SCIENTIFIC OPINION

Scientific Opinion on the safety of a copper chelate of hydroxy analogue of methionine (Mintrex®Cu) as feed additive for all species[1]

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 consider additional data provided by the applicant subsequent to its former opinion on the efficacy and safety of Mintrex®Cu for all animal species.

The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) assessed the supplementary information supplied by the applicant on the safety for the target animals and consumers.

Tolerance studies in piglets, laying hens and calves for rearing were submitted. Notwithstanding uncertainties due to the shortcomings of these studies, there were no indications suggesting that Mintrex®Cu would present additional or different concerns for tolerance of piglets, laying hens or calves as compared to the authorised copper sulfate. Taking also into account the already assessed safety of Mintrex®Cu for chickens for fattening, the FEEDAP Panel concluded that the use of Mintrex®Cu would not pose a greater safety concern for target species studied than the authorised copper sulfate. Thus, the FEEDAP Panel concluded that Mintrex®Cu is safe for all species up to the maximum copper (Cu) content authorised in feed.

Tissue/products Cu deposition data were submitted for piglets (muscle, liver, kidney, skin/fat), laying hens (eggs) and dairy cows (milk). The FEEDAP Panel retains the Cu tissue deposition in the piglets study with Mintrex®Cu for consumer exposure calculations. The use of this data is justified by (i) the high Cu content of piglet diet (170 mg/kg), and (ii) the higher supplementation of Cu in pigs over the entire production cycle compared to other animal species. Using this data as well as a model calculation based on SCOOP food consumption data, the FEEDAP Panel concluded that the use of Mintrex®Cu in all animal species would lead to an additional consumer exposure not higher than 0.5 mg/day, compared to the use of copper sulfate. This difference is almost entirely attributable to liver Cu content. The estimated increase would not lead to the UL being exceeded by consumers. Therefore,

[1] On request from the European Commission, Question No EFSA-Q-2009-00628, adopted on 12 November 2009.

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[3] Acknowledgement: The European Food Safety Authority 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.

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the FEEDAP Panel concluded that the use of Mintrex®Cu up to the maximum authorised Cu content in feed is safe for consumers.

KEY WORDS

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

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Regulation (EC) No 1831/2003[4] 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, Copper chelate of hydroxy analogue of methionine, as nutritional additive for all species.

On 16th 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®Cu (Copper chelate of hydroxy analogue of methionine) as feed additive for all species (Question No EFSA-Q-2007-097). It was concluded that Mintrex®Cu is safe for chickens for fattening. However, considering the marked differences in copper sensitivity among species, the FEEDAP Panel was unable to extend its conclusion from chickens for fattening to other animal species.

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

The Commission has now received supplementary dossier from the applicant, Novus Europe S.A., with information on this substance on the safety for the more sensitive species and data on Cu content in animal products. The data generated by the company and compiled in the above mentioned supplementary dossier have been sent directly to the Authority.[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 16th April 2008, 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-2009-0019

ASSESSMENT

1. Introduction

Mintrex®Cu is a chelate containing by weight a minimum of 15 % copper (Cu) and 78 % hydroxy analogue of methionine ((2-hydroxy-4-methylthio)butanoic acid), according to the specifications provided by the applicant. Mintrex®Cu is intended to supply Cu in final feed within EU legal limits for all species (total maximum Cu content: 25 mg/kg complete feed, except for the following: calves and ovine, 15 mg/kg complete feed; other cattle, 35 mg/kg complete feed; crustaceans, 50 mg/kg complete feed; piglets, 170 mg/kg complete feed). Currently, the Cu chelate of hydroxy analogue of methionine is authorised in the EU as a feed additive for chickens for fattening.[7]

The FEEDAP Panel previously adopted an opinion on the efficacy and safety of Mintrex®Cu 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 was unlikely to be different from that of inorganic Cu, with the reservation that such conclusion was based on limited evidence and did not include a direct assessment of Cu concentration in edible tissues.

In response to the FEEDAP Panel's opinion on Mintrex®Cu (EFSA, 2008), the applicant has supplied data to assess the safety of this product for all species and data on the transfer of Cu to edible tissues, eggs and milk. In the current opinion the FEEDAP Panel evaluated the new data submitted by the applicant, taking into account its previous opinion on Mintrex®Cu (EFSA, 2008).

2. Safety for the target animals

In its previous opinion on the same product the FEEDAP Panel stated the following: "The FEEDAP Panel notes that marked differences exist among species and even breeds regarding tolerance to dietary Cu, with avian species being amongst the most tolerant (EC, 2003a; Moeller, 2004; Thompson, 2007). Considering the maximum content of Cu approved for the most sensitive species (sheep, 15 mg/kg diet), the FEEDAP Panel cannot conclude on the safety of the compound for target animals, other than chickens for fattening." (EFSA, 2008).

In the current dossier, the applicant hasprovided 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 crossbreed (Large white male line x Landrace*Large white, sex ratio 1:1) piglets.[8] 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 Zn, Cu and Mn from sulfate and 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 supplemented) 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 Zn, Cu and Mn at NRC requirement levels (T1); a second control group supplemented with Zn, Cu and Mn from sulfate at maximum authorised levels (T2); a Mintrex®Cu group equivalent to T2, in which copper sulfate was replaced by Mintrex®Cu (T3); an overdose group supplemented with Cu (twice the level in

[7] OJ L 337, 16.12.2008, p.78
[8] Technical Dossier, Annex III.1.1.

T2) and Zn and Mn (three times the level of T2) from sulfate (T4); and a group corresponding to T4, in which copper sulfate was replaced by Mintrex®Cu (T5). The dietary content of all three elements supplemented was analysed.

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®Cu (42 days)

Group	**T1**[1]	**T2**[2]	**T3**[2]	**T4**[3]	**T5**[3]
Cu source	Sulfate	Sulfate	Mintrex®Cu	Sulfate	Mintrex®Cu
Cu supplementation (mg/kg)*	6/5	170	170	340	340
Cu analysed (mg/kg)*	15/11	149/145	169/160	319/271	345/365
Mn analysed (mg/kg)*	34/39	159/162	170/165	416/417	444/426
Zn analysed (mg/kg)*	194/119	195/180	198/173	454/398	447/444
Mortality (n out of 80)	4	3	3	6	8
Daily weight gain (g)	346[b]	346[b]	378[a]	295[c]	263[d]
Daily feed intake (g)	534[ab]	510[b]	544[a]	451[c]	416[d]
Feed/gain ratio	1.54[ab]	1.48[ab]	1.44[a]	1.54[bc]	1.59[c]
Haemoglobin (g/dl)	10.60[a]	8.15[b]	8.26[b]	7.66[b]	7.57[b]
Packed cell volume (%)	28.80[a]	23.47[b]	23.40[bc]	21.48b[c]	20.66[c]
Mean corpuscular Hb (pg)	15.3[a]	13.0[b]	12.8[bc]	11.4[cd]	10.8[d]
Plasma total protein (g/dl)	5.75[b]	5.81[b]	6.38[a]	6.36[a]	5.99[ab]
Plasma albumin (g/dl)	2.63[b]	3.03[a]	3.20[a]	3.02[a]	3.08[a]
Serum urea (mg/dl)	18.4[ab]	14.6[b]	18.2[ab]	20.6[a]	20.7[a]

* Pre-starter/starter feed

1: Supplemented also with 100/80 mg Zn and 4/3 mg Mn/kg pre-starter/starter feed from sulfates

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

3: Supplemented also with 450 mg Zn and 450 mg Mn/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 high doses of Zn and Mn in the Cu overdose groups (T4 and T5), does not allow assessing the influence of high Cu levels as the only experimental variable and particularly that of the overdosed Mintrex®Cu. The only correct comparisons that can be done 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). Feed intake was significantly lower in the Mintrex®Cu overdose group (T5) compared to the sulfate overdose group (T4), which resulted in smaller daily weight gain.

Haemoglobin and mean corpuscular haemoglobin showed the highest values in the control group (T1) (with a low supplementation level of Zn, Cu and Mn) and the lowest values in the overdose groups (T4 and T5). 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. Within the overdose groups no differences were seen between Cu from sulfate and from Mintrex®Cu.

It should be noted that the above haematological parameters declined during the study in all experimental groups.

Plasma total protein and urea showed a tendency to increase with increasing Cu levels (T2/T3 compared to T4/T5). Differences between the two Cu sources did not occur (except a significantly higher plasma protein in T3 (Mintrex®Cu) compared to T2 (copper sulfate)).

2.2. Tolerance study with laying hens

An 8-week tolerance study with different Mintrex products was carried out in a total of 392 laying hens (commercial brown Hy-Line layers, initial body weight 1940 g).[9] The hens were allocated to 14 treatments with seven replicates per treatment (four birds per replicate). A common basal diet was supplemented with Zn, Cu and Mn from sulfate and 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 supplemented) 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 Cu diets (6 mg supplemental Cu/kg either from sulfate (T1) or from Mintrex®Cu (T2)), two intermediate Cu diets (25 mg supplemental Cu/kg either from sulfate (T3) or from Mintrex®Cu (T4)), and two Cu overdose diets (75 mg supplemental Cu/kg either from sulfate (T5) or from Mintrex®Cu (T6)). The low Cu diets were also supplemented with 35 mg Zn and 25 mg Mn/kg from sulfates, the intermediate and the overdose Cu diets with 150 mg Zn and 150 mg Mn/kg. The data for the analytical contents of Zn, Cu and Mn 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, Hb, MCV, MCH, MCHC, WBC, heterophils, lymphocytes and monocytes) and blood biochemical (ALT, AST, APT, γ-GT, albumin, globulin, glucose and total protein) parameters were measured (n=10 per treatment) only for the groups with the low Cu-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®Cu (56 days). Zootechnical parameters

Group	T1	T2	T3	T4	T5	T6
Cu source	Sulfate	Mintrex®Cu	Sulfate	Mintrex®Cu	Sulfate	Mintrex®Cu
Cu supplementation (mg/kg)	6	6	25	25	75	75
Cu analysed (mg/kg)	11	11	36	37	57	95
Mn analysed (mg/kg)	69	60	145	158	172	162
Zn analysed (mg/kg)	82	79	186	185	156	199
Daily feed intake (g)	127	127	127	126	126	126
Laying rate (%)	94.1	93.4	94.9	94.4	92.7	94.1
Egg weight (g)	62.5	64.5	62.1	64.4	63.0	63.9
Daily egg mass (g/bird)	58.8	59.1	58.9	61.3	60.1	59.8
Egg mass/feed ratio	0.464	0.472	0.465	0.484	0.466	0.477

No health problems were observed, no mortality occurred. The hens increased their weight during the study by about 200 g. Feed intake, laying rate, egg weight, daily egg mass and egg mass/feed ratio did not show significant differences between the treatments. No relevant differences were observed in egg quality parameters (egg shell thickness, soft shells, cracked shells, yolk colour).

[9] Technical Dossier, Annex III.1.2.

The interpretation of the findings is hampered by the facts that (i) the intended Cu content in the overdose groups was not confirmed by analysis (57 and 95 in T5 and T6, respectively, instead of intended 75 mg/kg feed), and (ii) the hens of the intermediate Cu groups were not examined for haematology and blood biochemistry.

Haematological parameters were not affected by Cu dose or source, except WBC and heterophils, which both were decreased by the overdose of Cu in both groups, the sulfate (T5) and the Mintrex®Cu (T6). Table 3 summarises the main blood biochemical parameters.

Table 3: Tolerance study in laying hens with Mintrex®Cu (56 days). Key blood biochemical parameters

Group	T1	T2	T5	T6
Cu source	Sulfate	Mintrex®Cu	Sulfate	Mintrex®Cu
Cu supplementation (mg/kg)	6	6	75	75
Cu analysed (mg/kg)	11	11	57	95
AST (IU/L)	188.6	161.9	180.9	157.6
APT (IU/L)	410[a]	1370[b]	918[b]	706[ab]
ALT (IU/L)	3.40[a]	3.00[a]	5.10[b]	4.50[ab]
Blood glucose (mmol/L)	12.99[b]	13.03[b]	11.50[a]	12.34[ab]
Plasma total protein (g/L)	50.5[a]	54.1[ab]	59.4[c]	56.8[bc]

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

The serum enzyme AST in the Cu overdose groups (T5 and T6) was not significantly different from those of the two low Cu groups (T1 and T2), whereas ALT seemed to be elevated by Cu overdoses (mainly T5). The relevance of the significant differences observed for APT, blood glucose and plasma protein remains limited, particularly as regards to a lower tolerance of laying hens for Cu from Mintrex, showing no clear relation with Cu dose and source. Values were generally within a physiological range.

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.[10] After a 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 Zn, Cu and Mn from sulfate and 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 10 mg Cu, 30 mg Zn and 40 mg Mn/kg as sulfates (NRC requirement levels, T1), a high Cu control group supplemented with 15 mg Cu/ from Mintrex, 150 mg Zn and 150 mg Mn from sulfate (T2), a copper sulfate overdose (T3) and a Cu Mintrex overdose group (T4), both diets supplemented with 45 mg Cu, 150 mg Zn, and 150 mg Mn/kg. The contents of Zn, Cu and Mn in the 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.

[10] Technical Dossier, Annex III.1.1.

The health status of the calves was monitored daily. One calf in the copper sulfate overdose group (T3) died because of bloat. Four calves of the control group (T1), two calves of the high Mintrex®Cu group (T2) and three calves of the Mintrex®Cu overdose group (T4) were treated against respiratory disease. The study design and the results for zootechnical parameters are given in Table 4.

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

Group	T1	T2	T3	T4
Cu source	Sulfate	Mintrex®Cu	Sulfate	Mintrex®Cu
Cu supplementation (mg/kg)	10	15	45	45
Cu analysed (mg/kg)*	11.5/18.2	13.5/27.3	38.5/60.3	40.6/58.1
Mn analysed (mg/kg)*	43/89	174/229	170/247	165/248
Zn analysed (mg/kg)*	70/89	193/204	187/212	177/220
Body weight (kg)	105.9	101.8	103.2	106.9
Body weight gain (kg/day)	0.91	0.84	0.86	0.93
Total feed intake (kg DM)**	100.9	99.4	97.3	103.6
Feed : gain (kg DM/kg BW)	1.96	2.13	1.96	1.92

* 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 Cu sources at the overdose supplementation levels of 45 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.

All three tolerance studies are not conducted in full accordance with the guidelines of the above Regulation. The maximum authorised Cu content in diets was exceeded in the studies with laying hens and calves. Also these studies did not consider commonly accepted scientific principles required for a proper evaluation of the study variable. The following conclusions on the safety of Mintrex®Cu for target species must take into account these sources of uncertainties.

In piglets, although some adverse effects of Mintrex®Cu compared to copper sulfate overdose groups were observed, these were probably related to differences in the analysed Cu contents of the diets. Consequently, it is concluded that piglets fed Mintrex®Cu show a comparable degree of intolerance as the authorised copper sulfate.

In laying hens, there is evidence to conclude that zootechnical parameters are unaffected by the Cu supplementation level and source. The differences observed in haematology and blood biochemistry between Cu levels and source are considered being of limited relevance. Consequently, the response of laying hens to Mintrex®Cu was the same as that of Cu from another authorised source.

In calves, only limited conclusions can be drawn due to the limitation of the experimental design. However, there was no indication, particularly at the Cu overdose levels, which would suggest that Mintrex®Cu is any less safe for calves for rearing compared to copper sulfate.

The FEEDAP Panel concludes that the use of Mintrex®Cu up to the maximum authorised Cu content in feed would not pose a greater safety concern for target species studied than the authorised copper

sulfate. Taking also into account the already assessed safety of Mintrex®Cu for chickens for fattening (EFSA, 2008), the FEEDAP Panel concludes that Mintrex®Cu is safe for all species up to the maximum Cu content authorised in feed.

3. Safety for the consumer

3.1. Tissue/products deposition

The effect of dietary treatment on tissue Cu deposition was derived from the studies on tolerance, plus a dedicated study on Cu 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. Copper concentration in muscle, liver, kidney, skin/fat and bone was determined. The relevant data are summarised in Table 5.

The Cu concentration in liver responded to increasing Cu supplementation to feed by increased deposition of metal. Differences in Cu liver deposition between piglets given equivalent Cu doses from the authorised inorganic source (T2) and Mintrex®Cu (T3) were not significant due to small number of samples analysed (6 piglets per group) and large scatter in raw data (Cu liver of controls: SD ± 27 %, of high inorganic Cu: ± 40 %, of high Cu from Mintrex: ± 49 %); however, a clear tendency to higher Cu deposition from Mintrex compared to copper sulfate in liver of piglets was observed. The other tissues investigated did not show any difference in Cu deposition between equivalent Cu doses from copper sulfate and Mintrex®Cu. These findings are in agreement with those observed by the Scientific Committee for Animal Nutrition (EC, 2003a).

Table 5: Copper deposition in piglet tissues (mg/kg wet tissue) at 68 days of age (42 days of treatment with copper sulfate or Mintrex®Cu)

Group	T1	T2	T3
Cu source	Copper sulfate	Copper sulfate	Mintrex®Cu
Cu supplementation (mg/kg)*	6/5	170/170	170/170
Cu analysed (mg/kg)*	15/11	149/145	169/160
Muscle	0.6	0.5	0.5
Liver	6.8[a]	18.4[ab]	30.5[b]
Kidney	3.6	3.7	4.6
Skin/fat	1.1	1.4	1.4

* Pre-starter/starter feed

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

3.1.2. Laying hens

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

The limit of quantification (LOQ) of the method (ICP-OES) applied for Cu analysis in fresh eggs was given with 1.21 mg/kg. Submitted results show that only four eggs (all of them from group T1) of total 40 eggs analysed had Cu concentrations >LOQ. Consequently, data obtained could not be statistically evaluated.

For further calculations, the LOQ is taken as a presumptive highest Cu concentration in eggs without differences between sulfate and Mintrex.

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.[11]

The effect of the supplementing diets with Cu, Mn and Zn from Mintrex on the milk content of element supplemented was examined in comparison to equivalent doses of inorganic sources of the same trace elements (copper sulfate, 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).

An estimation of total Cu 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 Cu concentration was estimated to be of about 40 mg/kg complete feed DM for both groups.

Milk yield was not different between the two groups (27.1 and 27.7 kg/day in the control and in the Mintrex®Cu group, respectively). At the end of the study, 0.049 mg Cu/kg milk was found in the control group and 0.050 mg Cu/kg milk in the Mintrex®Cu group with LOQ of applied analytical method of 0.004 mg/kg.

These findings are in agreement with a study formerly assessed by the FEEDAP Panel (EFSA, 2008) showing no differences in Cu content of milk between an inorganic source of Cu and Mintrex®Cu at the level of 69 % of the maximum Cu authorised level.

3.1.4. Conclusions on tissue/products deposition

The FEEDAP Panel concludes that use of Mintrex®Cu to supplement feed up to the highest Cu content authorised would not result in increased Cu content of meat, kidney and skin/fat of piglets/pigs and of milk. Liver Cu of piglets was apparently higher in the Mintrex group compared to the copper sulfate group. The FEEDAP Panel concludes further on that 1.2 mg Cu per kg egg would not be exceeded independent from Cu source, if the maximum authorised level is maintained.

3.2. Consumer exposure

The FEEDAP Panel retains the Cu tissue deposition in the piglets study with Mintrex®Cu for consumer exposure calculations. The use of this data is justified by (i) the high Cu content of piglet diet (170 mg/kg), and (ii) the higher supplementation of Cu in pigs over the entire production cycle compared to other animal species. The FEEDAP Panel also considers that any differences that might have occurred in eggs below the LOQ would not have a significant impact on the overall consumer exposure.

Two exposure models have been used. The worst case calculation (Table 6) following Regulation (EC) No 429/2008 resulted in a daily Cu intake from food of animal origin of 2.4 and 3.7 mg, if copper sulfate and MintrexCu, respectively, are administered to feed. This difference is almost entirely attributable to the liver Cu content.

The second more realistic model calculation based on SCOOP (EC, 2004) food consumption data (Table 7) as used in earlier FEEDAP opinions (EFSA 2006a, 2006b, 2009), yielded a daily intake of 0.84 mg Cu for copper sulfate and 1.26 mg for Mintrex®Cu. Based on this data, the use of Mintrex®Cu would lead to an additional consumer exposure not higher than 0.5 mg/day.

[11] Technical Dossier, Annex III.1.4.

Table 6: Calculation of the maximum daily copper intake (mg/day) from edible tissues and/or animal products using exposure data given by Regulation (EC) No 429/2008

Tissue/Product	Cu content (mg/kg wet tissue or product)		Daily intake (g)	Cu intake (mg/day)	
	From copper sulfate	From Mintrex®Cu		From copper sulfate	From Mintrex®Cu
Muscle	0.5	0.5	300	0.15	0.15
Liver	18.4	30.5	100	1.84	3.05
Kidney	3.7	4.6	50	0.19	0.23
Fat	1.4	1.4	50	0.07	0.07
Milk	0.05	0.05	1500	0.07	0.08
Egg	1.2	1.2	100	0.12	0.12
Total exposure				2.44	3.70

Table 7: Calculation of the maximum daily copper intake (mg/day) from edible tissues and/or animal products using SCOOP food consumption data

Tissue/Product	Cu content (mg/kg wet tissue or product)		Daily intake (g)	Cu intake (mg/day)	
	From copper sulfate	From Mintrex®Cu		From copper sulfate	From Mintrex®Cu
Muscle	0.5	0.5	105	0.05	0.05
Liver	18.4	30.5	35	0.64	1.07
Kidney	3.7	4.6	3.5	0.013	0.016
Skin/fat*	1.4	1.4	50	0.07	0.07
Milk	0.05	0.05	280	0.014	0.014
Egg	1.2	1.2	36	0.04	0.04
Total exposure				0.84	1.26

*SCOOP data do not provide information on fat (mammals) or skin + fat (avian species) consumption figures Thus, the worst case figure of 50 g daily consumption is conservatively used.

The upper intake level (UL) in adults for Cu was set by the Scientific Committee on Food (SCF) (EC, 2003b) at 5 mg/day. In the same report of SCF, nutritional surveys in six European countries were cited, showing that the 97.5 % percentile intakes varied from 1.2 (The Netherlands) to 4.2 mg/day (Austria). An additional intake of 0.5 mg/day would lead to total intake not exceeding the UL.

CONCLUSIONS

Notwithstanding uncertainties due to the shortcomings of the studies, there were no indications suggesting that Mintrex®Cu would present additional or different concerns for tolerance of piglets, laying hens or calves as compared to the authorised copper sulfate. Taking also into account the already assessed safety of Mintrex®Cu for chickens for fattening, the FEEDAP Panel concludes that the use of Mintrex®Cu would not pose a greater safety concern for target species studied than the authorised copper sulfate. Thus, the FEEDAP Panel concludes that Mintrex®Cu is safe for all species up to the maximum authorised copper content authorised in feed.

Using deposition data in piglets, laying hens and dairy cows as well as a model calculation based on SCOOP food consumption data, the FEEDAP Panel concludes that the use of Mintrex®Cu in all animal species would not lead to an additional consumer exposure higher than 0.5 mg/day. This difference is almost entirely attributable to liver copper content. The estimated increase would not lead to the UL being exceeded by consumers. Therefore, the FEEDAP Panel concludes that the use of Mintrex®Cu up to the maximum authorised copper content in feed is safe for consumers.

DOCUMENTATION PROVIDED TO EFSA

1. Mintrex®Cu. All species. Supplementary information. May 2009. Submitted by NOVUS® Europe S.A.

2. Mintrex®Cu. All species. Supplementary information. September 2009. Submitted by NOVUS® Europe S.A.
3. Mintrex®Cu. All species. Supplementary information. October 2009. Submitted by NOVUS® Europe S.A.

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ABBREVIATIONS

γ-GT: Gamma-Glutamyl Transferase

ALT: Alanine Transminase

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

SCOOP: Scientific Cooperation

WBC: White Blood Cells

Zn: Zinc