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Opinion of the Scientific Panel on Additives and Products or Substances used in Animal Feed on the safety of Zeolite (sodium aluminosilicate, synthetic) for the reduction of risk of milk fever in dairy cows [1]

(Question No EFSA-Q-2006-184)

Adopted on 11 July 2007

SUMMARY

Following a request from the European Commission, the Panel on Additives and Products or Substances used in Animal Feed was asked to issue an opinion on the safety of Zeolite (sodium aluminosilicate, synthetic) when used to reduce the risk of milk fever in dairy cows.

In its former opinion on Zeolite, the FEEDAP Panel stated that Zeolite has the potential to reduce the risk of milk fever. Recent data confirm this conclusion, particularly for older cows with three or more calvings. Zeolite gradually prevents the decrease in serum calcium occurring after calving.

Although only 500 g day^{-1} Zeolite was shown to significantly reduce milk fever incidence, a dose range of 250 to 500 g day^{-1} (approximately 25 to 50 g kg^{-1} complete feed) may be realistic under field conditions.

The use of doses higher than 500 g of Zeolite leads to a dramatic depression of feed intake. Even the effective dose reduces feed intake and induces hypophosphataemia; however, these effects are considered transient. Zeolite may reduce serum Mg but this is without physiological significance. Serum levels of copper and zinc as well as milk yield and composition are not affected by Zeolite treatment.

The FEEDAP Panel concludes that (i) the observed side effects after a two-week treatment with Zeolite do not have long lasting consequences on health of dry cows, that (ii) aluminum from Zeolite does not lead to any safety concern for the dairy cow provided that the appropriate use level and duration are followed, and that (iii) Zeolite treatment of the dry cow does not result in adverse effect in calves.

Milk aluminum concentration was not affected by the use of Zeolite, but serum aluminum significantly increased. The FEEDAP Panel concludes that, considering the range of aluminum found in commercial milk samples, treatment of dry cows with Zeolite will not measurably increase consumer exposure to aluminum.

The FEEDAP Panel considers that the use of Zeolite to reduce the risk of milk fever does not pose a risk for the environment.

The FEEDAP Panel eventually gives some recommendations for the new entry on the use of Zeolite to reduce the risk of milk fever and on how this could be consequently introduced in the existing legislation on feedingstuffs for particular nutritional purposes.

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Key words: Zeolite A, sodium aluminum silicate, feedingstuffs for particular nutritional purposes, milk fever, dairy cow, safety

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BACKGROUND

Council Directive 93/74/EEC[2] establishes the rules governing the Community authorisation of feedingstuffs intended for particular nutritional purposes. The FEEDAP Panel adopted an opinion on a request from the Commission on the use of synthetic sodium aluminum silicate for the prevention of risk of milk fever in dairy cows (EFSA-Q-2003-059). The Panel could not conclude on the safety for animal and human health because of missing data. The European Commission received a supplementary dossier from the Danish Delegation. As a follow up, the European Commission asks the EFSA to issue an opinion on the safety of this product, in the light of the new information provided by the Danish Delegation.

TERMS OF REFERENCE

EFSA shall deliver an opinion on the safety for the target animals and consumer of the product Zeolite, which is a preparation of synthetic sodium aluminum silicate when used under the conditions described in Table 1.

Table 1. **Proposed Annex Entry**

Particular nutritional purpose	Essential nutritional characteristics	Species or categories of animals	Labelling declarations	Recommended length of time for use	Other provisions
Reduction of risk of milk fever	High levels of zeolite A (sodium aluminium silicate)	Dairy cows	Sodium aluminum silicate	1 to 4 weeks before calving	Indicate in the instructions for use: stop feeding after calving

[2] OJ L237, 22.09.1993, p.23

ASSESSMENT

1. Introduction

In December 2004, the Scientific Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) of the European Food Safety Authority (EFSA) adopted an opinion on the use of a synthetic sodium aluminum silicate for the reduction of risk of milk fever in dairy cows (EFSA, 2004). The Panel could not conclude on the safety for animal and human health because of missing data. The applicant has now submitted new data on efficacy and on safety for the target animal and the consumer.

2. Characterisation of the product and its influence on minerals

Zeolite A (hereafter referred to as Zeolite), a synthetic sodium aluminosilicate ($Na_{12}Al_{12}$, $Si_{12}O_{48}$ x 27 H_2O), is an authorised feed additive (E554) for all animal species and categories without maximum content. It can be used as binder, anticaking and coagulant agent.

Synthetic sodium aluminosilicate is capable of exchanging its sodium ion with calcium ions and with other cations, including heavy metals. The cation exchange capacity (CEC) expressed in terms of milliequivalents per grams, is 5.48 meq g^{-1} (for Zeolite). Based on this CEC, 1 g Zeolite could bind 0.126 g Na^+, 0.214 g K^+, 0.067 g Mg^{2+}, 0.11 g Ca^{2+}, 0.103 g NH^{4+} or 0.174 g Cu^{2+} (EFSA, 2004).

In vitro studies (EFSA 2004) showed a significant influence of pH-changes (rumen, small intestine) of the Ca, PO_4 and Mg binding capacity of Zeolite. The addition of Zeolite to the rumen fluid solution significantly reduced the amount of supernatant Ca and Mg at rumen pH, whereas the concentration of phosphorus was unchanged. After HCl addition, a large part of the Zeolite-bound Ca and Mg was released, increasing the supernatant Ca and Mg concentration.

Conversely, HCl addition led to a significant Zeolite-induced drop in supernatant phosphorus. The low level of supernatant phosphorus was maintained after HCO_{3-} addition. Additionally, the HCO_{3-} led to a Zeolite-induced drop in supernatant calcium and magnesium (Thilsing *et al.,* 2006). Binding effects should also be expected to some trace elements, but they are not described in detail.

At pH-values below 4.0, part of the Zeolite is hydrolysed and the crystal structure is partly destroyed releasing silica acid, amorphous aluminum silicates and aluminum (Cook *et al*., 1982).

3. Efficacy in reducing the risk of milk fever for dairy cows

The FEEDAP Panel concluded in 2004 that Zeolite has the potential to reduce the risk of milk fever in dairy cows, but that optimal dosage and duration of treatment are not well established (EFSA, 2004).

In a study with 30 non-lactating cows, Zeolite was given at 250 and 500 g d^{-1} for 14 days. Since neither the control group nor the experimental groups experienced parturient hypocalcaemia, the FEEDAP Panel could not conclude on efficacy (optimal dosage) from these data.[3]

Data of a large scale field study involving 22 dairy herds has been submitted.[4] Zeolite at 250 and 500 g per cow day^{-1}, for approximately two weeks before calving, was tested against the unsupplemented control group in two different runs (ten cows per group in each herd). In the first run, 500 g Zeolite day^{-1} (13 herds) significantly reduced the incidence of milk fever, when

[3] Technical Dossier/ Enclosure 2
[4] Technical Dossier/ Enclosure 3

compared with a control group, from 26 % (34 out of 129 cows) to 4 % (5 out of 130 cows). In the second run (nine herds), when 250 g Zeolite day^{-1} were given to the treated animals, five out of 90 animals showed true signs of milk fever. However, the incidence of milk fever in the untreated group (9 out of 90) was already rather low. This reduction of milk fever incidence from 10 % to 6 % was not statistically significant.

Feed intake was not determined; therefore, quantitative figures of Zeolite intake cannot be given. Great differences on palatability where recorded between the herds, which became more evident at the 500 g dose compared to the 250 g dose.

Grabherr *et al.* (2006) fed 46 dry Holstein cows a total mixed ration (TMR) containing 0 or 100 g Zeolite kg^{-1} DM. Zeolite reduced the 14 days precalving feed intake by about 50 % (from 11.3 to 5.6 kg DM). Zeolite (560 g Zeolite day^{-1}) significantly stabilised serum calcium at calving but reduced phosporus and magnesium concentration. These effects disappeared within one week after parturition.

In a second experiment of the same research group (Grabherr *et al*., 2007), a dose response to Zeolite was studied on 80 pregnant dry Holstein cows. TMR was supplemented with 0, 12, 24, and 46 g Zeolite kg^{-1}, DM resulting in daily DM consumption of 9.7, 10.4, 9.1, and 7.0 kg for the two weeks before calving, respectively, corresponding to a daily Zeolite intake of 0, 132, 227, and 329 g. The study confirms in principle the results on serum electrolytes of the previous experiment; however, the effects on stabilising serum calcium were more pronounced and reached significance in cows around or over the third lactation.

The FEEDAP Panel concludes that a daily dose of 500 g Zeolite given for two weeks prior to calving (and until calving) is effective in reducing the risk of milk fever.

4. Safety for dairy cows

The FEEDAP Panel concluded in 2004, that the risk of Zeolite for the health of dairy cows could not be fully assessed because of insufficient data on the influence of Zeolite on magnesium and bioavailability of trace elements (e.g. Mn, Zn, Cu, etc.).

Results obtained by Thilsing[5] and Pallesen[6] in unpublished studies showed that Zeolite (500 g day^{-1}) treatment of cows did not significantly affect plasma Mg, Cu and Zn concentration, and that additional Mg supplementation is not necessary.

When administering Zeolite to dairy cows, there is a dose-dependent depression of the feed intake (Grabherr *et al.,* 2006, 2007; Goff, 2006). From the data of Grabherr *et al*., it can roughly be estimated that Zeolite supplementation to a complete diet reduces feed intake at an intended daily dose of 500 g by about 25 % and at 250 g by about 10 %. Higher doses than 500 g result in a more dramatic reduction of feed intake, putting the required nutrient supply of dairy cows in question.

A hypophosphatemia was observed during Zeolite supplementation in treated cows. Hypophosphatemia is known to have an influence on feed intake, but the observed depression of feed intake during Zeolite treatment cannot be strictly related to hypophosphatemia. Nevertheless, those effects are considered transient. Feed intake will return to normal within about three days and serum iP after approximately one week.

Zeolite supplementation did not have any negative impact on milk yield of lactating cows or on the plasma electrolyte concentration of calves born from Zeolite treated cows.

[5] Technical Dossier/ Enclosure 5
[6] Technical Dossier/ Enclosure 6

Zeolite was considered for many years not to be absorbed in the gut. However, more recent findings indicate that absorption does occur, albeit in very small amounts. Sodium aluminosilicate may be partly hydrolysed in the digestive tract, mainly in the abomasum (because of the low pH value) resulting in release of Al and silicate ions. Intestinal absorption of Al from intestinal tract is very low (about 0.1 %) and many organic dietary components influence this process. However, Thilsing[7] reported, in an unpublished study, an increase of Al serum level from 13 µg L^{-1} before treatment to 85 µg L^{-1} during a three-week administration of 600 g Zeolite day^{-1}. Aluminum is efficiently excreted via the kidneys.

The FEEDAP Panel concludes that the observed side effects seen after a two-week treatment with Zeolite do not have long lasting consequences on the health of cows. Zeolite treatment of the dry cow did not show any adverse effect in calves. The FEEDAP Panel also concludes that aluminum from Zeolite does not lead to any safety concern for the dairy cow regarding the appropriate use level and duration.

5. Safety for the consumer

Aluminum is the only element in Zeolite of potential safety concern. Al is also a component of soil, especially clay soils, and it also appears in water. It was considered non-toxic and its excretion from organism in the urine is very efficient. However, the previously accepted view on the lack of Al toxicity is being questioned. The Joint FAO/WHO Expert Committee on food Additives (JECFA, 2006) withdrew the previous provisory tolerable weekly intake (PTWI) and proposed a lower one for Al of 1 mg/kg^{-1} bw, because aluminum was concluded to have the potential to affect the reproductive and developing nervous system at doses lower than those used in establishing the previous PTWI (7 mg Al kg^{-1} bw). The Committee noted that the PTWI is likely to be exceeded to a large extent by some population groups, particularly children. Aluminum was also recognised as potentially neurotoxic for humans and animals. It was shown that it inhibited the activity of acetylcholinesterase in brain (Moraes and Leite, 1994) and caused increased free radical effects (El-Demerdash, 2004).

Humans are frequently exposed to aluminum. The food supply comes from natural sources, water used in food preparation, food ingredients, and utensils used during food preparations. The amount of aluminum in the diet is small, compared with the amount of aluminum in antiacids and some buffered analgesics.

Zeolite (500 g day^{-1}) did not influence milk composition (milk fat, milk protein, milk somatic cell count or lactose). The data submitted for Al milk levels (from ten cows each treated before calving with 0, 250 and 500 g Zeolite daily, respectively) did not show significant differences (about one week and two weeks after parturition). The lowest measured mean concentration was 1.5 µg L^{-1} milk (control group, 14 days after parturition), the highest 5.6 µg L^{-1} (250 g Zeolite, one week after calving). The standard deviation in all groups was high; the 500 g Zeolite group showed about one week after parturition a mean value of 4.4 µg L^{-1}, individual values varying from 0 to 30 µg L^{-1}. Concentrations in colostrum may have been considerably higher.[8]

Arruda *et al.* (1994) found a range of 5 to 50 µg Al L^{-1} in commercial milk samples. Fernandez-Lorenzo *et al.* (1999) found even higher mean values (70 µg Al L^{-1}). Despite the differences in the values submitted by the applicant and others published, the FEEDAP Panel accepts the conclusion of the applicant, that pre-calving treatment of cows with Zeolite (up to 500 g for two weeks) does not affect significantly the aluminum content of milk.

Aluminum, when absorbed (< 1 %), is quickly cleared via the kidneys and mainly deposited in the bone. A significant deposition in edible tissues is considered unlikely. The time between

[7] Technical Dossier/ Enclosure 5
[8] Technical Dossier/ Enclosure 2

treatment and potential consumption of meat from treated dairy cows offers an additional margin of safety.

All values measured after Zeolite treatment remained in the range found for aluminum concentrations in commercial milk samples. The FEEDAP Panel does therefore not consider that the use of Zeolite in preventing the risk of milk fever poses an additional risk to the consumer.

6. Safety for the environment

Aluminium silicates are clay minerals which occur naturally in the environment. It is not expected that the spreading of manure from treated animals will significantly alter the concentration of aluminum silicate in agricultural soil. Consequently, the FEEDAP Panel considers that the use of Zeolite to reduce the risk of milk fever does not pose a risk for the environment.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

In its former opinion on Zeolite, the FEEDAP Panel stated that this product has the potential to reduce the risk of milk fever. Recent data confirm this conclusion, particularly for older cows with three or more calvings. Zeolite gradually prevents the decrease in serum calcium occurring after calving.

Although only 500 g day^{-1} Zeolite was shown to significantly reduce milk fever incidence, a dose range of 250 to 500 g day^{-1} (approximately 25 to 50 g kg^{-1} complete feed) may be realistic under field conditions.

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The FEEDAP Panel concludes that (i) the observed side effects after a two-week treatment with Zeolite do not have long lasting consequences on the health of cows, that (ii) aluminum from Zeolite does not lead to any safety concern for the dairy cow provided the appropriate use level and duration are followed, and that (iii) Zeolite treatment of the dry cow does not result in adverse effect in calves.

Milk aluminum concentration was not affected by the use of Zeolite but serum aluminum significantly increased. The FEEDAP Panel concludes that, considering the range of aluminum found in commercial milk samples, the treatment of dry cows with Zeolite will not measurably increase consumer exposure to aluminum.

The FEEDAP Panel considers the use of Zeolite to reduce the risk of milk fever does not pose a risk for the environment.

RECOMMENDATIONS

The FEEDAP Panel recommends modifying as follows the proposal of the applicant for the introduction of a new entry to the list in Directive 94/39/EC[9] concerning the prevention of the risk of milk fever:

Column 2: Substitute the text 'high levels of Zeolite A (sodium aluminium silicate) by: 'Reducing the bioavailability of calcium.'

Column 4: The FEEDAP Panel considers it desirable that the amount of the additive incorporated is labelled. The labelling proposed (sodium aluminum silicate) is not sufficiently informative.

Column 5: The recommended duration of use should be restricted to a maximum of two weeks considering particularly the depression of feed intake resulting from the use of 500 g sodium aluminosilicate, synthetic, daily.

Column 6: Under instructions for use, the amount of feed should be restricted (by figures) to ensure that a daily intake of 500 g sodium aluminosilicate, synthetic, is not exceeded.

Synthetic sodium aluminosilicate is already authorised as feed additive for all animal species without maximum content in feed. The FEEDAP Panel has no data on the use of Zeolite as binder,

[9] OJ L207, 10.08.1994, p.20

anticaking and coagulant additive, any in depth assessment of potential consumer health consequences (based on a current exposure assessment) should consider all uses of aluminum silicates in animal feeding.

DOCUMENTATION PROVIDED TO EFSA

1. Technical Dossier on Zeolite for dairy cows. November 2006. Submitted by the Danish Delegation
2. Supplementary information. April 2007. Submitted by the Danish delegation.

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SCIENTIFIC PANEL MEMBERS

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