use of Mintrex[®]Mn under the current authorised conditions of use is safe for all animal species, the consumers and the environment.

The FEEDAP Panel concludes that, owing to the manganese and nickel content of Mintrex[®]Mn, the handling of the additive poses a risk to users by inhalation. The additive is not a skin or eye irritant but is considered as a skin sensitiser.

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 Manganese chelate of hydroxy analogue of methionine (MINTREX [®] Mn). 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. <i>Issues: characterisation</i>
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. <i>Issues: safety for the users</i>
30/07/2020	Reception of supplementary information from the applicant - Scientific assessment re-started
30/09/2020	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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Abbreviations

CAS	Chemical Abstracts Service
DM	dry matter
EFSA FEEDAP Panel	EFSA Panel on Additives and Products or Substances used in Animal Feed
EURL	European Union Reference Laboratory
GLP	Good laboratory practice
HMTBa	2-hydroxy-4-methylthio)butanoic acid
LC ₅₀	lethal concentration, median
LD ₅₀	lethal dose, median
MTL	maximum tolerable level
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
PCB	polychlorinated biphenyl
PCDD/F	polychlorinated dibenzo- <i>p</i> -dioxin and dibenzofuran
TEQ	toxic equivalent
TLV	threshold limit value
WHO	World Health Organization