EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C2 - Management of scientific committees II; scientific co-operation and networks

Revision of the report of 22 March 2001 of the Scientific Committee on Animal Nutrition on the use of potassium diformate (Formi™ LHS) as feed additive

(adopted on 18 June 2002)

1. BACKGROUND

The Commission received a request for authorisation of product Formi™ LHS as feed additive in accordance with Council Directive 70/524/EEC. The Scientific Committee was requested to issue an opinion on the efficacy and the safety of that product, based on the data provided in the dossiers established by the Company Norsk Hydro.

The Scientific Committee on Animal Nutrition (SCAN) adopted its report on the use of potassium diformate (Formi™ LHS) as feed additive on 22 March 2001.

After reviewing the data provided by the company, the SCAN concluded that potassium diformate, when used at the dose of 1.8% to 2.0%, improves the growth performance of piglets, although it could not be stated whether the effect was based on changes observed in the gastrointestinal microflora. Regarding the lower dosage proposed for piglets (0.6%) and those proposed for the growing/finishing pigs, although there is a tendency for improved growth response, no sufficient statistically significant efficacy data have been presented.

Regarding the way of administration, the Committee underlined that, when administered with wet feed, Formi™ LHS is unstable, if water or sweet whey are used. If feed is administered in a water suspension or with non-acid whey with an almost neutral pH level, potassium diformate breaks down into formate and potassium ions. Under such conditions, pigs are no longer receiving the Formi™ LHS as an additive, but rather a mixture of formic acid, formate and potassium.

Concerning the safety of animals, on the basis of the data available, SCAN concluded that the product appears to be safe at the level of 0.6% for both animal categories (piglets and pigs for fattening). However, in order to fully demonstrate the safety of animals at the highest proposed level of the dose ranges, additional studies would be necessary.

For piglets, a tolerance test based on the highest dose recommended by the company would be needed. For pigs for fattening, experimental data on the increased water consumption and its origin at the highest level of use (1.2%) recommended by the Company should be provided.

The only detectable residue of potassium diformate in animal products is formate, and the levels in tissues in finishing pigs fed at the lowest recommended dose level

(0.6%) do not present a toxicological concern. There is however no sufficient information on the residue levels resulting from the higher dosages (1.2% for pigs for fattening, 1.8% for piglets), although the limited data available from the tolerance study suggest that the residues remain at a relatively low level.

Following this opinion, the Company submitted supplementary dossiers as listed under **3**.

Now the Company has amended its claim to cover other target animal categories. The product is used as a growth promoter. The proposed inclusion rate in feed is:

- 0.6% to 1.8% for piglets until 2 months of age
- 0.6% to 1.2 % for growing/finishing pigs until slaughter

2. TERMS OF REFERENCE

The Scientific Committee for Animal Nutrition is requested to evaluate the supplementary dossiers provided by the Company (list under **3**) and to advise the Commission on that basis on:

- the stability of the product when presented in liquid form
- the safety of the product for the different target animal categories, as claimed above.
- the safety for the consumer of the product when used at the above mentioned claimed levels

3. THE DATA PROVIDED BY THE COMPANY

- Letter of 17 May 2001 - Chemical behaviour of Potassium diformate in water solutions referenced under SCAN number SCAN 01-115

- Supplementary dossier n°12 of June 2001, including appendix A-C - Reply to the comments made by SCAN

- Supplementary dossier n° 13 of September 2001 - Final reply to the comments made by SCAN of 8 February 2001

4. OPINION OF THE COMMITTEE

4.1. Stability of the product when present in liquid form

The company investigated the chemical behaviour of potassium diformate solution in the laboratory by simply recording the pH-value of the solution when diluted and neutralised (titration curves). Potassium diformate is dissociated after the following equilibrium reactions in aqueous solutions:

$HCOOH\text{-}HCOOK \leftrightarrow HCOOH + HCOOK$ K_1

$HCOOH \leftrightarrow HCOO^- + H^+$ K_2

$HCOOK \leftrightarrow HCOO^- + K^+$ (totally dissociated)

Equilibrium constant $K_1 = C_{HCOOH} + C_{HCOOK} / C_{HCOOH} - {}_{HCOOK}$

$$K_2 = C_{HCOO^-} + C_{H^+} / C_{HCOOH}$$

The ratios between potassium diformate, formic acid and formate depend on the initial potassium diformate concentration as shown in Table 1.

By mapping pH as a function of dilution and titration it is possible to estimate the buffer effect of the diformate system (equation 1) and calculate the concentration profile for diformate, formic acid and formate as function of its dilution in water (Table 1). The calculations indicate that below pH 4 and diformate concentrations higher than 0.1 wt % in water the equilibrium in equation 1 is in favour of diformate. By further dilution to concentrations of 0.001% at pH-values between 4 and 5 most of the diformate is dissociated to formic acid. By further dilution and increased pH above 5, the concentrations of formic acid and diformate are decreasing so only formate is left when pH 7 is reached.

Table 1: Internal ratios of diformate, formic acid and formate as well as pH in dependence on diformate concentration

Initial diformate concentration (wt%)	Share as (in %)			
	Diformate	Formic acid	Formate	pH in solution
0.0000019	0.38	0.17	99.45	6.8
0.000019	2.51	1.29	96.20	5.8
0.00019	8.88	9.01	82.11	4.9
0.0019	11.33	27.09	61.58	4.3
0.01	19.43	33.77	46.80	4.0
0.1	93.18	2.92	3.90	3.7
1.0	99.16	0.29	0.45	3.7
5.0	99.79	0.06	0.10	3.7
10.0	99.89	0.03	0.05	3.7
20.0	99.96	0.01	0.02	3.85
30.0	99.94	0.03	0.03	3.9
40.0	99.98	0.01	0.01	4.05
50.0	99.99	0.005	0.005	4.25
60.0	100.00	0	0	4.45

Data in Table 1 suggest that potassium diformate dissociates in solution and that no dissociation is expected in dry feed.

Results do not allow drawing conclusions for dissociation of potassium diformate in different sections of the digestive tract because of different influencing factors (e.g. pH, concentration of diformate, absorption of substances, buffering substances in chymus.

4.2. Safety of potassium diformate (FORMI LHS)

4.2.1. Tolerance study on piglets

Design of the study

A four-week tolerance study in 30-33 day old weaned piglets was carried out. The dietary treatments consist of a control diet and four test diets

containing 1.8; 3.6; 5.4 and 7.2% Formi^{TM} LHS. Ten times of the highest recommended level of 1.8% Formi^{TM} LHS (18%!) could not be reached because of reduction in feed intake. In preliminary experiments up to 10% Formi^{TM} LHS were added to diets, the pigs refused to eat the feed.

A total of 40 piglets (8 per group; initial body weight: 11.4 kg) were used to investigate the effect of increasing levels of Formi^{TM} LHS in diets on growth performance and water intake (Table 2). All pigs were slaughtered at the end of the 4-week experimental period. Feeds were not removed before slaughter.

Blood samples were taken from all the animals before the commencement of the Formi^{TM} LHS administration and on the day of necropsy. The parameters that were measured were haemoglobin, red blood cell count, white blood cell count, differential leucocyte count, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase (AP), total bilirubin, urea, creatinine, glucose, sodium, potassium, calcium, chloride, and total serum protein.

A routine macroscopic examination of the carcasses and the internal organs was conducted during the necropsy. In particular, stomach alterations were recorded. These alterations were evaluated using the following scale of 0 to 9 : 1 – 3 hyperkeratosis, 4 – 6 erosive alterations, and 7 – 9 ulcerative alterations. Samples of any gross lesions in internal organs were taken for histopathological analysis. Residue analysis from muscle (neck region), skin, fat, liver, kidneys, lungs, and spleen were conducted with 24 piglets receiving 0, 1.8 (highest recommended level) and 7.2% Formi^{TM} LHS (4 times highest level) in the diet.

Results

Up to 7.2% Formi^{TM} LHS in the diets of piglets had no significantly ($p>0.05$) negative effects on general health status and growing performance of piglets (Table 2).

There were no significant differences in water consumption or water:feed ratio between the control piglets and those fed the highest recommended level of Formi^{TM} LHS of 1.8% (Table 2). At higher levels (3.6, 5.4 and 7.2%) there was a significant dose-response effect.

Table 2: Effects of increasing dietary level of Formi™ LHS on performance, water intake, some blood parameters and stomach alterations (n=8)

Formi™ LHS level (%)	0	1.8	3.6	5.4	7.2
Performance (28 days)					
Feed intake (g per day)	758	807	802	740	680
Weight gain (g per day)	532	608	583	556	525
Feed/gain (g/g)	1.42	1.32	1.37	1.33	1.29
Water intake					
Daily water intake (g, day 5-26)	2031[a]	2274[ab]	2554[bc]	2813[c]	2686[bc]
Water intake/feed intake (g/g)	2.19[a]	2.59[ab]	2.92[b]	3.51[c]	3.73[c]
Blood parameters					
Electrolyte concentration (mmol/l serum, day 26)					
• Sodium	151[ab]	153[a]	151[ab]	154[a]	149[b]
• Potassium	2.6[ab]	2.7[a]	2.7[a]	2.7[a]	2.5[b]
• Urea	2.9	3.5	3.2	2.7	2.9
• Glucose	6.4	6.9	7.0	7.0	6.9
Red blood cells count ($x10^{12}$/l)	5.6[a]	5.7[a]	6.3[a]	6.2[a]	3.5[b]
White blood cells count ($x10^{9}$/l)	15.7	14.3	17.5	16.3	10.0
Haemoglobin (g/l)	100[a]	105[a]	111[a]	109[a]	64[b]
Stomach alterations					
Average scores	2.1	2.0	2.2	2.2	3.1

[a, b, c] Average with different superscript letters within a row are significantly different ($p<0.05$)

There were no significant differences in the serum values of urea, glucose, creatinine, bilirubin, or in the ALAT, ASAT or AP activities between the dietary groups. The range of total serum values in the final day samples was between 4.7 (in the dietary group of 5.4% Formi™ LHS) and 4.0 $g.l^{-1}$ (the 7.2 % group) while the value in the control group was 4.5 $g.l^{-1}$. Thus, although some of the differences in the protein values were statistically significant between the dietary groups, the differences were small, there were no dose related effects nor were the values outside the normal range (see Table 2 for some values).

Haematologically, the 7.2% Formi™ LHS group differed from the rest (Table 2). Both the red blood cell count and haemoglobin values were significantly ($P<0.001$) lower than in the other dietary groups or controls. The actual average haemoglobin values and blood cell counts (3.5×10^{12} cells l^{-1} and 64 g l^{-1}, respectively) in this group were also lower than the values considered normal for pigs. In the 7.2% group there was also a tendency to a lower total white blood cell count ($p <0.07$), while the counts of basophilic lymphocytes were higher ($p<0.05$) than in other groups and controls.

The average scores of stomach alterations in the controls and in the 1.8, 3.6, 5.4 and 7.2 % Formi™ LHS-groups were 2.1, 2.0, 2.2, 2.2, and 3.1,

respectively (Table 2). No treatment related pathological lesions were observed.

4.2.2. The water intake in fattening pigs

Design of the study

A trial was conducted to measure the effect of the inclusion of 1.2 % Formi^{TM} LHS in the feed on the water consumption of growing–finishing pigs. The test group consisted of 12 pigs with an average initial weight of 47 kg. The study was performed using a double cross-over design. Two experimental diets supplemented with either 1.2% maize starch or 1.2 % Formi^{TM} LHS were tested in four experimental periods, each two weeks' period consisting of one week of adaptation and one week of observations. Each treatment block consisted of two animals, each in an individual cage. In the beginning of each experimental one of the animals in each block was receiving the control feed and the other the experimental feed. At the end of the period, the feeds were switched, and another period started.

During the study, body weight, daily weight gain, feed intake and feed conversion rate were measured. During the observation period the water consumption was followed daily by weighing the water left in the 20 l water tank connected to the nipple system of each cage (during week-ends this measurement was done only once). Urine was collected during the two final experimental periods (finisher phase, 72 – 97 kg).

Temperature and humidity were automatically recorded during the whole study period. For the most of the experimental period the temperature was 25 °C or more (however always below 30 °C).

Results

No statistically significant differences in performance parameters were observed during the study. There was a tendency to increased water consumption during the administration of Formi^{TM} LHS in feed. When the results were pooled, the average intake was 5.35 l water per day for control compared with 6.26 l water per day for pigs supplemented with 1.2% Formi^{TM} LHS. The increase in water intake tended to be significant ($p=0.075$).

Urine excretion of animals fed Formi^{TM} LHS was increased, the average daily amounts being 3.37 kg for the controls and 4.34 kg for the treated animals. The increase was not statistically significant ($p>0.05$).

The potassium content of Formi^{TM} LHS (30%) and consequently the higher potassium intake can explain the higher water intake observed. Addition of 1.8% Formi^{TM} LHS increases the potassium content of diet by ~5.4 g per kg feed. Normally the potassium content of pig diets varies between 5 and 15 g per kg diet. Excess of potassium intake will to a large extent be absorbed by the pigs and excreted in the urine (Mc Dowell, 1992). Pigs can tolerate 25 to 30 g potassium per kg feed if plenty of drinking water is provided (Farries, 1958). This implies higher water consumption in order to maintain a

constant osmolality of the urine. Kidney weights are not given in the new dossiers.

The higher urine excretion is unlikely to increase the nitrogen load, but it may be of importance for the storage of slurry.

4.2.3. Safety for the consumer

The formate concentration in edible tissue (Table 3) was generally low. Similar values were measured in edible tissue of control piglets and animals supplemented with the highest recommended level (1.8% Formi^{TM} LHS). Unfortunately no samples from piglets supplemented with 3.6 or 5.4 Formi^{TM} LHS were analysed. No significant differences ($p > 0.05$) among the highest Formi^{TM} LHS treatment (7.2%) and the other groups were observed due to the large Standard Deviation (SD, Table 2). In conclusion no adverse effects on consumers can be expected if Formi^{TM} LHS is supplemented with the levels recommended.

Table 3: Effects of increasing dietary levels of Formi^{TM} LHS on concentration of formate in different edible tissues in pig (n=8)

Formi^{TM} LHS level (%)	0	1.8	7.2
	Average concentration of formate (µg/g; average (SD)		
Muscle	2.4(0.5)[a]	1.6 (0.7)[b]	16.3 (23.2)[ab]
Skin	4.1 (1.1)[a]	4.4 (1.7)[ab]	34.0 (34.3)[b]
Adipose	3.8 (1.0)	4.0 (1.6)	15.3 (21.3)
Liver	3.6 (0.7)	3.3 (1.0)	7.8 (10.4)
Kidney	8.5 (2.9)	6.6 (2.5)	50.4 (65.7)

[a, b] Average with different superscript letters within a row are significantly different ($p<0.05$)

4.3. Remarks on efficacy and studies made with recommended dosages

In addition to safety studies, some new data for efficacy of the substance were presented in the dossiers.

Potassium diformate (Formi^{TM} LHS) is used as growth promoter in pig nutrition. The proposed inclusion rates in feed are:

(1) 0.6 – 1.8% for piglets until 2 month of age

(2) 0.6 – 1.2% for growing/finishing pigs until slaughter

Efficacy trials for piglets and fattening pigs are summarised in the dossiers to justify the proposed inclusion rates.

Two additional studies in piglets (in Dossier n° 12, June 2001) with significant effects (improved feed/gain ratio, if 0.6 or 1.8% Formi^{TM} LHS added) are shown. Altogether at least three efficacy studies demonstrate significant effects ($p<0.05$) for the lowest inclusion level of 0.6% Formi^{TM}

LHS, more than three studies demonstrated significant effects for the highest inclusion level of 1.8% Formi^{TM} LHS in feed of piglets.

No further studies with significant effects were presented in the new dossiers for fattening pigs. All data were already evaluated by SCAN report on 22 March 2001. Two studies demonstrate significant effects on efficacy for the lowest inclusion level of 0.6% Formi^{TM} LHS, two further studies for the 0.8% inclusion level. The company considered this level close to the lowest recommended inclusion level of 0.6% and considered it as relevant in the context.

Two efficacy studies demonstrate significant effects ($p<0.05$) on efficacy for the highest inclusion level of 1.2% Formi^{TM} LHS, a third one tends to improve feed:gain ratio ($p<0.1$). Therefore the company should be requested to offer more data with significant effects for the lowest (0.6%) and the highest (1.2%) inclusion level of Formi^{TM} LHS in feed of fattening pigs.

4.4. Conclusions

The company presented new data on the stability of potassium diformate in liquid form: two new feeding experiments with piglets, a new tolerance study including water intake and residue studies in piglets, and a water intake study in fattening pigs.

Stability of Formi^{TM} LHS depends on concentration of substance in water. No conclusions can be drawn for dissociation of Formi^{TM} LHS in different sections of the digestive tract.

There were no significant differences in metabolic parameters and stomach alterations between control piglets and Formi^{TM} LHS dosages up to 5.4% (three times the recommended level).

Piglets and pigs given the recommended Formi^{TM} LHS supplementation had increased water intake and urine excretion, but the increases were not statistically different ($p>0.05$) from the control group, most likely because of the low number of animals and the variation of the values.

The concentration of formate in edible tissues was not significantly increased ($p>0.05$).

New overall efficacy studies in piglets have demonstrated significant effects for the lowest (0.6%) and the highest (1.8%) recommended inclusion level. For fattening pigs significant effects have not been demonstrated in the new studies. Thus more experiments are needed to demonstrate the efficacy in pigs.

No adverse effects of Formi^{TM} LHS were observed in animals given up to three times the recommended dose.

In conclusion, the substance can be considered as safe for animals and consumers at the recommended dosages.

5. REFERENCES:

Farries, F.E. (1958): The nutrient requirements of pigs. Agricult. Res. Council, Commonwealth Agric. Bureaux, Slough, England, p. 240

Mc Dowell, L.R. (1992): Minerals in animal and human nutrition. Academic Press. Inc., 98-114