

SCIENTIFIC OPINION

Scientific Opinion on the safety of a manganese chelate of hydroxy analogue of methionine (Mintrex[®]Mn) as feed additive for all species¹

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

Following a request from the European Commission, the European Food Safety Authority (EFSA) was asked to deliver an opinion on the safety for the target animals and consumers of Mintrex[®]Mn as nutritional additive for all species taking into account the earlier opinions on the product and the supplementary data provided by the applicant.

Tolerance studies in piglets, laying hens and calves for rearing were submitted. In piglets, effects of manganese on hematological and biochemical parameters were observed, irrespective of the manganese source. In laying hens there was sufficient evidence to conclude that zootechnical parameters were unaffected by the manganese supplementation and source at an overdose. In calves for rearing there were no indications to suggest that Mintrex[®]Mn is less safe compared to manganese sulfate. Taking also into account the already assessed safety of Mintrex[®]Mn for chickens for fattening, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concluded that Mintrex[®]Mn is safe for all species up to the maximum total manganese content authorised in feed.

Mintrex[®]Mn did not induce significant changes in manganese deposition in edible tissues and products (piglet muscle, liver and kidney; hen's eggs; cow's milk) compared with already authorised inorganic manganese sources. Therefore, an increased manganese exposure of the consumers due to the use of Mintrex[®]Mn is not expected. The FEEDAP Panel concludes that the use of Mintrex[®]Mn up to the maximum authorised total manganese content in complete feeds is safe for consumers.

KEY WORDS

Nutritional additive, trace element, manganese, chelate, hydroxy methionine analogue, tissue deposition, safety

¹ On request from the European Commission, Question No EFSA-Q-2009-00630, adopted on 9 December 2009.

² Panel members: Gabriele Aquilina, Georges Bories, Paul Brantom, Francesca Caloni, Andrew Chesson, Pier Sandro Cocconcelli, Joop de Knecht, Noël Albert Dierick, Mikolaj Antoni Gralak, Jürgen Gropp, Ingrid Halle, Nils-Gunnar Ilbäck, Reinhard Kroker, Lubomir Leng, Sven Lindgren, Anne-Katrine Lundebye Haldorsen, Alberto Mantovani, Miklós Mézes, Derek Renshaw and Maria Saarela. Correspondence: FEEDAP@efsa.europa.eu

³ Acknowledgement: The Panel wishes to thank the members of the Working Group on Trace Elements including Bogdan Debski, Christer Hogstrand and Carlo Nebbia for the preparation of this opinion.

TABLE OF CONTENTS

Table of contents	2
Background as provided by the European Commission.....	3
Terms of reference as provided by the European Commission.....	3
Assessment	4
1. Introduction	4
2. Safety for the target animals	4
2.1. Tolerance study with piglets	4
2.2. Tolerance study with laying hens.....	6
2.3. Tolerance study with calves for rearing	7
2.4. Conclusions on the safety for the target species	8
3. Safety for the consumer	9
3.1. Tissue/products deposition.....	9
3.1.1. Piglets	9
3.1.2. Laying hens	9
3.1.3. Dairy cows.....	9
3.1.4. Conclusions on tissue/products deposition	10
3.2. Consumer exposure.....	10
Conclusions	10
Documentation provided to EFSA	10
References	11
Abbreviations	12

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Regulation (EC) No 1831/2003⁴ establishes rules governing the Community authorisation of additives for use in animal nutrition and in particular, Article 9 defines the terms of the authorisation by the Commission.

The company Novus Europe S.A.⁵ is seeking Community authorisation of its product, Manganese chelate of hydroxy analogue of methionine, as nutritional additive for all species.

On 15th April 2008, the Scientific Panel on Additives and Products or Substances used in Animal Feed of the European Food Safety Authority (FEEDAP) adopted an opinion on the efficacy and safety of Mintrex[®]Mn (Manganese chelate of hydroxy analogue of methionine) as feed additive for all species (Question No EFSA-Q-2007-094). It was concluded that Mintrex[®]Mn could be considered safe for chickens for fattening, but due to the marked differences in manganese sensitivity existing among species the FEEDAP Panel was unable to extend its conclusion from chickens for fattening to other animal species. Additionally it could not conclude on the safety for consumers.

Therefore, the Commission gave the possibility to the company to submit complementary information to complete the assessment.

The Commission had received a supplementary report from the applicant, Novus Europe S.A., for this nutritional additive on the safety of the consumer once the product is incorporated in diets of chickens for fattening. By letter of 18.03.2009 (SANCO/D2(2009)/WT7ci/420079) the Commission requested an update of the above mentioned opinion for the animal category chickens for fattening. The Commission has now received a supplementary report from the applicant, Novus Europe S.A., with supplementary information on the safety for all species and with respect to consumer safety data on Mn content in animal products.⁶

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In view of the above, the Commission asks to the European Food Safety Authority to deliver an opinion on the safety for the target animals and consumers of this product as nutritional additive for all species taking into account its earlier opinion on 15th April 2008, the supplementary information already submitted concerning the transfer of Mn from Mintrex[®]Mn into tissues of chickens for fattening, and the new dossier received as specified in the Background.

⁴ OJ L 268, 18.10.2003, p.29

⁵ Novus Europe S.A. Avenue Marcel Thiry 200. 1200 Brussels, Belgium

⁶ EFSA Dossier reference: FAD-2009-0020

ASSESSMENT

1. Introduction

Mintrex[®]Mn is a chelate containing by weight a minimum of 13 % manganese (Mn) and 76 % hydroxy analogue of methionine ((2-hydroxy-4-methylthio)butanoic acid), according to the specifications provided by the applicant. Mintrex[®]Mn is intended to supply Mn in final feed within EU legal limits for all species (total Mn content: 100 mg/kg complete feed for fish and 150 mg/kg for other species).

The FEEDAP Panel previously adopted an opinion on the efficacy and safety of Mintrex[®]Mn as feed additive for all species (EFSA, 2008). With regard to the safety for the target species, the FEEDAP Panel could only conclude on that for chickens for fattening. As for the consumer exposure, the FEEDAP Panel concluded that it would be unlikely to be different from that of inorganic Mn, but this conclusion was based on limited evidence and did not include a direct assessment of Mn concentration in edible tissues. In respect to the safety for consumers, the FEEDAP Panel could not conclude because of the limited data available, and taking into account the recommendation made by the Scientific Committee on Food (EC, 2000) that additional exposure to Mn may carry a health risk.

In response to the FEEDAP Panel's opinion on Mintrex[®]Mn (EFSA, 2008), the applicant supplied data to assess the consumer exposure, and hence the consumer safety of Mintrex[®]Mn when used as feed additive for chickens for fattening. EFSA delivered an opinion in which it was concluded that "Mintrex[®]Mn would not increase Mn deposition in edible tissues of chickens for fattening compared to other authorised inorganic Mn sources. Consequently, the use of Mintrex[®]Mn as a feed additive for chickens for fattening is unlikely to present a safety concern to consumers" (EFSA, 2009). Furthermore, the applicant has supplied additional data to assess the safety for the target species and the safety for consumer of Mintrex[®]Mn when used as a feed additive for all species.

2. Safety for the target animals

In its previous opinion on the same product, the FEEDAP Panel concluded that Mintrex[®]Mn was safe for chickens for fattening (EFSA, 2008). In the current dossier, the applicant provided data on the safety of the product for piglets, laying hens and calves for rearing.

2.1. Tolerance study with piglets

A 42-day tolerance study with different Mintrex products was carried out on a total of 720 crossbred (Large white male line x Landrace*Large white, sex ratio 1:1) piglets.⁷ Piglets of 26 days (initial weight: 7.4 kg) were allocated to nine treatments with eight replicates per treatment (ten piglets per replicate). Common basal diets (a pre-started feed during the first two weeks and a starter feed for the subsequent four weeks) were supplemented with Mn, Zn, and Cu from sulfate or Mintrex at different levels. All diets were adjusted to the same content of the hydroxy analogue of methionine (MHA) as provided by 0.346 % Mintrex[®]Mn (equivalent to 450 mg Mn/kg and 0.313 % MHA feed supplement) by addition of the calcium salt of MHA.

For the purpose of the dossier provided, the applicant extracted five groups and applied a separate statistical evaluation (ANOVA) on this part of the experiment, expressing all experimental parameters as least square corrected means. The treatments were: a control feed supplemented with Mn, Zn, and Cu as their sulfates at NRC requirement levels (T1); a second control group supplemented with Mn, Zn and Cu from sulfate and at maximum authorised levels (T2); a Mintrex[®]Mn group equivalent to T2, in which manganese sulfate was replaced by Mintrex[®]Mn (T3); an overdose group supplemented with Mn and Zn (three times the level of T2) and Cu (twice the level in T2) from sulphate (T4); and a group corresponding to T4, in which manganese sulfate was replaced by Mintrex[®]Mn (T5). The dietary content of all three trace elements supplemented was analysed.

⁷ Technical Dossier, Annex III.1.1.

Performance parameters (mortality, body weight, weight gain, feed intake, feed/gain) were recorded. Haematological (RBC, Hb, PCV, MCV, MCH, MCHC, WBC, platelet count, mean platelet volume) and blood biochemical (total protein, albumin, γ -GT, AST, ALT and urea) parameters were measured (n=8 per treatment, one piglet per replicate).

Table 1 gives an overview on the experimental design and summarises the zootechnical parameters as well as the other endpoints showing significant differences.

Table 1: Tolerance study in piglets with Mintrex[®]Mn (42 days)

Group	T1 ¹	T2 ²	T3 ²	T4 ³	T5 ³
Mn source	Sulfate	Sulfate	Mintrex [®] Mn	Sulfate	Mintrex [®] Mn
Mn supplementation (mg/kg)*	4/3	150/150	150/150	450/450	450/450
Mn analysed (mg/kg)*	34/39	159/162	195/192	416/417	543/515
Cu analysed (mg/kg)	15/11	149/145	153/159	319/271	323/294
Zn analysed (mg/kg)	194/119	195/180	191/182	454/398	472/405
Mortality (n out of 80)	4	3	5	6	9
Daily weight gain (g)	346 ^a	346 ^a	356 ^a	295 ^b	310 ^b
Daily feed intake (g)	534 ^a	510 ^{ab}	495 ^{bc}	451 ^d	471 ^{cd}
Feed/gain (g/g)	1.54 ^b	1.47 ^{ab}	1.38 ^a	1.54 ^b	1.52 ^b
Haemoglobin (g/dL)	10.34 ^a	8.14 ^{bc}	8.93 ^b	7.64 ^c	8.17 ^{bc}
Packed cell volume (%)	28.73 ^a	23.40 ^{bc}	24.65 ^b	21.41 ^c	22.54 ^{bc}
Mean corpuscular Hb (pg)	15.3 ^a	13.0 ^b	12.2 ^{bc}	11.4 ^c	11.6 ^{bc}
Plasma total protein (g/dL)	5.75 ^c	5.83 ^{bc}	5.88 ^{bc}	6.36 ^{ab}	6.64 ^a
Plasma albumin (g/dL)	2.63 ^b	3.03 ^a	2.79 ^{ab}	3.02 ^a	3.09 ^a
Serum urea (mg/dL)	18.4 ^{bc}	14.6 ^c	15.9 ^c	20.6 ^{ab}	23.3 ^a

* Pre-starter/starter feed

1: Supplemented also with 6/5 mg Cu and 100/80 mg Zn/kg pre-starter/starter feed from sulfates

2: Supplemented also with 170 mg Cu and 150 mg Zn/kg feed from sulfates

3: Supplemented also with 340 mg Cu and 450 mg Zn/kg feed from sulfates

a, b, c, d: Different letter superscripts in the same row indicate significant differences (P < 0.05).

The design of the experiment, namely the simultaneous delivery of high doses of Cu and Zn in the Mn overdose groups (T4 and T5), does not allow the influence of Mn levels, and particularly that of Mintrex[®]Mn, to be isolated as the only experimental variable. The only comparisons that could be made are those between T2 and T3 and between T4 and T5. The high level of supplemental Cu (170 mg/kg in T2/T3 and 340 mg in T4/T5) would have required an adjustment of dietary iron (Fe). However, Fe was supplemented to all diets at the same level (100 mg/kg) and from a poorly available source (Fe-carbonate).

Mortality/culls was not significantly affected by the treatments; results of necropsies were not reported. However, daily weight gain and feed intake were depressed in the overdose groups (T4 and T5). Differences in these parameters between the sulfate and the Mintrex[®]Mn groups (T2 vs T3 and T4 vs T5) were not observed.

Haemoglobin, mean corpuscular Hb and PCV were reduced at both Mn doses 150 and 450 mg/kg feed (T2, T3, T4 and T5) compared to the NRC Mn dose group (T1), unrelated to Mn source. This may be related to the low and constant supplementation rate of Fe, in combination with high Zn and Cu supplementation. Copper and Zn are known to interact with Fe metabolism. The values of other haematological parameters (RBC, WBC and platelet counts) did not show changes related to Mn dose and source.

Manganese doses of 150 and 450 mg/kg feed (T2, T3, T4, and T5) from either Mn source resulted in increased levels of total protein and albumin in plasma and serum urea, without differences related to Mn source. No changes in other biochemical parameters monitored were observed.

2.2. Tolerance study with laying hens

An eight-week tolerance study with different Mintrex products was carried out with a total of 392 laying hens (commercial brown Hy-Line layers, initial body weight 1940 g).⁸ The hens were allocated to 14 treatments with seven replicates per treatment (four birds per replicate). A common basal diet was supplemented with Mn, Zn and Cu from sulfate or Mintrex at different levels. All diets were adjusted to the same content of the MHA as provided by 0.346 % Mintrex[®]Mn (equivalent to 450 mg Mn/kg and 0.313 % MHA feed supplement) by addition of the calcium salt of MHA.

For the purpose of the dossier provided, the applicant extracted six groups and applied a separate statistical evaluation (ANOVA) on this part of the experiment, expressing all experimental parameters as least square corrected means. The treatments were: two low Mn diets (20 mg supplemental Mn/kg, either from sulfate (T1) or from Mintrex[®]Mn (T2)), two intermediate Mn diets (150 mg supplemental Mn/kg either from sulfate (T3) or from Mintrex[®]Mn (T4)), and two Mn overdose diets (450 mg supplemental Mn/kg either from sulfate (T5) or from Mintrex[®]Mn (T6)). The low Mn diets were also supplemented with 6 mg Cu and 35 mg Zn/kg, the intermediate and the overdose of Mn with 25 Cu and 150 Zn mg/kg. The data for the analytical contents of Mn, Cu and Zn were provided.

Performance parameters (mortality, body weight, weight gain, feed intake), egg production (egg weight, egg numbers, egg mass, egg mass/feed ratio), egg quality (yolk colour, egg-shell thickness) were recorded. Haematological (PCV, RBC, HGB, MCV, MCH, MCHC, WBC, heterophils, lymphocytes and monocytes) and blood biochemical (ALT, AST, APT, γ -GT, albumin, globulins, glucose and total protein) parameters were measured (n=10 per treatment) only for the groups with the low Mn supply (T1 and T2) and the overdose groups (T5 and T6).

Table 2 gives an overview on the experimental design and summarises the zootechnical parameters.

Table 2: Tolerance study in laying hens with Mintrex[®]Mn (56 days). Zootechnical parameters*

Group	T1	T2	T3	T4	T5	T6
Mn source	Sulfate	Mintrex [®] Mn	Sulfate	Mintrex [®] Mn	Sulfate	Mintrex [®] Mn
Mn supplementation (mg/kg)	20	20	150	150	450	450
Mn analysed (mg/kg)	69	61	145	147	387	522
Cu analysed (mg/kg)	11	10	36	38	32	33
Zn analysed (mg/kg)	82	89	186	183	244	189
Daily feed intake (g)	127	126	127	127	126	127
Laying rate (%)	94.1	94.9	94.9	92.9	92.5	94.3
Daily egg mass (g/bird)	58.8	61.3	58.8	60.5	59.1	61.6
Egg mass/feed (g/g)	0.47	0.49	0.47	0.48	0.48	0.46

*: Egg weight was not listed in the table because of incorrectly reported raw data.

No health problems were observed, no mortality occurred. The hens increased their weight during the study by about 208 g. Feed intake, laying rate, and egg mass/feed ratio did not show significant differences between the treatments. Egg shell thickness was significantly increased by Mintrex[®]Mn at a maximum EU authorised level of Mn compared to equivalent Mn dose from sulfate. No treatment or dose related differences were observed in other egg quality parameters (soft shells, cracked shells, yolk colour).

The interpretation of the findings is hampered by the facts that (i) the intended Mn content in the overdose groups was not confirmed by analysis (387 and 522 in T5 and T6, respectively, instead of the intended 450 mg/kg), and (ii) the hens of the intermediate Mn groups (T3, T4) were not examined for haematology and blood biochemistry.

⁸ Technical Dossier, Annex III.1.2.

Table 3 summarises haematological and blood biochemical parameters.

Table 3: Tolerance study in laying hens with Mintrex[®] Mn (56 days). Key haematology and blood biochemistry data

Group	T1	T2	T5	T6
Mn source	Sulfate	Mintrex [®] Mn	Sulfate	Mintrex [®] Mn
Mn supplementation (mg/kg)	20	20	450	450
Mn analysed (mg/kg)	69	61	387	522
Cu analysed (mg/kg)	11	10	32	33
Zn analysed (mg/kg)	82	89	244	189
Haemoglobin (g/dL)	6.39 ^a	7.01 ^b	6.89 ^b	6.40 ^a
Heterophiles (x10 ⁹ /L)	8.86 ^c	7.01 ^b	4.35 ^a	4.72 ^a
Monocytes (x10 ⁹ /L)	0.51 ^b	0.39 ^{ab}	0.09 ^a	0.43 ^{ab}
AST (IU/L)	189 ^{ab}	249 ^b	164 ^a	182 ^a
ALT (IU/L)	3.4 ^a	4.9 ^b	5.0 ^b	3.6 ^a
APT (IU/L)	410 ^a	1100 ^c	1483 ^d	971 ^b
Serum albumin (g/L)	19.8 ^a	21.8 ^b	21.6 ^b	21.6 ^b
Serum total protein (g/L)	50.5 ^a	58.4 ^c	50.9 ^{ab}	55.2 ^b

a, b, c, d: Different superscripts in the same row indicate significant differences ($P < 0.05$)

Several significant changes were observed in haematological and biochemical parameters, however showing a lack of apparent relationship to Mn dose or source.

2.3. Tolerance study with calves for rearing

A 57-day tolerance study with different Mintrex products was carried out on a total of 60 male Holstein calves for rearing.⁹ After an 11-day pre-period the calves of an age of about 50 days (initial weight about 54 kg) were allocated to ten treatments with six calves per treatment. Common basal diets (a milk replacer fed at a restricted level (2 x 250 g/day)) and a wheat, oat, soybean meal, corn based starter) were supplemented with Mn, Zn, and Cu from sulfate or Mintrex at different levels. All diets were adjusted to the same content of the MHA as provided by 0.346 % Mintrex[®] Mn (equivalent to 450 mg Mn/kg and 0.313 % MHA feed supplement) by addition of the calcium salt of MHA.

For the purpose of the dossier provided, the applicant extracted four groups and applied a separate statistical evaluation (ANOVA) on this part of the experiment, expressing all experimental parameters as least square corrected means. The treatments were: a control feed supplemented with 40 mg Mn/kg, 30 mg Zn and 10 mg Cu as sulfates (NRC requirement levels, T1), a high Mn control group supplemented with 150 mg Mn/kg from Mintrex[®] Mn, 15 mg Cu and 150 mg Zn from sulfate (T2), a manganese sulfate overdose (T3) and a Mn from Mintrex[®] Mn overdose group (T4), both diets supplemented with 150 mg Zn and 15 mg Cu mg /kg. The contents of Zn, Cu and Mn in the final diets and the unsupplemented basal diets were analysed.

Feed intake was registered daily; body weight at days 0, 30 and 57. At the end of the trials, haematology (RBC, PCV, Hb, MCV, MCH, MCHC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets) and blood biochemistry (ALT, AST, γ -GT, total serum protein, albumin, glucose and urea) were performed.

The health status of the calves was monitored daily. Four calves of the control group (T1), one of T2, two of T3 and one of T4 were treated against respiratory disease. The health status of the calves was good throughout the experimental period, with no adverse effects being recorded in any treatment groups. The study design and the results for zootechnical parameters are given in Table 4.

⁹ Technical Dossier, Annex III.1.3.

Table 4: Tolerance study in calves for rearing with Mintrex[®]Mn (57 days)

Group	T1	T2	T3	T4
Mn source	Sulfate	Mintrex [®] Mn	Sulfate	Mintrex [®] Mn
Mn supplementation (mg/kg)	40	150	450	450
Mn analysed (mg/kg)*	43/89	166/221	497/613	414/713
Cu analysed (mg/kg)*	12/18	14/27	9/24	18/33
Zn analysed (mg/kg)*	70/89	193/204	187/228	184/222
Body weight (kg)	105.9	105.4	100.4	100.8
Body weight gain (kg/day)	0.91	0.90	0.81	0.82
Total feed intake (kg DM)**	100.9	102.8	94.5	102.7
Feed/gain (kg DM/kg BW)	1.96	2.00	2.04	2.17

* Milk replacer/starter feed; **Milk replacer plus starter feed during the whole experimental period.

Background levels: Milk replacer: 28 mg Zn, 0.8 mg Cu, 3 mg Mn; Starter: 46 mg Zn, 6.8 mg Cu, 36 mg Mn/kg

No significant differences were observed concerning the zootechnical (Table 4) haematological or biochemical parameters. However, the FEEDAP Panel notes that the study design only allows a comparison between the two Mn sources at the overdose supplementation levels of 450 mg/kg complete feed. Moreover, the statistical power of the study was low since only six animals were allocated to each treatment.

2.4. Conclusions on the safety for the target species

For compounds of trace elements already authorised, tolerance studies are not required (Regulation (EC) No 429/2008). A safety assessment of novel compounds of trace elements for target species can therefore be limited to a comparison of the effects of the novel compound with a compound of trace elements already authorised at different supplementation levels.

The three tolerance studies were not conducted in full accordance with the above Regulation. The maximum authorised Mn content in diets was exceeded in the studies with piglets and calves, and did not consider commonly accepted scientific principles required for a proper evaluation of the study variable. The following conclusions on the safety of Mintrex[®]Mn for target species must take into account these sources of uncertainties.

In piglets, some significant adverse effects of Mn were observed already at the EU maximum authorised level (150 mg/kg feed) irrespective of the source. It is concluded that piglets fed Mintrex[®]Mn show a comparable degree of intolerance as to the authorised manganese sulfate.

In laying hens, there is sufficient evidence to conclude that zootechnical parameters were unaffected by the Mn supplementation source at the maximum level authorised in the EU. No conclusions could be drawn from the haematological and biochemical parameters.

In calves, only limited conclusions can be drawn due to the limitation of the experimental design. However, there were no indications, particularly at the Mn overdose levels, to suggest that Mintrex[®]Mn is less safe for calves for rearing compared to manganese sulfate.

The FEEDAP Panel concludes that the use of Mintrex[®]Mn up to the maximum authorised Mn content in feed would not pose a greater safety concern for target species studied than the authorised manganese sulfate. Taking also into account the already assessed safety of Mintrex[®]Mn for chickens for fattening (EFSA, 2008), the FEEDAP Panel concludes that Mintrex[®]Mn is safe for all species up to the maximum total Mn content authorised in feed.

3. Safety for the consumer

3.1. Tissue/products deposition

The effect of dietary treatment on tissue Mn deposition was derived from the studies on tolerance, plus a dedicated study on Mn transfer into milk.

3.1.1. Piglets

At the end of the tolerance study (see section 2.1) six piglets per treatment T1, T2 and T3 were slaughtered. Manganese concentration in muscle, liver, kidney, skin/fat and bone was determined. The relevant data are summarised in Table 5.

The use of Mintrex[®] Mn did not result in significantly higher tissue concentration than manganese sulphate at the same dietary level (150 mg/kg).

Table 5: Manganese deposition in piglet tissues (mg/kg wet tissue) at 68 days of age (42 days of treatment with manganese sulfate or Mintrex[®] Mn)

Group	T1	T2	T3
Mn source	Sulfate	Sulfate	Mintrex [®] Mn
Mn supplementation (mg/kg)*	4/3	150/150	150/150
Analysed Mn (mg/kg)*	34/39	159/162	195/192
Muscle	0.15	0.11	0.12
Liver	2.90	2.80	3.30
Kidney	1.10	1.10	1.20
Skin/fat	0.50	0.72	0.66

* Pre-starter/starter feed

3.1.2. Laying hens

The eggs from hens fed low and intermediate Mn doses from sulfate and Mintrex[®] Mn (tolerance study with laying hens, section 2.2, groups T1, T2, T3 and T4) and collected in week 8, were examined for Mn content.

According to applicant, the limit of quantification (LOQ) of the method (ICP-OES) applied for Mn analysis in fresh egg was 0.49 mg/kg. Submitted results show that only eight eggs from a total of 40 eggs analysed had Mn concentrations \geq LOQ; two of these were found in the group supplemented with manganese sulfate and six in the group with Mintrex[®] Mn at maximum EU authorised Mn level (0.51 and 0.55 mg Mn/kg fresh egg matter, respectively). Although the Mn content appeared to be slightly higher in the supplemented groups, data obtained could not be statistically evaluated.

3.1.3. Dairy cows

A 60-day study was carried out with 40 Holstein cows divided into four groups (homogeneous in parity and days in lactation) with ten animals in each.¹⁰

The effect of the supplementing diets with Cu, Mn and Zn from Mintrex on the milk content of the element supplemented was examined in comparison to equivalent doses of inorganic sources of the same trace elements (copper sulphate, manganese oxide and zinc oxide). The different trace elements were added to complementary feed limited to 2 kg/cow/day, calculated to provide a concentration of 150 mg Zn and Mn or 35 mg Cu/kg complete feed. A partial mixed ration (PMR) was offered in addition, probably at 19 kg DM, but intake was not measured. The intake of concentrate was recorded (1.93 kg/day without differences between the treatments).

¹⁰ Technical Dossier, Annex III.1.4.

An estimation of total Mn intake is based on analysed values of the PMR and the complementary feed, on the measured intake of the complementary feed and the assumption that PMR has been quantitatively consumed. The total dietary Mn concentration was estimated to be of about 175 mg/kg complete feed DM for both groups.

Milk yield was not significantly different between the two groups (27.1 and 26.6 kg/day in the control and in the Mintrex[®]Mn group, respectively). At the end of the study, 0.018 mg Mn/kg milk was found in the control group and 0.015 mg Mn/kg milk in the Mintrex[®]Mn group (LOQ of the applied analytical method 0.004 mg/kg).

3.1.4. Conclusions on tissue/products deposition

The FEEDAP Panel concludes that use of Mintrex[®]Mn to supplement feed of piglets and dairy cows will not lead to different Mn concentrations in edible tissues from pigs and milk from cows compared to the use of authorised inorganic Mn sources (manganese sulfate and manganese oxide, respectively). Regarding Mn deposition in eggs, the FEEDAP Panel concludes that Mn content of 0.49 mg/kg egg would not be significantly exceeded by the use of Mintrex[®]Mn if the total maximum authorised level of Mn in complete feed is maintained.

3.2. Consumer exposure

Mintrex[®]Mn did not change Mn deposition in edible pig's tissue and cow's milk compared with inorganic authorised sources. The same conclusion was previously reached concerning tissues from chickens for fattening (EFSA, 2009). Concerning eggs, any differences that might have occurred below the LOQ would not have a significant impact on the overall consumer exposure, as indicated by the similar values in the groups supplemented with Mintrex[®]Mn and manganese sulfate at the maximum EU authorised level.

Therefore, the FEEDAP Panel concludes that an increased Mn exposure of the consumers due to the use of Mintrex[®]Mn is not expected.

CONCLUSIONS

Notwithstanding uncertainties due to the shortcomings of the studies, there were no indications suggesting that Mintrex[®]Mn would present additional or different concerns for tolerance of piglets, laying hens or calves as compared to the authorised manganese sulfate. Taking also into account the already assessed safety of Mintrex[®]Mn for chickens for fattening, the FEEDAP Panel concludes that Mintrex[®]Mn is safe for all species up to the maximum total manganese content authorised in feed.

Mintrex[®]Mn did not induce significant changes in manganese deposition in edible tissues and products compared with the inorganic authorised sources. Therefore, an increased manganese exposure of the consumers due to the use of Mintrex[®]Mn is not expected. The FEEDAP Panel concludes that the use of Mintrex[®]Mn up to the maximum authorised manganese content in complete feeds is safe for consumers.

DOCUMENTATION PROVIDED TO EFSA

1. Mintrex[®]Mn. All species. Supplementary information. May 2009. Submitted by NOVUS[®] Europe S.A.
2. Mintrex[®]Mn. All species. Supplementary information. September 2009. Submitted by NOVUS[®] Europe S.A.
3. Mintrex[®]Mn. All species. Supplementary information. October 2009. Submitted by NOVUS[®] Europe S.A.

REFERENCES

- EC (European Commission), 2000. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of manganese. http://ec.europa.eu/food/fs/sc/scf/out80f_en.pdf
- EFSA (European Food Safety Authority), 2008. 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. *The EFSA Journal* (2008) 692, 1-17. http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178706515725.htm
- EFSA (European Food Safety Authority), 2009. Consumer safety of a manganese chelate of hydroxyl analogue of methionine (Mintrex[®]Mn) as feed additive for chickens for fattening. *EFSA Journal* (2009); 7(9):1316. http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902905600.htm

ABBREVIATIONS

γ -GT: Gamma-Glutamyl Transferase

ALT: Alanine Transaminase

ANOVA: Analysis Of Variance

APT: Alkaline Phosphatase

AST: Aspartate Aminotransferase

Cu: Copper

EFSA: The European Food Safety Authority

Fe: Iron

FEEDAP: The Panel on Additives and Products or Substances used in Animal Feed

Hb: Haemoglobin

ICP-OES: Inductively Coupled Plasma - Optical Emission Spectrometry

LOQ: Limit Of Quantification

MCV: Mean Corpuscular Volume

MCH: Mean Corpuscular Haemoglobin

MCHC: Mean Corpuscular Haemoglobin Concentration

MHA: Hydroxy Analogue of Methionine

Mn: Manganese

NRC: National Research Council

UL: Upper intake Level

PCV: Packed Cell Volume

PMR: Partial Mixed Ration

RBC: Red Blood Cells

WBC: White Blood Cells

Zn: Zinc