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

(Question N° EFSA-Q-2003-150)

Adopted on 8 December 2004

SUMMARY

Milk fever is a hypocalcaemic paresis (disorder of nerve and muscle function) at parturition, caused by the sudden and large demand of calcium from blood due to the onset of lactation. Milk fever, more frequent in older cows with high milk yields, is an economically important disease of dairy cows. If left untreated, about 60 to 70% of such cows die. Surviving cows show reduced milk yield and productive life time.

Most dietary prevention principles of milk fever are directed to the homeostatic regulation of blood calcium and its efficacy, respectively. Low dietary calcium in the prepartum period is seen as one of these preventative dietary regimes. The decrease of availability of feed calcium by adding calcium binding substances may be seen as a further development of the low dietary calcium principle. The crystalline clay mineral zeolite (sodium aluminium silicate) may act as such a calcium binder exchanging its sodium ion with calcium ions and/or other cations.

Zeolite is approved as an anti-caking and anti-coagulant feed additive (Directive 70/524/EC) for all species or categories of animals, for all feedingstuffs. Synthetic sodium aluminium silicate is also used as food additive (E 554).

The present submission requests the use of Zeolite A, a synthetic sodium aluminium silicate with a high cation-exchange-capacity. Its use is proposed at 500-1000 g per day to pregnant dairy cows during the last 2-4 weeks before parturition, subsequently reduced to 500 g for 2 weeks, as calcium binder for the particular nutritional propose of reducing the risk of milk fever in dairy cows. The European Commission asked the European Food Safety Authority to evaluate the effects of these zeolite concentrations on human or animals health or on the environment.

Seven experiments comprising a total of 148 calvings were carried out under a variety of farm conditions. Emphasis was given on the zeolite dose (500-1000 g day^{-1}), the duration of application (14 or 28 days before expected calving), on the mineral content of the daily ration offered and the effects on Ca, Mg and P blood concentration. No attention was given to animal nutrition details (feed intake etc.) and milk composition.

In nearly all experiments zeolite A supplementation increased the mean serum calcium concentration on the day of calving. Inorganic phosphate and magnesium concentration in blood was lower than in control cows around calving. No information was provided on trace element concentrations.

Zeolite A has the potential to reduce the risk of milk fever in dairy cows, but optimal dosage and duration of treatment are not well established. The FEEDAP Panel is aware of the short term intended use of zeolite, but needs to know also the potential longer term consequences (3 months) in the view of animal health and welfare.

The risk for the health of the dairy cow can not be fully assessed because there is insufficient data on magnesium supply and bioavailability of trace elements in treated cows.

No data are given on the potential influence of a zeolite treatment on composition and quality of milk, including the possibility that aluminium content in milk may be increased by release from zeolite at pH < 4.0.

No detrimental effects of zeolite on the environment is expected.

Key words: Milk fever, periparturient paresis, dairy cow, calcium binder, zeolite, clay, sodium aluminium silicate, feedingstuffs intended for particular nutritional purposes

BACKGROUND

The Danish delegation submitted a dossier prepared by the Department of Clinical Studies of the Royal Veterinary and Agricultural University of Copenhagen, to modify Directive 93/74/EEC on feedingstuffs intended for particular nutritional purposes.

The *"reduction of the risk of milk fever"* is a particular nutritional purpose already included in the annex of Directive 93/74/EEC. In this dossier the applicant proposes another way to achieve the same objective already specified in the above-referred Directive.

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 aluminium silicate	1 to 4 weeks before calving	Indicate in the instructions for use: stop feeding after calving

Zeolite is added to the feed and is capable of binding calcium to bring the daily amount of available calcium from feed below 20 g. This allows to reduce the risk of milk fever in dairy cows.

Zeolite is authorised by Directive 70/524/EEC as binding agent to be used for all species or categories of animals, for all feedstuffs and without a time limit.

Authorisation of zeolite under Directive 70/524/EC.

EC N°	Element	Chemical formula description	Species or categories of animal	Maximum age	Minimum content	Maximum content	Other provisions	Period of authorisation
E 552	Calcium silicate, synthetic	Maximum content:[1]	All species or categories of animals	-	-	-	All feedingstuffs	Without a time limit

[1] In the absence of the establishment, if required, of a specific limit based on sufficient data on the presence of dioxins , the maximum limit of 500 pg WHO-PCCD/F-TEQ/kg will apply from 15 October 2000.

TERMS OF REFERENCE

Due to the high daily intake of zeolite recommended by the applicant (daily intake of 500-1000 g of zeolite to pregnant dairy cows during the last 2-4 weeks of dry period), does zeolite, when used at the levels recommended, have detrimental effect on human or animal health or on the environment?

ASSESSMENT

1. Introduction

The onset of lactation places such a large demand on the calcium homeostatic mechanisms that most cows develop some degree of hypocalcaemia at calving; (Horst *et al.* 1994). In some cases plasma calcium concentrations become too low to support nerve and muscle function, resulting in parturient paresis (commonly called milk fever).

Milk fever is an economically important disease due to milk losses and can reduce the productive life of a dairy cow (Horst *et al.* 1997). Despite much research, milk fever incidence has remained steady in some countries at about 10%. If left untreated, about 60 to 70% of such cows die (Mc Dowell 2003). Hypocalcaemia has also some widespread effects on the cow that predispose the cow to other periparturient diseases as mastitis, ketosis, dystocia, displaced abomasum, and retained placenta (Curtis *et al*., 1983).

Factors known to predispose cows to milk fever are age (older cows are more predisposed than younger), milk yield (cows with higher yield are more predisposed than cows with lower yield), breed, body condition, length of dry period and diet (for reviews see Horst *et al.* 1994, 1997, Houe *et al.* 2001, Mc Dowell 2003).

To prevent decrease in blood calcium, the cow must replace calcium lost to milk by increasing the absorption of dietary calcium and by mobilising calcium from the bone. Principally two hormones act in maintaining blood calcium. Bone calcium mobilization is regulated by the parathyroid hormone (PTH), which also stimulates the formation of 1,25-dihydroxyvitamin D_3 (Dihydroxycholecalciferol) in the kidney increasing calcium absorption. If blood calcium drops down, both hormones are released and blood calcium increases.

The cow in the dry period has a rather low calcium requirement, so that these mechanisms are not adjusted to the high requirement which suddenly starts with milk production at calving. In addition, ruminant diets are often excessively high in potassium which in turn results in an alkaline blood pH. But PTH acts only poorly on bone and kidney tissues when the blood pH is high.

Milk fever prevention has been subject of intensive research during the last 50 years. Most prevention principles of milk fever consider the homeostatic regulation of blood calcium to minimize the unavoidable fall of blood calcium during parturition. The dietary principles are thought to prepare the calcium homeostatic mechanisms for the later higher requirement by reducing the calcium (and other cations) supply:

- Low dietary calcium (<20 g day^{-1}) administered and low Ca/P proportion in the last weeks of pregnancy
- High dietary phosphorus administered in the last weeks of dry period
- Decrease of availability of feed calcium by supplementing the feed with substances capable of binding calcium in the intestinal tract.

In contrast to the above described feeding schedules, treatments as

- Oral calcium drenching around calving with a supplement of easily absorbed calcium, and
- Oral or parenteral dosing of high levels of vitamin D_3 or metabolic active cholecalciferols (25-OH-D_3, 1,25 $(OH)_2D_3$)

are directed to an immediate filling of the blood calcium compartment from oral uptake or by bone mobilization.

Other prevention principles are based on the provision of a better (less alkaline) milieu for the efficacy of PTH by:

- Reduction of dietary potassium (K) (and sodium (Na))
- Acidification of ration by acid salts for an adjustment of the Dietary Cation-Anion-Balance (DCAB) during the last weeks of pregnancy.

All the methods have some advantages and disadvantages (see various references for summaries, e.g. Horst *et al.* 1997, Houe *et al.* 2001, Mc Dowell 2003, Pehrson *et al.* 1998, Thilsing-Hansen *et al.* 2002b).

It is believed that feeding the cow less calcium during 10 to 14 days before calving, followed by a diet ensuring sufficient calcium supply around calving and in early lactation (or oral calcium drenching) may prevent milk fever. Low calcium diets stimulate calcium homeostatic mechanisms before parturition. This allows the cow to absorb calcium more efficiently in the lactation period and also draws on bone calcium stores immediately after calving. Unfortunately it is extremely difficult to formulate low calcium diets from commonly used feedstuffs. This is the main reason why the principle of low calcium diets before calving is not successful and has not been widely used (e.g. Goff *et al.* 1987, Mc Dowell 2003).

Another attempt to limit the calcium supply is the reduction of dietary calcium availability in the gastrointestinal tract by oral administration of calcium antagonists like zinc oxide (Smidt *et al.* 1984) or calcium binders like silicon-aluminium compounds as zeolite (e.g. Enemark *et al.* 2003, Thilsing-Hansen and Jorgensen 2001, Thilsing-Hansen *et al.* 2002a, 2003).

The subject of the present dossier is the synthetic Zeolite A (sodium aluminium silicate) composed of hydrogen, oxygen, aluminium and silicon. Documentation provided on this product is listed under the Annex.

2. Characterization of the product

Zeolite A is a crystalline clay mineral [$(Na_{12}\,Al_{12}\,Si_{12}\,O_{48}) \times 27\ H_2O$] available in an industrially produced (synthetic) pure form or as natural zeolite originating from open mines. Sodium aluminium silicate is capable of exchanging its sodium ion with calcium ions and with other ions including heavy metals.

Synthetic sodium aluminium silicate is used as a food additive (E 554), but may also be used in feedingstuffs as filler, as anti-caking and anti-coagulant feed additive (Com. 97/6/EU).

According to the producer, the calcium binding capacity of the zeolite is $\geq$286 mg Ca g^{-1} of zeolite (anhydrous basis) at pH 11 corresponding to $\geq$ 115 mg Ca g^{-1} zeolite under feeding conditions. As the water content of zeolite is typically around 20% the Ca binding capacity decreases to 92 mg Ca g^{-1} zeolite. Using CEC (cation exchange capacity) expressed in terms of milliequivalents per grams (meq g^{-1}) makes it easy to compare how much of any cation can be exchanged. For synthetic Zeolite A 5.48 meq g^{-1} are given. Under consideration of the CEC of Zeolite A (5.48 meq g^{-1}) the following amounts (g of various ions) are taken up by one gram of zeolite: Na^+: 0.126; K^+:0.214; Mg^{2+}: 0.067; Ca^{2+}: 0.11; NH_4^+: 0.103; Cu^{2+}: 0.174.

In vitro studies showed a significant influence of pH-changes (rumen, small intestine) of the Ca-, PO_4- and Mg-binding capacity of Zeolite A. The addition of Zeolite A 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.

On the other hand 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.

3. Effects on animal health

Seven experiments comprising a total of 148 calvings (Control: 70; Exp.: 78 cows, Tables 1 and 2) were carried out with the focus on the effect of Zeolite A under a variety of farm conditions. Emphasis was given on the dose of zeolite used (500 - 1000 g day^{-1}), the duration of application (14-28 days), on the main mineral content of the daily rations offered and the effects on Ca, Mg and P blood concentrations.

3.1. Feed intake

Animal nutrition details (feed intake etc.), body weight changes, milk composition and milk yield were not subjects of examination in six experiments. Feed refusals were only measured in experiment 7 (Table 2) showing that more experimental cows refused larger feed amounts. No details are given on feed or energy intake, but the factor feed intake is very important for the effectiveness of zeolite concerning the prevention of milk fever.

3.2. Influence on calcium (Ca)

The Zeolite A supplementation increased in nearly all experiments the mean serum Ca level on the day of calving (Table 1). 39 of 54 control cows and only 19 of 63 Zeolite A cows showed hypocalcaemia (<2.0 mmol Ca L^{-1} serum). No effect between control and experimental animals was observed in experiment 5 (Table 1). From the results it seems, that zeolite-calcium ratios below 5 did not effectively prevent parturient hypocalcaemia, whereas ratios of 10 to 20 proved very efficient in preventing hypocalcaemia. There was apparently no additional effect from feeding zeolite for 28 instead of 14 days prepartum.

Based on this data the authors of the response to EFSA and to UK recommended that a zeolite/Ca ratio in the range of 10-12 g zeolite g^{-1} Ca. Furthermore they recommended a supplementation of 500 g sodium aluminium silicate, or up to 5% of ration dry matter per dry cow per day from 2 weeks before expected calving and until actual calving.

Table 1. Experimental design and results of six experiments
(Response to Member States, Encl. B, see Annex)

Farm	A	A	B	B	C	C
Experiment No.	1	2	3	4	5	6
Control group (n)	8	4	4	11	18	9
Treated cows (n)	9	6	4	14	17	13
Zeolite (g day^{-1})[1]	1000	500	500	500	500	700
Days on Zeolite[1]	28	28	28	14	14	14
Calcium intake (g day^{-1})[1]	38-45	38-45	63-81	81	91	34
Phosphorus intake (g day^{-1})[1]	23-28	23-28	46-66	66	59	39
Magnesium intake (g day^{-1})[1]	13-16	13-16	52-55	52	120	19
Zeolite/calcium ratio	26-22	14-11	8-6	6	5	20
Zeolite/magnesium ratio	67	33	9	10	n.g.	n.g.
Serum Ca <2.0 mmol L^{-1} on the day of calving						
Control group (n/n)	5/8	4/4	3/4	6/11	14/18	7/9
Treated group (n/n)	0/9	0/6	1/4	3/14	13/17	2/13
Serum P (mmol L^{-1}) on the day of calving						
Control group	0.86	0.86	n.d.	n.d.	n.g	n.g
Treated group	0.99	0.81	n.d.	n.d.	n.g.	n.g.
Serum Mg (mmol L^{-1}) on the day of calving						
Control group	1.26	1.08	1.23	1.14	n.g.	n.g.
Treated group	0.91	0.84	0.86	0.93	n.g.	n.g.

[1]Intended experimental values
n.g. = not given n.d. = not determined

3.3. Influence on phosphate

In some studies (Table 2, Annex) mean plasma inorganic phosphate of Zeolite A supplemented cows was below the lower limit of the reference interval (1.8-2.1 mmol P L^{-1} plasma, Kaneko *et al.* 1997) and was lower than values of unsupplemented control cows one week before calving as well as around calving. One week after calving, the phosphate level of experimental cows increased to within the reference interval (Table 2).

Pond and Mumpton (1984) found also a lower plasma phosphate concentration in lambs fed sodium aluminium-silicate than in controls and suggested a reduced bioavailability of phosphate due to formation of insoluble aluminium phosphate complexes in the intestinal lumen. An activation of the calcium homeostatic mechanisms during the zeolite supplementation could lead to a higher level of circulating parathyroid hormone (PTH) and thereby an increased salivary and renal excretion of phosphorus.

Table 2. **Feed refusals and selected blood parameters** (Experiment 7)

Parameter	Control	Treated	P
Number of animals	16	15	
Zeolite A (Pellets with 50% Zeolite A, g d^{-1} for 14 days)	-	700	
Major element content of TMR (g d^{-1})			
Calcium	66		
Phosphorus	33		
Magnesium	19		
Mean parity after calving	4.2	3.9	
Feed refusal, day 14-day 8			
Number of cows,	1	7	
% of feed	3	9	
Feed refusal, day 7-day 4			
Number of cows	3	9	
% of feed	2	16	
Feed refusal, day 3 -day 1			
Number of cows	1	10	
% of feed	5	20	
Plasma-Ca (mmol L^{-1})			
at calving	2.05	2.35	
7 days post partum	2.30	2.55	
Plasma-inorganic P (mmol L^{-1})			
at calving	1.1	0.65	< 0.05
7 days post partum	1.6	2.1	
Plasma-Mg (mmol L^{-1})			
at calving	1.07	0.91	< 0.05
7 days post partum	0.88	0.99	
Serum 1,25 $(OH)_2$ D (pg mL^{-1})	43.7	64.7	< 0.05

TMR= Total Mixed Ration

3.4. Influence on magnesium (Mg)

As shown in Table 1, in four experiments in which blood was analysed for Mg this parameter remind within the reference concentration for blood Mg (>0.75 mmol L^{-1}). Differences in blood Mg between unsupplemented and Zeolite A supplemented cows were observed at calving. Similar results were observed in experiment 7 (Table 2). It can not be excluded that Zeolite A supplementation can increase the risk of hypomagnesaemia in Mg deficient cows.

3.5. Influence on trace elements and other substances

No information is given on absorption and serum concentration of trace elements especially bivalent cations (Cu^{2+}, Zn^{2+}, Mn^{2+} etc.) with a high binding capacity to zeolite.

At pH values below 4.0 part of the zeolite is hydrolysed (information from Degussa-Hüls, Germany) and the crystal structure is partially destroyed releasing silica acid, amorphous aluminium silicates and aluminium (Cook *et al.* 1982). Soluble aluminium may exert toxic effects (Allen 1984, Mc Dowell 2003), not by absorption, but by interfering with the utilization of several minerals being phosphorus absorption and metabolism most affected. More research seems to be necessary to phosphorus metabolisms (addition of phosphorus etc.). Although aluminium is generally low in toxicity (Mc Dowell 2003, Underwood and Suttle 1999) any other effects of aluminium released from the zeolite (transfer to milk etc.) should be investigated in future experiments.

There exist only few data on the influence of Zeolite A on further metabolic parameters. After daily application of 700 g Zeolite A per cow for the last two weeks of pregnancy serum 1,25-$(OH)_2$-D_3 was significantly increased from 43.7 pg mL^{-1} (control) to 64.7 pg mL^{-1} ($P \leq 0.05$, Table 2) probably as a consequence of the presumed calcium binding effect of zeolite.

4. Effects on the milk and human health

No information is given on the influence of Zeolite A on composition and quality of milk. In one paper by Thilsing-Hansen *et al.* (2002a) there was a tendency to a slightly lower milk fat yield among the zeolite-treated cows after 105 days of lactation.

As replied by the applicants to EFSA questions, effects of zeolite on milk composition and quality were not given a high priority.

Although important influence of Zeolite A on milk composition and quality should not be expected further studies seems to be necessary to investigate both parameters especially the aluminium content of milk.

5. Effects on the environment

Since aluminosilicates are clay minerals which occur naturally in the environment, no detrimental effects are expected following the use of Zeolite A to prevent milk fever. Above all, it is not expected that spreading of manure from treated animals will significantly alter the concentration of aluminosilicates in agricultural soils.

CONCLUSIONS

Zeolite A has the potential to reduce the risk of milk fever in dairy cows, but optimal dosage and duration of treatment are not well established. The FEEDAP Panel is aware of the short term intended use of zeolite, but needs to know also the potential longer term consequences (3 months) in the view of animal health and welfare.

The risk for the health of the dairy cow can not be fully assessed because there is insufficient data on magnesium supply and bioavailability of trace elements in treated cows.

No data are given on the potential influence of a zeolite treatment on composition and quality of milk, including the possibility that aluminium content in milk may be increased by release from zeolite at pH < 4.0.

A detrimental effect of zeolite on the environment is not expected.

DOCUMENTATION PROVIDED TO EFSA (SEE ANNEX)

1. Dossier supporting a proposal for change of Commission Directive 94/39/EC including a short overview and eight enclosures prepared by The Royal Veterinary and Agricultural University, Copenhagen, and submitted by Denmark.
2. Answer of the Danish delegation to questions of the EU member states (summary and two enclosures, February 2003)
3. Reply by the applicant (February 2004): Response to the complementary information request of 26 November 2003 from including answers to the questions of the FEEDAP-Panel given by Dr. J. Jorgensen from the Royal Veterinary and Agricultural University and 11 enclosures.
4. Reply to questions from the French expert group (December 4, 2003) and to questions from UK and Germany by the Notifier (June 29, 2004).
5. Comments on parnuts dossier (reduction of risk of milk fever) from UK (September 2004)
6. Reply from the Danish Cattle Production Medicine Research Group to Germany (dated October 27 2004) and to UK (dated October 27 2004).

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ANNEX . Information submitted by the Notifier

Source	Kind of document (authors)	Publication	No of cows (control/ treated)	Zeolite (g d^{-1}) (duration, days)	Content/results
Original dossier					
Enclosure 1	Review on milk fever (MF) (Hone *et al.*)	Acta vet. Scand. 2001;42: 1-29			Incidence, reasons and effects of milk fever
Enclosure 2	Review on MF control (Thilsing-Hansen *et al.*)	Manuscript, Unpublished, 28 p.			Evalutation of principles in prevention of milk fever
Enclosure 3	Zeolites	Unpublished, 1 p.			Zeolite description
Enclosure 4	Zeolite and blood Ca (Jørgensen *et al.*)	J. Dairy Sci. 2001; 84: 609-613	(5/5)	500 (2.5)	Small decrease of serum-Ca (P=0.1) Ca homeostatic mechanisms.
Enclosure 5	Zeolite in dry period (Thilsing-Hansen and Jorgensen)	J. Dairy Sci. 2001; 84:691-693	(8/8)	1000 (28)	MF in 3 control, 0 treated cows; Serum Ca below 2 mmol L^{-1}: 8 control, 0 treated
Enclosure 6	3 figures in serum Ca	Unpublished			Zeolite: higher blood Ca
Enclosure 7	Se and Zn status In calves, review	Unpublished, 19 p (in Danish)			S- and Zn deficiency description
Enclosure 8	2 figures on blood Mg and phosphorus	Unpublished	31	700	Zeolite: lower blood Mg and PO_4, see enclosure 1
Answers to questions of Member States (5.02.03) Summary					Side effects from potential binding of other ions by Zeolite, reduced appetite, transient hypo-phosphataemia and -magnesaemia, but no consequences on cow health; not risk for consumer
Enclosure A (also encl. E in response to EFSA)	Zeolite: effect on Ca, P and Mg homeostasis (Thilsing-Hansen *et al.*)	J. Dairy Sci. 2002; 85:1855-1862	(16/15)	700 (14)	Reduced feed intake and subsequent milk production; at calving higher plasma Ca and lower plasma P and Mg; Increase in serum 1,25-$(OH)_2$-D_3
Enclosure B	Zeolite: peripartal blood mineral status (Thilsing-Hansen *et al.*)	Unpublished, 24 p.	(54/83) 6 studies	500-1000 (14-28)	Higher plasma Ca, but lower plasma Mg and PO_4; no differences between 2 and 4 weeks application; dietary zeolite/Ca ratio <5 inefficient, > 10-20 highly efficient

Answer to questions of EFSA (November 2003) **Summary**					Answers to 7 EFSA questions, some suggestions for further studies and product development: • Studies in calves of zeolite supplemented cows • Metabolic studies in cows including Ca, P, Mg, Zn, Se, Cu, Al • Dose-response studies, Mg effects • Improved palatability of Zeolite A • Addition of other nutrients to Zeolite A
Enclosure A	Cation-Exchange Capacity (CEC)	Unpublished, 4 p. Prepared by F.A. Mumpton	-	-	$Na_{12}(Al_{12}Si_{12}O_{48})$x 27 H_2O, Synth. Zeolite A 5.48 meq/g
Enclosure B	Chem. Composition of synth. Zeolite A, Safety data	Unpublished 3 and 4 p.			
Enclosure C	Oral drenching with ZnO and Zeolite A on blood Ca of cows (Jørgensen *et al.*)	J. Dairy Sci. 84, 2001, 605-613			Repetition to Dossier 1, Encl. 4
Enclosure D	Zeolite A in dry period of dairy cows (Thilsing-Hansen and Jørgensen)	J. Dairy Sci. 84, 2001, 691-693			Repetition to Dossier 1, Encl. 5
Enclosure E	Effect of Zeolite A on Ca, P and Mg homeostasis (Thilsing-Hansen et al.)	J. Dairy Sci. 85, 2002, 1855-1862			Repetition to answers to questions of member states, Encl. A
Enclosure F	Effect of Zeolite A on blood mineral status around calving (Thilsing-Hansen *et al.*)	Acta vet. Scand. 97, 2003, 87-95			Repetition to answers to questions of member states, Encl. B
Enclosure G	Physiological effects of Zeolite A in cows fed grass silage (Enemark *et al.*)	Acta Vet. Scand. 97, 2003, 97-117	(4/4)	1000 (7)	Slight decrease in serum Ca and renal Ca-excretion in Zeolite A group, increment after Zeolite withdraw
Enclosure H	Effect of Zeolite A on renal Ca-excretion	Acta vet. Scand. 97, 2003, 119-136	(5/5)	800 (14)	No effect on urine pH; renal Ca-excretion peaked at the first day of

	(Enemark *et al.*)				supplementation, it decreased steadily to pre-exposure level
Enclosure I	Effect of Zeolite A on milk production and digestion (Roussel *et al.*)	J. Dairy Sci. 71, 1988, 946-953	(4/4)	2% zeolite (~400 g/day)	DMI: 20.7/18.7 kg/day 4% FCM: 25.6/23.6 kg/day Fat yield: 0.93/0.86 kg/day Protein yield: 0.95/0.85 kg/day Decrease of digestibility of DM, OM and crude protein
Enclosure J	*In vitro* binding capacity (Ca, P, Mg) of Zeolite A (Thilsing *et al.*)	Unpublished, 14 p.	-	Adequate to 600 g in 80 kg digesta	*In vitro* study with rumen fluid solutions (varying in Ca and/or P content, without or with Zeolite A) Zeolite A reduced supernatant Ca and Mg at rumen pH, not P. HCl addition increased supernatant Ca and Mg level, decreased P. Physiological consequences of Mg and P binding have to be evaluated in *in vivo* experiments
Enclosure K	*In vitro* study on the effect of Mg supplementation with or without Zeolite A	Unpublished (Abstract) 3 p.	-	-	Zeolite A supplementation showed a slow decrease in supernatant Mg
Reply to questions from the French expert group **(4.12. 2003)**	4 questions	Answers: 2 pages	SUMMARY Questions concerning the amount of sodium to be liberated from zeolite, feed consumption during zeolite supplementation, incompatibility between DCAD and zeolite and legal matters. Answers give no substantial new information		
Reply to questions from UK and Germany (29.6.2004)	7 questions	Answers: 2 pages -	SUMMARY Questions of intended effect, side effects, misuse, recommended dose, legal matters, effect and efficiency. Answers contain some new aspects: Side effects: Effects seems to be possible, but commercial producers must take responsibilities for their products Recommended dose: 500 g Zeolite A per cow per day or up to 5% of DM from 2 weeks before expected calving and until actual calving		