Opinion of the Scientific Panel on Additives and Products or Substances used in Animal Feed on the safety of feedingstuffs with high calcium content for the reduction of risk of milk fever in dairy cows¹

(Question No EFSA-Q-2007-017)

Adopted on 12 June 2007

SUMMARY

Milk fever (also called parturient paresis or parturient hypocalcemia) is one of the production diseases which primarily occur among older high yielding dairy cows during the period around calving. The increased demand for calcium (Ca) at parturition due to the onset of lactation may result in a Ca deficiency potentially provoking the outbreak of milk fever in dairy cows.

The FEEDAP Panel concludes that oral Ca treatment around parturition can be very effective in treating mild cases of hypocalcemia and in preventing relapses in dairy cattle. The first administration of Ca should be at signs of parturition and then should be limited to two days after parturition (a total of three days). Marginal risk of this complementary feed use cannot be completely excluded, but the individual risk should be balanced against the overall benefits of treatment.

Due to the strong hormonally regulated homeostasis of plasma Ca, an increase of plasma Ca above the physiological range is not expected in the cow. Thus the Ca in edible tissues and milk will not be affected. Therefore, the FEEDAP Panel does not expect any risk for the consumer.

In relation to the total yearly intake of Ca, the effect of the administration of additional Ca for the prevention of the risk of milk fever is considered negligible and not to pose any additional risk for the environment.

The FEEDAP Panel recommends modifying the proposed regulation for the introduction of a new principle in Directive 94/39/EC concerning the prevention of the risk of milk fever.

Key words: feedingstuffs for particular nutritional purpose, milk fever, nutritional characteristics, calcium, dairy cows

¹ For citation purposes: Opinion of the Scientific Panel on Additives and Products or Substances used in Animal Feed on a request from the European Commission on the safety of feedingstuffs with high calcium content for the reduction of risk of milk fever in dairy cows, The EFSA Journal (2007), 504, 1-10
BACKGROUND

The Swedish delegation submitted a dossier to modify Council Directive 93/74/EEC\(^2\) that establishes the rules governing the Community authorisation of feedingstuffs intended for particular nutritional purposes. The reduction of the risk of milk fever in dairy cows is a particular nutritional purpose already included in the Annex to Directive 93/74/EEC and Directive 94/39/EC,\(^3\) respectively. The Member State proposes a modification to the Annex entry. The European Commission asks EFSA to issue an opinion on the safety of use of feedingstuffs with high calcium for the reduction of milk fever in dairy cows.

TERMS OF REFERENCE

EFSA shall deliver an opinion on the safety for the target species, the consumer and the environment of the use of feedingstuffs with high calcium for the reduction of milk fever in dairy cows when used under the conditions described in Table 1.

\(^2\) OJ L237, 22.09.1993, p.23
\(^3\) OJ L207, 10.08.1994, p.20
<table>
<thead>
<tr>
<th>Particular nutritional purpose</th>
<th>Essential nutritional characteristics</th>
<th>Species or categories of animals</th>
<th>Labelling declarations</th>
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<tr>
<td>Reduction of risk of milk fever</td>
<td>High levels of calcium</td>
<td>Dairy cows</td>
<td>The total content of calcium and the specific name of the calcium compounds such as inorganic and/or organic salts of calcium should be labelled</td>
<td>Application/s of calcium should be given within one day before calving at sign(s) of calving and before any clinical signs of paresis/milk fever. Application/s of calcium should also be given up to two days post calving</td>
<td>Indicate on the package, container or label: -The instructions of use i.e. the number of applications and the time before and after calving. -The text “It is recommended that a veterinarian’s opinion be sought before use.”</td>
</tr>
</tbody>
</table>
Opinion on feedingstuffs with high calcium content for dairy cow

ASSESSMENT

1. Introduction

Milk fever (also called parturient paresis or parturient hypocalcemia) is one of the production diseases which primarily occur among older high-yielding dairy cows during the period around calving. The increased demand for calcium (Ca) at parturition due to the onset of lactation may result in a Ca deficiency situation potentially provoking the outbreak of milk fever in dairy cows. Milk fever usually occurs within 72 hrs after parturition. In cows suffering milk fever, three stages of this disease are generally recognized.

Stage I – Without typical symptoms (often unobserved, duration around one hour). Signs observed: lack of appetite, excitability, nervousness, hypersensitivity, weakness, weight shifting and shuffling of the hind feet. Cow exhibits movement in-coordination, muscle trembling and quivering.

Stage II – Lasting 1 to 12 h. Cows are unable to stand but can maintain sternal recumbency. The affected animal appears dull and listless. The digestive tract is inactive, heart rate increases very often over 100 bpm and body temperature is decreased.

Stage III – Progressive loss of consciousness (finally coma) is observed. Further increase of heart rate can approach 120 bpm and the body temperature decreases. Untreated cows may die within 12 h of onset of the first clinical signs.

During the dry period (no lactation), the demand for Ca for maintenance and foetus growth is very limited (< 30 g day⁻¹) (GfE, 2001, NRC, 2001), and the Ca content of a typical dry cow ration contains substantially more Ca than this demand (≈ 30 g Ca day⁻¹). As a result, the animal reacts by reducing the Ca gastrointestinal absorption rate. This amount of dietary Ca will not stimulate the parathyroid glands adequately and will not effectively prevent milk fever. The excretion of hormones responsible for active Ca transport from gut and mobilisation of Ca from bone (parathyroid hormone, 1,25-Dihydroxy-Vitamin D) occurs therefore at a minimum extent during this period. The onset of lactation around calving demands large amounts of Ca from the blood to the mammary gland. Therefore the blood Ca decreases dramatically. If the Ca concentration falls below 1.8 mMol L⁻¹, some cows may express symptoms of milk fever. In general, low plasma Ca concentration (< 2 mMol L⁻¹) has consequences for many nerve and muscle functions (Horst et al., 1994). An additional 48 g Ca should be fed to meet the Ca demand for 20 L milk d⁻¹ containing 24 g Ca.

Milk fever is an economically important disease due to milk secretion that can reduce the productive live of a dairy cow (Horst et al., 1997). Milk fever incidence has remained steady in some countries at about ten per cent (Fleischer et al., 2001, Rehage, 2002). Milk fever affects about six percent of dairy cows in the United States each year, according to the 1996 National Animal Health Monitoring Survey. If left untreated, about 60 to 70 % of the affected cows may die (McDowell, 2003). Hypocalcemia has also some widespread effects that predispose to other periparturient diseases such as mastitis, ketosis, displaced abomasum and retained placenta (Curtis et al., 1983; Fleischer et al., 2001). Even successful treatment of hypocalcemia does not eliminate further complications associated with milk fever, which results in further economic losses. This stresses the demand for an effective prevention.

There are some factors which influence incidence and severity of milk fever. These are: age (older cows are more sensitive than younger), milk yield (cows with higher yield are more predisposed than cows with lower yield) (Fleischer et al., 2001; Rehage and Kaske, 2004; Taylor et al., 2001), breed, body condition, length of dry period and diet composition (for
more details see reviews by Horst et al., 1994, 1997; Houe et al., 2001; McDowell, 2003; Underwood and Suttle, 1999).

Any prevention of milk fever is directed to minimise the decrease in plasma Ca concentration and consequently cover the actual Ca demand. This can only be achieved by stimulation of bone Ca release and/or by oral administration.

The following nutritional strategies based on these principles have been developed:

1. Low Ca supply by feedingstuffs provided low amounts of Ca or reduced availability of dietary Ca during the last weeks of the dry period of cows (two to four weeks before calving):
   - Low dietary Ca (< 20 g day⁻¹) administered and low Ca/P proportion,
   - High dietary phosphorus,
   - Supplementation of feed with feed materials or additives capable of binding Ca in the intestinal tract and reducing its absorption (e.g. zeolite) (EFSA, 2004).

   This nutritional characteristic is the only one introduced so far by Directive 94/39/EC.

2. Acidification of dry diet or less alkaline milieu for higher Ca release from the bone (improved efficiency of parathyroid hormone) during the last weeks of the dry period of cows (two to four weeks before calving):
   - Reduction of dietary potassium (and sodium),
   - Adjustment of the Cation-Anion-Balance (DCAB) by addition of acidifying salts (e.g., MgSO₄, MgCl₂, NH₄Cl₂, (NH₄)₂SO₄, CaCl₂, CaSO₄).

3. Administration of easily available Ca during the period close to calving:
   - Oral Ca drenching with a supplement of easily absorbable Ca to overcome the blood Ca decrease

4. Activation of Ca absorption/mobilisation during the period close to calving:
   - Oral or parenteral administration of either high levels of vitamin D₃ or trace amounts of Vitamin D metabolites (e.g., 25-OH-D₃, 1,25 (OH)₂-D₃)

The applicant requested the introduction of oral Ca drenching of dairy cows around parturition as a nutritional characteristic for feedingstuffs for particular nutritional purposes, by amendment of Directive 94/39/EC. The applicant submitted limited data on different feedingstuffs formulations commercially available consisting of various Ca sources.

The FEEDAP Panel therefore makes a general assessment of the safety of oral Ca drenching of dairy cows as a measure to reduce the risk of milk fever in dairy cows.

2. Efficacy and safety

Oral Ca supplementation around calving is a common and effective practice in the reduction of hypocalcemia and milk fever prophylaxis in dairy cows, but carries a slight risk of inducing aspiration pneumonia.

Feeding easily soluble Ca salts as complementary feed in the dry period around parturition is easy to handle for the dairy man. An inclusion of additional 40-50 g of Ca to the complete diet is difficult to handle without changing the herd management. In fact the first administration of such a feedingstuff for particular nutritional purpose should be given a day before calving, at signs of parturition, and the subsequent two doses within the first two days after parturition (before any clinical symptoms of milk fever/paresis). However, it is difficult to predict and to monitor the calving date with sufficient accuracy.
In Europe, different forms of complementary feed are commercially available, mainly boluses (Ca salts covered by a protective layer of fat in solid form) and paste (Ca salts dissolved in water, propylene glycol or oil).

The concept of feeding easily soluble Ca salts was developed in 1970 (Jönnson and Pehrson, 1970). Jönnson and Pehrson advised three or four oral doses of 36 or 54 g of Ca in form of Ca chloride (dispersed in hydroxyethyl cellulose to prevent eventual aspiration, and water ± 450 ml) administered, respectively, one day before expecting calving, at calving and optionally one day later. This treatment has however the disadvantage that the solution is strongly acidic, which causes digestive tract irritation (focal reactions at the intestinal wall, caustic burns of the digestive tract mucosa); the unpleasant taste is also very difficult to mask. It was shown by Wentink and van den Ingh (1992) that oral administration of CaCl₂-containing products caused minor to severe damage to the mucosa of the fore stomach and abomasums. The gel solution especially proved to be highly caustic, while the oil emulsion appeared to be safer.

Aspiration of the product can provoke pneumonia (Pehrson and Jönnson, 1990; Mathieu and Pelletier, 1966); gel forms of CaCl₂ may reduce the risk of aspiration compared to aqueous solutions.

Mathieu and Pelletier (1966) studied the tolerance of dry or lactating cows to Ca chloride in water (0.3 %) as the only source of drinking water during 75 days. No major changes in appetite, body weight or milk production were noticed. In cows receiving 58-72 g Ca daily, only slight signs of gastro-intestinal irritation were observed, apart from an increased water daily intake (ca 20 %) and urine acidification (pH ± 5.8).

Also in dry cows which were given, within 21 days, 80 g Ca daily in form of chloride (22 g), phosphate (12 g) and carbonate (46 g) no adverse effect was stated (Kurosaki et al., 2007). The daily dose should not exceed 288 g Ca chloride to avoid induction of severe metabolic acidosis. However, slight acidosis as that observed after administration of 75 g Ca from Ca chloride may be considered as beneficial because of its stimulating effect on Ca release from bone (Goff and Horst, 1994).

From the late 1980’s, different formulations of oral Ca boluses are available on the market (e.g. Ca chloride and Ca sulphate) for which no adverse effect have been reported (Pehrson and Jönnson, 1990), despite some cases of pharyngeal perforation connected mainly with the application method of Ca boluses (Braun et al., 2004).

More recently, Ca formate has been introduced in the prevention of milk fever with the argument that this form should be less irritant than Ca chloride, but this was not confirmed in all studies of the same authors (Scott and Vijk, 2000, 2002).

Goff and Horst (1993) compared oral administration of different Ca salts concerning plasma Ca changes. CaCl₂ increased plasma Ca more than Ca propionate, which was more efficient than Ca carbonate. CaCl₂ gel also proved to be more efficient than Ca carbonate, but not as much as Ca propionate. Oral administration of 50 g Ca as CaCl₂ raised plasma concentration to the same extent as 4 g Ca given intravenously in form of CaCl₂. The authors conclude that it is unlikely that oral Ca treatment could successfully prevent all milk fever cases; however, oral Ca treatment may be very effective in treating mild cases of hypocalcemia and in preventing relapses. Agger (2003) noticed that in cows treated with 50 g of Ca in form of CaCl₂ one day before and two doses of 25 g Ca (Ca propionate) within one day after parturition, milk fever appearance was reduced from 44% (control group) to 19.4 % in animals suffering from the sub-clinical form of disease, and from 21.9 to 3.1 % in cows showing the clinical form. Thilsing-Hansen et al. (2002) evaluated results of 13 studies on Ca supplementation around the parturition period. These showed a reduction of milk fever incidence caused by different Ca treatment of cows oscillating from 30 to 86 % (experimental versus control animals).
2.1. Conclusion on efficacy and safety for the target animal

Oral Ca treatment around parturition can be very effective in treating mild cases of hypocalcemia and in preventing relapses in dairy cattle. The first administration of Ca should be at signs of parturition and then should be limited to two days after parturition (a total of three days).

To avoid irritation of mucosal membranes, the amount of CaCl₂ should be restricted to 10% of total 40-50 g Ca. Based on data from literature, the other Ca salts should be mainly in organic form. The composition of Ca-rich complementary feedingstuffs (in water solutions) supposedly have a certain acidifying property, which is considered beneficial as it will positively adjust DCAB. Encapsulation, the use of oily emulsion or other forms of pharmaceutical formulations can reduce the risk of irritations of the gastro-intestinal tract. When such formulations result in a reduction of CaCl₂ side effects, the content of CaCl₂, which is the most effective Ca salt, in such a complementary feedingstuff for particular nutritional purpose might be increased.

Marginal risk of this complementary feed use cannot be completely excluded, but the individual risk should be balanced against the overall benefits of treatment. Decisions should be taken by the dairy herd manager though it is recommended that the advice of a nutritional expert be sought before use.

3. Safety for the consumer

Due to the strong hormonally regulated homeostasis of plasma Ca, an increase of plasma Ca above the physiological range is not expected in the cow. Thus the Ca in edible tissues and milk will not be affected.

Therefore the FEEDAP Panel does not expect any risk for the consumer.

4. Safety for the environment

A dairy cow in full lactation (30-40 L day⁻¹) will consume about 95-120 g Ca day⁻¹ to cover the requirement (milk and maintenance). For 300 days lactation with a milk yield of 7500 L, about 25 kg Ca will be consumed. The additional Ca supplied by feeding a Ca-rich complementary feedingstuff in order to reduce the risk of milk fever may amount to a total of 150 g. The extra supply by the Ca-rich feedingstuff amounts to 0.6 % of the 300 days intake only.

In relation to the total yearly intake of Ca, the effect of the administration of additional Ca for the prevention of the risk of milk fever is considered negligible and not to pose any additional risk for the environment.

CONCLUSIONS

Oral Ca treatment around parturition can be very effective in treating mild cases of hypocalcemia and in preventing relapses in dairy cattle. The first administration of Ca should be at signs of parturition and then should be limited to two days after parturition (a total of three days).

Marginal risk of this complementary feed use cannot be completely excluded, but the individual risk should be balanced against the overall benefits of treatment.

Due to the strong hormonally regulated homeostasis of plasma Ca, an increase of plasma Ca above the physiological range is not expected in the cow. Thus the Ca in edible tissues and milk will not be affected. Therefore, the FEEDAP Panel does not expect any risk for the consumer.
In relation to the total yearly intake of Ca, the effect of the administration of additional Ca for the prevention of the risk of milk fever is considered negligible and not to pose any additional risk for the environment.

**RECOMMENDATIONS**

The FEEDAP Panel recommends modifying as follows the proposed regulation for the introduction of a new principle in Directive 94/39/EC concerning the prevention of the risk of milk fever:

Column 2 (essential nutritional characteristics)
Substitute the proposed text ‘high levels of calcium’ by: High calcium and highly available calcium salts.

Column 4 (labelling declarations)
Substitute the proposed text ‘the total content of calcium and the specific name of the calcium compounds such as inorganic and/or organic salts of calcium’ by: Total calcium content, source and quantity of calcium.

Column 5 (recommended length of time for use)
Substitute the proposed text ‘Application/s of calcium should be given within one day before calving at sign(s) of calving and before any clinical signs of paresis/milk fever. Application/s of calcium should also be given up to two days post calving’ by: Oral treatment should start at first signs of parturition and be limited to two days subsequent to parturition.

Column 6 (other provisions)
Substitute the proposed text ‘It is recommended that a veterinarian’s opinion be sought before use’ by: The advice of a nutrition expert shall be sought before use.

**DOCUMENTATION PROVIDED TO EFSA**


**REFERENCES**


EFSA 2004. Opinion of the Scientific Panel on Additives and Products or Substances used in Animal Feed on the request from the Commission on the use of synthetic sodium aluminium silicate (zeolite) for the reduction of risk of milk fever in dairy cows. The EFSA Journal, 160, 1-11

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