Safety and efficacy of Mintrex® Mn (Manganese chelate of hydroxy analogue of methionine) as feed additive for all species

Scientific Opinion of the Panel on Additives and Products or Substances used in Animal Feed

(Question No EFSA-Q-2007-094)

Adopted on 15 April 2008

PANEL MEMBERS

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SUMMARY

Following a request from the European Commission, the European Food Safety Authority was asked to deliver a scientific opinion on the safety and efficacy of a manganese chelate of the hydroxy analogue of methionine (Mintrex® Mn) as a feed additive for all species.

Mintrex® Mn contains a minimum of 16 % manganese and 76 % hydroxy methionine analogue ((2-hydroxy-4-methylthio)butanoic acid, HMTBa), as shown from analyses of the product. It is intended to be used as a source of the essential trace element manganese. Manganese (in several forms) and HMTBa are already separately authorised as nutritional feed additives in the European Union.

In a study on chickens for fattening using a wide dose range, Mintrex® Mn supplementation increased tibia bone deposition, an indicator of manganese bioavailability. The concentration of manganese in tibia bone supplied by Mintrex® Mn did not differ from that supplied by manganese sulphate, a recognised source of available manganese in animal nutrition. Thus Mintrex® Mn can be considered as a bioavailable manganese source, comparable to other authorised sources of manganese.

No specific studies on tolerance in target animals to Mintrex® Mn were provided. The efficacy study, which included supplemented doses of up to 800 mg manganese kg−1 diet, provided some evidence of safety but alone was not adequate to draw conclusions on the safety for target animals. However, considering the published data on manganese tolerance in poultry with other manganese sources, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concludes that manganese from Mintrex® Mn is safe for chickens for fattening.
There is evidence that chickens for fattening are not the most sensitive animal species/category to manganese toxicity. Therefore, the FEEDAP Panel is unable to extend its conclusion on chickens for fattening to other animal species.

Based on the data from acute toxicity and genotoxicity studies, the FEEDAP Panel considers that Mintrex® Mn does not introduce any additional toxicity compared to other sources of dietary manganese.

Based on the available data there appears to be no essential differences in bioavailability (assessed from bone manganese concentration) and therefore in edible tissue deposition of manganese from Mintrex® Mn compared to other authorised sources of manganese. However, this conclusion is based on limited evidence and does not include an adequate assessment of manganese concentrations in edible tissues/products.

With regards to consumer safety, the FEEDAP Panel retains manganese as the component of potential toxicological significance of Mintrex® Mn. The FEEDAP Panel considers that the data available are limited and do not allow an assessment of consumer exposure to manganese derived from Mintrex® Mn. In the light of the recommendation made by the former Scientific Committee on Food that additional dietary exposure to manganese may carry a health risk, the FEEDAP Panel cannot conclude on the safety for consumers of Mintrex® Mn when used in animal nutrition.

The FEEDAP Panel considers that Mintrex® Mn is safe for the user provided that protective measures are taken and that it does not represent additional risks to the environment compared to other sources of manganese for which it will substitute.

The FEEDAP Panel made some recommendations with regards to the Register entry and highlighted the need for analytical methods specific to the determination of the chelates rather than the trace element.

**Key words:** nutritional additive, trace element, Mintrex® Mn, manganese, chelate, HMTBa, hydroxy methionine, bioavailability, efficacy, safety, chickens for fattening
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BACKGROUND

Regulation (EC) No 1831/2003 establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lies down that any person seeking an authorisation for a feed additive or for a new use of a feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from the company Novus Europe SA, for authorisation of manganese chelate with the hydroxy analogue of methionine (Mintrex®Mn) to be used as a feed additive for all species (category: nutritional additives; functional group: compounds of trace elements) under the conditions mentioned in Table 1.

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 4.1 (authorisation of a feed additive or new use of a feed additive). EFSA received directly from the applicant the technical dossier in support of this application. According to Article 8 of that Regulation, 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. The particulars and documents in support of the application were considered valid by EFSA as of 3 September 2007.

The additive Mintrex®Mn is a manganese chelate of hydroxy analogue of methionine. Ten compounds of manganese are authorised in the EU for all animal species without a time limit. Among these, two are chelates: the manganese chelate of amino acids (derived from hydrolysed soya protein) hydrate and the manganese chelate of glycine (synthetic) hydrate. The hydroxy analogue of methionine is authorised as nutritional additive in the functional group aminoacids, their salts and derivatives.

The Scientific Committee on Animal Nutrition (SCAN) issued a report on the use of manganomanganic oxide in feedingstuffs (6 February 2002). EFSA issued an opinion on the safety of the “Chelated forms of iron, copper, manganese and zinc with synthetic feed grade glycine” (29 November 2005).

TERMS OF REFERENCE

According to Article 8 of Regulation (EC) No 1831/2003 EFSA shall determine whether the feed additive complies with the conditions laid down in Article 5. Therefore, EFSA shall deliver an opinion on the efficacy and safety for the target animals, consumer, user and the environment, of manganese chelate of the hydroxy analogue of methionine (Mintrex®Mn), based on, when used under the conditions described in Table 1.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group on Trace Elements for the preparation of this opinion.
Table 1. Register entry as proposed by the applicant

<table>
<thead>
<tr>
<th>Additive</th>
<th>Mintrex® Mn</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Registration number/EC No/No (if appropriate)</th>
<th>3b5.xx</th>
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<tbody>
<tr>
<td>Category of additive</td>
<td>Nutritional</td>
</tr>
<tr>
<td>Functional group of additive</td>
<td>Compounds of trace elements</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Description</th>
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<tbody>
<tr>
<td>Composition, description</td>
</tr>
<tr>
<td>Manganese chelate of hydroxy analogue of methionine 13% Mn 76% HMTBa</td>
</tr>
<tr>
<td>Trade name (if appropriate)</td>
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<tr>
<td>Name of the holder of authorisation (if appropriate)</td>
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</table>

<table>
<thead>
<tr>
<th>Conditions of use</th>
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</thead>
<tbody>
<tr>
<td>Species or category of animal</td>
</tr>
<tr>
<td>All species</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other provisions and additional requirements for the labelling</th>
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</thead>
<tbody>
<tr>
<td>Specific conditions or restrictions for use (if appropriate)</td>
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<tr>
<td>Specific conditions or restrictions for handling (if appropriate)</td>
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<tr>
<td>Post market monitoring (if appropriate)</td>
</tr>
<tr>
<td>Specific conditions for use in complementary feedingstuffs (if appropriate)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Maximum Residue Limit (MRL) (if appropriate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marker residue</td>
</tr>
<tr>
<td>Not relevant</td>
</tr>
</tbody>
</table>
ASSESSMENT

1. Introduction

Mintrex\textsuperscript{®}Mn is a chelate containing a minimum of 13 % manganese and 76 % hydroxy methionine analogue ((2-hydroxy-4-methylthio)butanoic acid, HMTBa), according to the specifications provided by the applicant. It is intended to be used as a source of the essential trace element manganese for all animal species.

The biological role, requirements and deficiency symptoms of manganese in farm animals have been already described in a former SCAN Opinion (EC, 2002).

2. Characterisation of the product

2.1. Description of the product

The product is composed of manganese bis(-2-hydroxy-4-methylthio)butanoic acid and a maximum of 1 % mineral oil (specifications not given). The formula is Mn(CH\textsubscript{3}S(CH\textsubscript{2})\textsubscript{2}-CH(OH)-COO\textsubscript{2} and its molecular weight is 353.3 Daltons. The CAS number of the complexed compound is 292140-32-0. The molecular structure of the manganese-HMTBa chelate has been examined by assessment of ligand coordination from infrared spectra.\textsuperscript{9}

2.2. Production

Mintrex\textsuperscript{®}Mn is manufactured by mixing synthetic liquid HMTBa with inorganic manganous oxide under specific heat and moisture conditions in a reactor/dryer.\textsuperscript{10} The dry Mintrex\textsuperscript{®}Mn chelate is milled to a standard particle size and then blended with feed grade mineral oil.

2.3. Composition

Based on the analyses of nine batches, the additive contents of HMTBa and manganese were 77.2±1.0 and 17.1±0.6 %, respectively (only one analytical certificate submitted). Mintrex\textsuperscript{®}Mn is declared to contain not more than 1 % of mineral oil; however, quantification of the content of this component was not confirmed by analytical data. The remaining constituents of the additive (up to ca. 5 %, based on the analysed values) were not identified.

In three different batches microbial impurities, mycotoxins (aflatoxin B1), heavy metals and dioxins were determined. Microbial contamination and aflatoxin content (<0.001 mg kg\textsuperscript{-1} Mintrex\textsuperscript{®}Mn) did not raise concern. Contents of As, Pb, Hg, Cd and F were found to be 12-15, 6-7, <0.1, <0.8 and <0.15 mg kg\textsuperscript{-1} Mintrex\textsuperscript{®}Mn, respectively. Although the content of As appeared to be high, the contribution from Mintrex\textsuperscript{®}Mn to the final feed As content will be insignificant. Dioxins were found at levels of 0.104 to 0.132 ng WHO TEQ kg\textsuperscript{-1} Mintrex\textsuperscript{®}Mn. Dioxin like PCBs were not analysed.\textsuperscript{11}

2.4. Physicochemical properties

The final product is a brown powder composed of spherical granules with a bulk density of 0.79 g (cm\textsuperscript{3})\textsuperscript{-1}. Around 10 % of particles show a diameter of <105 µm; this fraction is considered inhalable. The respirable fraction (particles ≤10µm) was not determined.

\textsuperscript{9} Technical Dossier, Section II, Annex II.2.2.4.1
\textsuperscript{10} Technical Dossier, Section II
\textsuperscript{11} Technical Dossier, Section II
Dusting potential was examined in one batch only and the product classified as ‘very dusty’ by the applicant (based on dustiness measured by ‘Dustmon L Anatec’ apparatus).12

2.5. Stability

A method for direct determination of the manganese complex in Mintrex®Mn was not provided. The stability of the chelate has therefore not been directly analysed. Instead, stability was derived from the calculation of changes in the free HMTBa, assuming that the manganese/HMTBa ratio in Mintrex®Mn would remain constant and that HMTBa does not interact with any other components.13

The applicant proposes a provisional expected shelf life of three years. At present, the shelf life of Mintrex®Mn has only been demonstrated for 12 months under standard conditions (25°C, 60 % RH) and for six months under accelerated conditions (40°C, 75 % RH). Calculated recoveries of complexed manganese from three batches at the end of the test periods showed values of 102 % for both standard and accelerated conditions. Recovery rates of total HMTBa were 100 %. Stability towards light, air oxygen and pH of Mintrex®Mn is considered by the applicant to be guaranteed by packaging the additive in light-tight sealed bags when stored under normal atmospheric conditions.

All data on HMTBa stability in feed and premixtures are mean values obtained from stability studies performed with Mintrex®Cu, Mintrex®Zn and Mintrex®Mn given together.

In premixtures, mash feed, pelleted feed and during pelleting (in each case at both standard and accelerated conditions), manganese concentration, as expected, remained constant. HMTBa measurements could not be attributed to any one of the Mintrex® products.

2.6. Homogeneity

Homogeneity data were based on ten samples each of premixtures, pelleted and mash feed collected from one lot of Mintrex®Mn. The coefficient of variation (CV) of manganese from Mintrex®Mn was 1.3 % in premixtures, 4.9 % in mash feed and 9.3 % in pellets.

The data indicate that Mintrex®Mn can be homogeneously distributed in premixtures and, to a lesser extent, in mash and pelleted complete feedingstuffs.14

2.7. Conditions of use

Mintrex®Mn is intended to supply manganese in final feed within EU legal limits for all species (100 mg kg\(^{-1}\) complete feed for fish and 150 mg kg\(^{-1}\) for other species).

According to the applicant, feed formulations should be adjusted to account for the methionine efficacy of HMTBa in Mintrex®Mn.

According to the current knowledge, no incompatibilities or adverse interactions –with feed components, carriers, other approved additives or medical products– are to be expected other than those widely recognised for manganese in animal nutrition.

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12 Technical Dossier, Section II
13 Technical Dossier, Section II. Supplementary information. August 2007
14 Technical Dossier, Section II, Annex II.2.3.1.
2.8. Evaluation of the analytical methods by the Community Reference Laboratory (CRL)

EFSA has verified the report submitted by the Community Reference Laboratory (CRL) concerning the analytical method(s) for Mintrex® Mn. The executive summary of the report can be found in the Appendix.

3. Efficacy

Evidence of in vivo bioavailability is required to support efficacy for compounds of trace elements not already authorised as feed additives. A single trial in a single animal species/category, including laboratory animals, is considered sufficient.

Bone manganese is one of the best response criteria to assess the biological value of manganese sources in animals, below and above requirements (Jongbloed et al., 2002).

Studies with Mintrex® in which the diet was supplemented simultaneously with Mintrex® Cu, Mintrex® Mn and Mintrex® Zn are not considered further in the present assessment because potential interactions could not be excluded.

3.1. Bioavailability

Four hundred and eighty male chicks (Cobb 500) were allocated to 16 dietary treatments (96 pens with six pens of five animals per treatment). Manganese from MnO, MnSO₄·5H₂O and Mintrex® Mn was added at 0, 100, 200, 400, 600, and 800 mg manganese kg⁻¹ to a low manganese basal diet (analysed value 34 mg kg⁻¹) based on yellow corn and soybean meal. The concentrations of manganese in the diets were confirmed by analysis. Diets were adjusted for the amount of hydroxymethionine added from Mintrex® Mn by reducing another source of hydroxymethionine. All diets were fortified with 50 mg iron kg⁻¹ from ferrous sulphate, 100 mg zinc kg⁻¹ from zinc sulphate, and 10 mg copper kg⁻¹ from copper sulphate. Diets were fed in mash form for 20 days. At the end of the trial, birds were killed and tibias, grouped by pen, were analysed for bone ash and manganese content.

There were no significant differences among treatments for body weight, feed conversion, feed intake, mortality, or tibia ash. The effects of different sources and dietary levels of manganese on bone deposition are shown in Table 2.

Table 2. Effect of source and level of manganese on tibia manganese concentration (mg kg⁻¹) of 20 d old broilers

<table>
<thead>
<tr>
<th>Supplemental level of manganese, mg kg⁻¹ diet</th>
<th>Mintrex® Mn</th>
<th>Manganese oxide</th>
<th>Manganese sulphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>------------</td>
<td>4.3 i</td>
<td>-------------------</td>
</tr>
<tr>
<td>100</td>
<td>8.5 bhi</td>
<td>7.5 hi</td>
<td>6.9 i</td>
</tr>
<tr>
<td>200</td>
<td>11.2 ef</td>
<td>9.2 gb</td>
<td>9.7 fg</td>
</tr>
<tr>
<td>400</td>
<td>15.1 d</td>
<td>11.9 e</td>
<td>14.1 d</td>
</tr>
<tr>
<td>600</td>
<td>18.0 c</td>
<td>14.8 d</td>
<td>17.7 e</td>
</tr>
<tr>
<td>800</td>
<td>25.6 a</td>
<td>17.4 c</td>
<td>21.1 b</td>
</tr>
</tbody>
</table>

a-j: Different letter superscripts indicate significant differences (P<0.05)

Significant differences in tibia manganese content were observed between both source and level of manganese. Tibial manganese of chicks fed MnO, MnSO₄·5H₂O, and Mintrex® Mn steadily increased with increasing manganese concentrations. Data indicate that manganese

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15 Technical Dossier, Section III, Annex III.3.2.Mn1
from Mintrex® Mn was at least as available to broiler chicks as manganese from inorganic sources.

Supportive evidence for the conclusion on Mintrex® Mn can be drawn from the studies of Weiss and Socha (2005) and Ji et al. (2006) who demonstrated the bioavailability of manganese from manganese-methionine.

3.2. Conclusions on efficacy

Mintrex® Mn shows the same pattern as manganese sulphate in increasing tibia bone manganese in chickens for fattening when added to a basal diet in concentrations between 100 and 600 mg kg\(^{-1}\) diet. Since inorganic manganese sulphate is generally recognised and used as a source of available manganese in animal nutrition, Mintrex® Mn can be considered as a bioavailable manganese source, comparable to manganese sulphate, for all animal species.

4. Safety for the target species

The FEEDAP Panel considers that tolerance of the target animals should be demonstrated for compounds of trace elements not previously authorised. When the application concerns all animal species, one tolerance study with the most sensitive species (or even a laboratory animal) may be sufficient.

Manganese has low to moderate oral toxicity in farm animals. With a well balanced diet, ruminant species appear to tolerate up to 1000 mg manganese kg\(^{-1}\) feed and poultry up to 2000 mg manganese kg\(^{-1}\) feed. Some reports indicate a greater sensitivity for swine, for which the tolerance level is set at 400 mg manganese kg\(^{-1}\) feed (NRC, 1980).

As for efficacy assessment, studies with Mintrex® in which the diet contains the three trace elements copper, manganese and zinc from Mintrex® given simultaneously are not further considered because potential interactions cannot be excluded.

4.1. Tolerance study in chickens for fattening

A specific tolerance study was not submitted. However, the study already described under the efficacy section (see Section 3.1.) can be considered as a tolerance study because it included an unsupplemented control, a diet delivering approximately the maximum permitted concentration and a series of diets with higher concentrations of manganese from Mintrex® Mn. Limitations of the experimental design as a tolerance study were the short duration (20 days instead of 35), the small number of animals used (5 x 6 broilers per dose group) and the lack of satisfactory endpoints (only zootechnical parameters). A summary of the results is given in Table 3.
Table 3. **Effect of source and level of manganese on performance of chicken for fattening**

<table>
<thead>
<tr>
<th>Manganese Source</th>
<th>Supplemental manganese (mg kg(^{-1}) feed)</th>
<th>Body weight (g)</th>
<th>Feed intake (g)</th>
<th>Feed:gain (g g(^{-1}))</th>
<th>Mortality (n/30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td>782</td>
<td>1054</td>
<td>1.43</td>
<td>2</td>
</tr>
<tr>
<td>Manganese oxide</td>
<td>100</td>
<td>780</td>
<td>1030</td>
<td>1.41</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>802</td>
<td>1032</td>
<td>1.37</td>
<td>2</td>
</tr>
<tr>
<td>Manganese sulphate</td>
<td>100</td>
<td>760</td>
<td>1015</td>
<td>1.43</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>758</td>
<td>1010</td>
<td>1.42</td>
<td>0</td>
</tr>
<tr>
<td>Mintrex(^{\circledast})Mn</td>
<td>100</td>
<td>799</td>
<td>1044</td>
<td>1.39</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>777</td>
<td>1041</td>
<td>1.43</td>
<td>0</td>
</tr>
</tbody>
</table>

There were no significant differences between treatments for body weight, feed conversion, feed intake, mortality or tibia ash content. These results were not unexpected as the manganese basal diet in this trial was analysed to contain 34 mg kg\(^{-1}\). Watson et al. (1970) reported that 10 mg kg\(^{-1}\) manganese added to a semi-purified diet containing 4 mg kg\(^{-1}\) manganese was adequate to maintain normal growth and bone ash and to prevent the occurrence of perosis for chicks up to 28 days of age, when supplied from sulphate or oxide. This result was confirmed later by the same research group (Watson et al., 1971). Manganese supplementation up to 1000 mg kg\(^{-1}\) diet from various sources has been reported to be non-toxic (Gallup and Norris, 1939; Black et al., 1985; Miles et al., 2003).

### 4.2. Conclusions on target species safety

The FEEDAP Panel considers Mintrex\(^{\circledast}\)Mn as a new compound of a trace element and therefore requires demonstration of safety for target species.

The efficacy study, although providing some evidence of safety, alone is not adequate to draw conclusions on target animal safety. However, taken in conjunction with published data on manganese tolerance in chickens for fattening, with inorganic manganese sources of up to 1000 mg manganese kg\(^{-1}\) diet, the FEEDAP Panel concludes that manganese from Mintrex\(^{\circledast}\)Mn is safe for chickens for fattening. However, there is evidence that chickens for fattening are not the most sensitive animal species/category. Therefore, the FEEDAP Panel is unable to extend its conclusion from chickens for fattening to other animal species.

The HTMBa contribution from Mintrex\(^{\circledast}\)Mn needs consideration to keep total methionine at desired levels.

### 5. Tissue/products deposition

Absorption of oral manganese is low in all animal species (EC, 2002). Less than 0.1 % of an oral dose was apparently absorbed by avian species whereas cattle absorb about 1 % of ingested manganese. Manganese absorption depends on the age of the animals (younger animals absorb better than older ones), the source (e.g. organic sources, MnSO\(_4\), Cl\(^{-}\) and CO\(_3\)^{2-}\) are better absorbed than oxides), the presence of some antagonists in feed (e.g., Ca, P, Fe, Co etc.), the physiological stage of animal (e.g. pregnancy, lactation) and other influencing factors (Männer and Bronsch, 1987).

Literature data indicate that manganese-methionine (Henry et al., 1989) as well as Mintrex\(^{\circledast}\)Mn (Yan and Waldroup, 2006) may have a greater bioavailability in broilers compared with some manganese inorganic forms. This may be evident in doses higher than the permitted use levels,
as was shown in the bioavailability trial on chickens for fattening (see Table 2). In two recent studies, there were no differences found in the deposition in eggs (Huyghebaert et al., 2006) or breast and leg meat in chickens for fattening (Lu et al., 2007) of manganese from inorganic or organic sources supplied in diet at EU authorised use levels. Literature data indicate that the liver is the main storage organ for manganese as well as the primary excretory organ via the bile (Carter et al., 1974).

In a study with dairy cows, milk manganese was examined comparing manganese (zinc and copper) from Mintrex® with inorganic sources. After 103 days of feeding, manganese could not be detected in milk on either group. However, the LOD and information on the analytical method used were not provided. No further data on edible tissue/product deposition of manganese from Mintrex® Mn were reported.

Based on the available data there appears to be no essential differences in bioavailability (assessed from bone manganese concentration) and therefore in edible tissue deposition of manganese from Mintrex® Mn compared to other authorised sources of manganese. However, this conclusion is based on limited evidence and does not include an adequate assessment of manganese concentration in edible tissues/products.

6. Safety for the consumer

6.1. Toxicity studies

The applicant presented acute oral toxicity and genotoxicity studies on Mintrex® Mn.

6.1.1. Acute toxicity

In an acute toxic class dose study (OECD, 2001) female rats were treated by oral gavage with 300 or 2000 mg Mintrex® Mn kg⁻¹ bw. A 100 % mortality, within day 2 following treatment, was observed at the top dose. No mortality or signs of toxicity were observed at 300 mg kg⁻¹ bw; accordingly, the median lethal dose was estimated to be between 300 and 500 mg Mintrex® Mn kg⁻¹ bw.

6.1.2. Genotoxicity studies including mutagenicity

Mutagenicity of Mintrex® Mn was assessed in a reverse mutation assay on five S. typhimurium strains (TA98, TA100, TA1535, TA1537 and TA102) with and without metabolic activation. No significant increase of revertant colonies was observed up to the limit concentration of 5000 µg mL⁻¹.

Mintrex® Mn was also tested in CHO cells for chromosomal aberrations without and with S-9 metabolic activation. No effects were seen up to concentrations reducing cell viability by 50 %, i.e. 1400 µg mL⁻¹ and 80 µg mL⁻¹, without and with S-9 activation, respectively.

6.1.3. Conclusions

The median lethal dose was estimated to be between 300 and 500 mg Mintrex® Mn kg⁻¹ bw. Mintrex® Mn is not mutagenic and does not induce chromosomal aberrations in vitro. Therefore
the FEEDAP Panel considers that Mintrex® Mn does not introduce any additional toxicity effects compared to other sources of dietary manganese.

6.2. Consumer exposure

Although no data was supplied on the metabolic fate of manganese-HMTBa, the FEEDAP Panel considers that the deposition pattern of manganese in chicken tibia and the nutritional equivalence of HMTBa from Mintrex® and from free HMTBa concerning the incorporation (as methionine) into body protein (Yi et al., 2007), are sufficient indications of an extended dissociation of the molecule. As manganese is the component of potential toxicological significance (see Section 6.1), its deposition in tissues and products represents the relevant issue for the appraisal of consumer safety.

The Scientific Committee on Food (SCF) delivered an opinion on the tolerable upper intake level (UL) of manganese (EC, 2000). Due to insufficient data and remaining concerns about oral neurotoxicity and genotoxicity, it was not possible to derive a UL. However, the SCF concluded that, given the low margin of safety between oral effect levels in humans as well as experimental animals and the estimated intake from food and the higher potential vulnerability of very young children and the elderly, ‘oral exposure to manganese beyond the normally present in food and beverages could represent a risk of adverse health effects without evidence of any health benefit.’

A provisional oral reference dose of 10 mg manganese day⁻¹ in adults was proposed by the US Environmental Protection Agency (EPA, 1988), which corresponds to the upper intake in the US studies. No other international bodies have proposed a UL or a PMTDI (Provisional Maximum Tolerable Daily Intake).

According to the SCF assessment of manganese (EC, 2000), the dietary intakes by adults range broadly between 1 and 9 mg day⁻¹. In the UK the average dietary intake was 4.9 mg day⁻¹, with 45% provided by beverages. This average level of intake is likely adequate to meet the nutritional requirements of humans. Vegetable foods (grains, rice, nuts) and tea are major dietary sources; indeed vegetarians have a higher than average manganese intake.

6.3. Conclusions on safety for the consumers

The FEEDAP Panel retains manganese as the component of potential toxicological significance of Mintrex® Mn. The FEEDAP Panel considers that a) the data available are limited and do not allow an assessment of consumer exposure to manganese from Mintrex® Mn; b) Mintrex® Mn might alter manganese concentration in edible tissues and products, compared to other sources of manganese; c) Mintrex® Mn would be used to substitute for other inorganic sources; and d) concern for consumer safety remains, particularly for the subgroups with a higher potential vulnerability identified by the SCF.

Based on the above considerations and in the light of the recommendation by the SCF that additional exposure may carry a health risk, the FEEDAP Panel cannot conclude on the safety for consumers of Mintrex® Mn when used in animal nutrition.

7. Safety for the user

No specific studies on the safety of Mintrex® Mn for the user were conducted. The product has a significant dusting potential: 10% of particles are < 105 µm, thus inhalation exposure may occur.

Manganese is recognised as a significant occupational toxicant eliciting a neurotoxic syndrome (‘manganism’) upon inhalation. Therefore, the FEEDAP Panel supports the recommendations
made by the applicant in the Register entry (under other provisions) and makes further recommendations (see Recommendations).

8. Safety for the environment

Manganese is a natural element that is essential for life and is present almost everywhere in the environment. However, at high concentrations manganese may be toxic and a maximum content of the element in feed has therefore been set. There is no reason to believe that chelates such as Mintrex®Mn would be more harmful to the environment than the inorganic element. The FEEDAP Panel considers that the use of Mintrex®Mn in feed does not represent additional risks to the environment, compared to other sources of manganese for which it will substitute, as long as the maximum authorised content in feedingstuffs is not exceeded.

9. Post-market monitoring

The FEEDAP Panel does not see a need for specific requirements of post-market monitoring other than the need for traceability and recall procedures established by Regulation (EC) No 183/2005.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

Mintrex®Mn can be considered as a bioavailable manganese source, comparable to other authorised sources of manganese, for all animal species.

The FEEDAP Panel concludes that Mintrex®Mn is safe for chickens for fattening. However there is evidence that chickens for fattening are not the most sensitive animal species/category. Therefore the FEEDAP Panel is unable to extend its conclusion from chickens for fattening to other animal species.

Based on the available data there appears to be no essential differences in bioavailability (assessed from bone manganese concentration) and therefore in edible tissue deposition of manganese from Mintrex®Mn compared to other authorised sources of manganese. However, this conclusion is based on limited evidence and does not include an adequate assessment of manganese concentration in edible tissues/products.

Based on the data from acute toxicity and genotoxicity studies, the FEEDAP Panel considers that Mintrex®Mn does not introduce any additional toxicity compared to other sources of dietary manganese.

With regards to consumer safety, the FEEDAP Panel retains manganese as the component of potential toxicological significance of Mintrex®Mn. The FEEDAP Panel considers that the data available are limited and do not allow an assessment of consumer exposure to manganese derived from Mintrex®Mn. In the light of the recommendation made by the former SCF that additional dietary exposure to manganese may carry a health risk, the FEEDAP Panel cannot conclude on the safety for consumers of Mintrex®Mn when used in animal nutrition.

The FEEDAP Panel considers that Mintrex®Mn is safe for the user provided that protective measures are taken.

The FEEDAP Panel considers that the use of Mintrex®Mn in feed does not represent additional risks to the environment compared to other sources of manganese for which it will substitute.

20 OJ L 35, 8.2.2005, p.1
**RECOMMENDATIONS**

The FEEDAP Panel recommends that the following modifications should be made to the Register entry as proposed by the applicant:

1. **Additive**
   
   In the view of the FEEDAP Panel the additive name is: Manganese chelate of hydroxy analogue of methionine.

2. **Description**
   
   Composition, description. Manganese chelate of hydroxy analogue of methionine containing a minimum of 16 % manganese and 76 % (2-hydroxy-4-methylthio)butanoic acid.
   
   Chemical formula. \( \text{Mn(CH}_3\text{S(CH}_2\text{)}_2\text{-CH(OH)-COO)}_2 \). 

   Purity criteria. The FEEDAP Panel recommends the setting of maximum levels as follows: \( \text{As} \leq 15 \), \( \text{Pb} \leq 10 \), \( \text{Hg} \leq 0.1 \), \( \text{Cd} \leq 1 \) and \( \text{F} \leq 0.2 \) mg kg\(^{-1}\) Mintrex\(^{\circledR}\)Mn. Dioxins (sum of PCDDs and PCDFs)\( \leq 0.2 \) ng WHO-PCDD/F-TEQ kg\(^{-1}\) Mintrex\(^{\circledR}\)Mn.

3. **Conditions of use**
   
   Feed formulations should be adjusted to account for the methionine efficacy of HMTBa in Mintrex\(^{\circledR}\)Mn.

4. **Other provisions and additional requirements for labelling**
   
   Specific conditions or restrictions for handling. In addition to the applicant’s proposal, the FEEDAP Panel recommends appropriate ventilation of working rooms and the reduction of the inhalable fraction as far as technically feasible.

**GENERAL REMARK**

The FEEDAP Panel wishes to draw attention to the following.

Considering:

- the increasing number of applications for organic forms of trace elements to be used in animal nutrition,

- the potential higher bioavailability of those compounds in feedingstuffs, and consequently (i) the potential reduction of maximum content for those trace elements in feed, and (ii) the higher deposition of trace elements of organic origin in animal tissues, and

- the resulting need for maximum content of organic forms of trace elements different from those already existing,

the FEEDAP Panel stresses the need for analytical methods to detect those organic compounds in the feed, independent from the trace element background. The availability of such methods would allow lower maximum contents in feed which would in turn reduce concerns relating to the assessment of consumer safety and reduce environmental load.

**DOCUMENTATION PROVIDED TO EFSA**

1. Dossier Mintrex\(^{\circledR}\)Mn as nutritional additive for all species. March 2007. Submitted by Novus Europe SA.


5. Comments from the Member States received through the EFSAnet.

REFERENCES


APPENDIX

Executive Summary of the Evaluation Report of the Community Reference Laboratory Feed Additives on the Method(s) of Analysis of Mintrex® Mn for all species

*Mintrex® Mn* is a product for which authorisation is sought under the category "nutritional additives", functional group 3b "compounds of trace elements", according to the classification system of Annex I, of Regulation (EC) No 1831/2003. According to the applicant, *Mintrex® Mn* contains 13% of Manganese as chelate of hydroxyl analogue of methionine, 2-hydroxy-4-methylthiobutanoic acid (HMTBa) as active substance. *Mintrex® Mn* is also a source of methionine activity as HMTBa.

In the current application authorisation is sought for use of *Mintrex® Mn* for all animal species. *Mintrex® Mn* is intended to be added to complete feed to supplement Mn within legal limits for each species which are: fish 100 mg/kg, other species 150 mg/kg.

For the determination of Mn in the feed additive, premixtures and feedingstuffs for official control the CEN standard method EN 15510:2007, as proposed by the applicant, is recommended by the CRL.

The proposed methods for the determination of HMTBa are considered suitable for the intended purpose.