**SCIENTIFIC OPINION**

# Scientific Opinion on the safety and efficacy of Formi™ LHS (potassium diformate) as a feed additive for sows[1]

**EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)[2]**

European Food Safety Authority (EFSA), Parma, Italy

## SUMMARY

Following a request from the European Commission, the European Food Safety Authority (EFSA) was asked to deliver a scientific opinion on the safety and efficacy of Formi™ LHS when used as a zootechnical additive in sows. This product has been authorised for use in piglets, pigs for fattening and sows. The applicant is now seeking re-evaluation of this additive for use in sows.

Formi™ LHS is a feed additive consisting of potassium diformate intended to be used in sows at a proposed dose range of 8000 - 12000 mg/kg of complete feedingstuffs.

A tolerance study made with sows and including Formi™ LHS at doses up to 5% showed no adverse effects. Consequently, the FEEDAP Panel concludes that Formi™ LHS is safe for use in sows at a maximum dose of 1.2%, with a margin of safety of approximately four.

Although Formi™ LHS has a potential antimicrobial effect in the gastrointestinal tract, the nature of the product makes selection for bacteria resistant to clinically relevant antibiotics unlikely.

There was no evidence of genotoxicity of Formi™ LHS. The acute oral toxicity was low, and no adverse subchronic effects at the tested dose levels were detected in laboratory animal studies. In chronic studies, the NOAEL was 50 mg/kg body weight/day for forestomach irritation in rats. In addition, data from residues studies in pigs indicate that no increase in the intake of formate is expected from consumption of animal tissues when Formi™ LHS is used. The FEEDAP Panel concludes that the use of Formi™ LHS as a feed additive in sows under the proposed conditions of use is safe for the consumer.

Formi™ LHS is an eye irritant. No other effects requiring specific user protection measures were identified.

The FEEDAP Panel concludes that use of Formi™ LHS would not pose a risk for the environment.

[1] On request from the European Commission, Question No EFSA-Q-2008-693, adopted on 15 September 2009.

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The results from three of four studies show that supplementing sows' diets with Formi™ LHS has some effects directly on sows (increase in feed intake in two studies) or indirectly on litter's performance (increase in daily litter weight gain in two studies and an increase in weaning weight in another study). The data support a potential for efficacy at the highest proposed level (1.2%) over the period from one week before farrowing until weaning of piglets. The efficacy of the product at the lowest proposed dose (0.8%) is not demonstrated.

No negative effects on meat quality would be expected from the use of Formi™ LHS in sows' feed at the proposed dose range.

**KEY WORDS**

zootechnical additive, Formi™ LHS, potassium diformate, sows, safety, efficacy

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## BACKGROUND

Regulation (EC) No 1831/2003[3] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 10(2) of that Regulation lays down that an application shall be submitted in accordance with Article 7, at the latest one year before the expiry date of the authorization given pursuant to Directive 70/524/EEC for additives with a limited authorization period.

The European Commission received a request from the company BASF SE[4] for the re-evaluation of the product Formi™ LHS, potassium diformate, to be used as a feed additive for sows (category: zootechnical additives; functional group: other zootechnical additives) under the conditions mentioned under Table 1. According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 10(2) (re-evaluation of an existing feed additive) of that regulation. EFSA received directly from the applicant the technical dossier in support of this application.[5] According to Article 8 of that Regulation, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. The particulars and documents in support of the application were considered valid by EFSA as of 13 February 2009.

Formi™ LHS is based on potassium diformate. This additive is currently authorised at Community level, under Council Directive 70/524/EEC,[6] as "growth promoter" for sows[7] until 30 July 2009, and under Regulation (EC) 1831/2003, as "zootechnical additive; functional group: other zootechnical additives" for piglets (weaned) and pigs for fattening[8] until 21 March 2017.

The Scientific Committee on Animal Nutrition (SCAN) delivered an opinion on the safety of this product for use in piglets and pigs for fattening, consumer, user and environment on 22 March 2001,[9] updated on 18 June 2002.[10] EFSA issued two opinions on Formi™ LHS: one of the efficacy and safety for the sows, consumers, users and the environment when used as an additive in feeds for sows[11] and another one on the safety and efficacy for weaned piglets and pigs for fattening.[12]

## TERMS OF REFERENCE

According to Article 8 of Regulation (EC) No 1831/2003 EFSA shall determine whether the feed additive complies with the conditions laid down in Article 5. Therefore, EFSA shall deliver an opinion on the efficacy and the safety for the target animals, user and consumer and the environment of the product "Formi™ LHS" when used under the conditions described in Table 1.

## ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group on Organic Acids and to Walter Rambeck, Atte von Wright and Piet Wester for the preparation of this opinion.

[3] OJ L 268, 18.10.2003, p.29
[4] BASF SE, 67056 Ludwigshafen, Germany.
[5] Dossier reference: FAD-2008-0044
[6] OJ L 270, 14.12.1970, p. 1
[7] Comission Regulation (EC) No 1200/2005
[8] Comission Regulation (EC) No 184/2007
[9] http://europa.eu.int/comm/food/fs/sc/scan/out83bis_en.pdf
[10] http://europa.eu.int/comm/food/fs/sc/scan/out83_en.pdf
[11] The EFSA Journal (2004) 139, 1-9
http://www.efsa.europa.eu/EFSA/Scientific_Opinion/feedap_opinion34_formilhs_adopted1.pdf?ssbinary=true
[12] The EFSA Journal (2006) 2006, 325, 1-16
http://www.efsa.europa.eu/EFSA/Scientific_Opinion/feedap_op_ej325_formi_en1.pdf?ssbinary=true

**Table 1.** Description and conditions of use of the additive as proposed by the applicant

| | |
|---|---|
| **Additive** | Potassium diformate (Formi LHS) |
| **Registration number/EC No/No** (if appropriate) | 1 |
| **Category of additive** | Zootechnical additives |
| **Functional group of additive** | Other zootechnical additive |

| **Description** | | | |
|---|---|---|---|
| Additive | Chemical formula, description | Purity criteria (if appropriate) | Method of analysis (if appropriate) |
| Potassium diformate (Formi™ LHS) | **Additive composition:** Potassium diformate, solid min. 98 %, Silicate max. 1,5 % Water max. 0,5 % **Active substance:** Potassium diformate, solid $KH(COOH)_2$ CAS No 20642-05-1 | | |

| | |
|---|---|
| **Trade name** (if appropriate) | Formi LHS |
| **Name of the holder of authorisation** (if appropriate) | BASF SE, 67056 Ludwigshafen/Germany |

| **Conditions of use** | | | | |
|---|---|---|---|---|
| Species or category of animal | Maximum Age | Minimum content | Maximum content | Withdrawal period (if appropriate) |
| | | mg/kg of complete feedingstuffs | | |
| Sows | | 8 000 | 12 000 | - |

| **Other provisions and additional requirements for the labelling** | |
|---|---|
| Specific conditions or restrictions for use (if appropriate) | |
| Specific conditions or restrictions for handling (if appropriate) | not appropriate |
| Post market monitoring (if appropriate) | BASF has a general traceability system and a complaint procedure in place. An emergency telephone number is printed on each label. |
| Specific conditions for use in complementary feedingstuffs (if appropriate) | not appropriate |

| **Maximum Residue Limit (MRL)** (if appropriate) | | | |
|---|---|---|---|
| Marker residue | Species or category of animal | Target tissue(s) or food products | Maximum content in tissues |
| Not appropriate | - | - | - |

## ASSESSMENT

### 1. Introduction

The additive Formi™ LHS is a feed additive based on potassium diformate. This additive is currently authorised as "growth promoter" for sows until 30 July 2009 and as "zootechnical additive" for piglets (weaned) and pigs for fattening until 21 March 2017.

The Scientific Committee on Animal Nutrition (SCAN) delivered an opinion on the safety of this product for use in piglets and pigs for fattening, consumer and user and environment on 22 March 2001, updated on 18 June 2002 (EC, 2001; 2002). The European Food Safety Authority (EFSA) issued two opinions on Formi™ LHS; one on the efficacy for sows and safety for the target animal, consumers, users and the environment (EFSA, 2004) and another one on the safety and efficacy for weaned piglets and pigs for fattening (EFSA, 2006). The applicant is currently asking for the re-evaluation of the product Formi™ LHS, potassium diformate, to be used as a feed additive for sows (category: zootechnical additives; functional group: other zootechnical additives).

### 2. Characterisation

#### 2.1. Characterisation of the product

Potassium diformate (KCOOH*HCOOH) is an association of potassium formate and formic acid. The molecules are linked by a hydrogen bond between the hydroxyl group of the potassium formate molecule and the carbonyl group of the formate. The chemical formula is $C_2H_3O_4K$ and the molecular weight is 130.1. The product is described as a dry, white and free flowing crystalline product containing, by weight, 98% ± 1% potassium diformate as active ingredient with a maximum of 1.5% silicate as anticaking agent and a maximum of 0.5% water.

Potassium formate is produced from formic acid and potassium hydroxide. The crystal mass and the saturated solution of potassium diformate are separated by centrifugation. Solid potassium diformate is obtained by drying. The potassium diformate is mixed with the anticaking agent to improve the physical characteristics. The final product is bagged.

Seven batches of the product were analysed and met the specification set by the applicant as 98% ± 1% potassium diformate and analysis confirmed that potassium diformate and the anticaking agent account for more than 99% of the product. The specification would be better expressed as minimum content of 97%.

Analysis of particle size distribution showed that particles below 75 µm represent < 1% of the product, while most of the particles are in the range 75 - 3150 µm (< 425 µm: 10.2 - 59.0%; < 3150: 100%). The bulk density is 900 - 1000 g/dm$^3$.

The product is monitored for heavy metals and As. Data from three independent production batches showed values of As < 12 mg/kg, Cd < 15 mg/kg, Pb < 40 mg/kg and Hg < 0.5 mg/kg.

#### 2.2. Stability and homogeneity

The shelf-life of the product (in plastic packages) has been tested on three different batches of Formi™ LHS stored at 25 ºC and 55-60% relative humidity or at 40 ºC and 75-90% relative humidity for up to six months.[13] After six months, 97.4% and 96.6% potassium diformate was recovered in the product, at 25 and 40 ºC respectively. Similar results were obtained during storage of commercial

[13] Technical dossier/Section III/III-09

samples (25 kg or 500 kg bags) for up to 24 months at temperatures of 25 or 40 ºC (recovery > 97%).[14] The applicant proposes a shelf-life of 12 months.

Stability of Formi™ LHS has been tested in one vitamin-mineral premix containing 20, 30 or 40% Formi™ LHS. The content of potassium diformate remained almost unchanged after 11 months storage at room temperature (20-22 ºC). The concentration of vitamins in the premix was not affected by the presence of Formi™ LHS.

Feedingstuffs (12 samples) containing Formi™ LHS in the range of 0.8-6.0%, showed a loss of maximum 3% of formic acid after storage at 20 ºC, up to six months.[15] Loss of Formi™ LHS during pelleting of feedingstuffs (70-110 ºC), tested at three production facilities, amounted to 1.5 - 8.2%.

Homogeneity of Formi™ LHS in feedingstuffs was investigated after transport and loading.[16] The coefficients of variation (n=10) were 3.1% and 2.2% for a fine and coarse meal, respectively.

### 2.3. Conditions of use

Formi™ LHS is intended to be used as a feed additive for sows (category: zootechnical additives; functional group: other zootechnical additives). The proposed inclusion rate in feed is 8000 - 12000 mg/kg of complete feedingstuffs (0.8 - 1.2%).

### 2.4. Evaluation of the analytical methods by the Community Reference Laboratory (CRL)

EFSA has verified the CRL report as it relates to the methods used for the control of the active substance/marker in tissues in animal feed. The Executive Summary of the CRL report can be found in the Appendix.

## 3. Safety

### 3.1. Safety for the target species

#### 3.1.1. Tolerance studies

Earlier studies, particularly in piglets, have shown evidence of adverse effects (feed refusal, increase water intake) when Formi™ LHS was included in diets at approximately ten times the highest recommended level.

A tolerance study in sows was performed with Formi™ LHS at intended levels of 0, 1.2, 3 and 6% in the feed, during pregnancy, parturition and lactation.[17] The concentrations of formate recovered from feed samples were below the intended values (mean values range between 73% and 88% of intended values). Forty-three non-pregnant gilts (Large White x Landrace hybrid breed) of between approximately 7.5 and 10 months of age were selected for service (by artificial insemination). However, only 25 sows became pregnant and were allocated to one of the four treatment groups.

Growth parameters in sows were not affected by dietary inclusion of Formi™ LHS at any of the tested concentrations. Sow mortality, birth rates, and rates of piglet mortality *in utero*, at birth and between birth and weaning and piglet gender were not adversely affected by inclusion of Formi™ LHS at any of the three levels (Table 2).

[14] Technical dossier/Section III/III-11
[15] Technical dossier/Supplementary information April 2009
[16] Technical dossier/Section II/II-20
[17] Technical dossier/Section III/ V03_REG03_III-1

There was a dose dependent enhancement of piglet growth rates when Formi™ LHS was present in the diets of their dams. The magnitude of this trend was relatively small and it was not statistically significant (P>0.05).

Within the study, where animals were fed a restricted diet, there was no significant effect on feed or water intake of inclusion of Formi™ LHS at any of the levels. Water intake was obviously higher post-partum, with the greatest intake shown by the group receiving Formi™ LHS at the highest dose (although it was not statistically significant).

**Table 2.** Effect of Formi™ LHS on performance parameters of sows and piglets

| | Formi™ LHS (%) | | | |
|---|---|---|---|---|
| | 0 | 1.2 | 3 | 6 |
| Number of sows per group* | 6 | 7 | 6 | 6 |
| Mean piglet numbers born | | | | |
| Born alive | 11.3 | 9.1 | 12.7 | 10.3 |
| Born dead | 0.7 | 1.0 | 0.5 | 1.0 |
| Mean piglet body weights (kg) | | | | |
| Litter mean, day 1 | 1.44 | 1.39 | 1.30 | 1.27 |
| Weaning | 6.06 | 6.25 | 6.31 | 6.31 |
| Mean piglet survival rates birth to weaning (%) | 70.5 | 76.0 | 69.0 | 69.7 |
| Sows group mean feed intake (kg/day) | | | | |
| Service to farrowing | 2.58 | 2.56 | 2.58 | 2.54 |
| Farrowing to weaning | 4.46 | 4.44 | 4.32 | 4.75 |
| Sows group mean water intake (L/day) | | | | |
| Service to farrowing | 9.9 | 8.8 | 9.7 | 10.2 |
| Farrowing to weaning | 17.8 | 15.5 | 17.0 | 23.6 |

* Other sows failed routine pregnancy test or returned to oestrus

Blood samples were collected from each animal once during acclimatisation, during week 15 of gestation and on day 21 post-partum for clinical chemistry.

Duplicate samples of urine were obtained from animals either by direct catheterisation or by free capture if the animal was seen to urinate. Samples were collected once during acclimatisation, again in week 15 of gestation and a further sample was collected either by free capture or after euthanasia.

Sows were killed and necropsied at litter weaning, between day 21 and day 28 post-partum. A sample of each of the following tissues was retained for macroscopic and microscopic examination: oesophagus, glandular stomach, non-glandular stomach, duodenum, jejunum, ileum, caecum, colon, rectum, liver and kidneys.

The majority of the clinical chemistry, haematology and urinalysis parameters were not affected by any of the dietary Formi™ LHS inclusion rates. Some minor dose-dependent effects were observed in some of the measured blood chemistry, haematology and urine chemistry parameters. A significant ($P \leq 0.05$) dose-response decrease in serum albumin, creatinine, haemoglobin and red blood cells were observed in the samples taken at week 15, but not at 21 days post-partum. However, all values remained within their phisiological ranges. A significant ($P \leq 0.05$) dose-response increase in urine potassium was observed at samples taken at week 15, but not at samples taken 21 days post-partum. This observation is likely to be associated with the increased potassium absorption resulting from the ingestion of potassium diformate, and otherwise of no clinical significance.

No adverse effects related to the use of Formi™ LHS were observed in the macroscopic and microscopic examination of tissues.

### 3.1.2. Microbiological studies

The minimum inhibitory concentration (MIC) values against a selection of Gram-negative and Gram-positive bacteria were determined in liquid medium using microtitre plates and two-fold dilution series of Formi™ LHS (6.0 - 0.01%).[18] The results are given in Table 3.

**Table 3.** The MIC values of Formi™ LHS

| Strain | MIC (%) |
|---|---|
| *Salmonella enteriditis* 17554 | 0.4 |
| *Yersinia enterocolitica* 52180 | 0.2 - 0.4 |
| *Escherichia coli* ATCC 8739 | 0.4 |
| *Acinetobacter baumanii* ATCC 19096 | 0.2 - 0.4 |
| *Enterococcus faecium* 20026 | 0.4 |
| *Enterococcus faecalis* ATCC 19433 | 0.4 |
| *Staphylococcus aureus* ATCC 6538P | 0.4 |
| *Staphylococcus epidermidis* 2742 | 0.4 |
| *Streptococcus* group A | 0.2 |

The MICs are below four times the proposed inclusion rate in the feed (0.8 - 1.2%). Accordingly, Formi™ LHS should be considered as a potential antimicrobial agent in the digestive tract. However, the possibility of Formi™ LHS selecting for bacteria resistant to clinically relevant antibiotics is considered remote, given the nature of the compound (a salt of a simple organic acid).

No clinically manifest disturbances in the digestive tract were observed in the tolerance study (or in any efficacy study where this was monitored) which would demand the specific investigation of the effect of Formi™ LHS on the gut microbiota and the potential to shed enteropathogens.

### 3.1.3. Conclusions on the safety for sows

The additive Formi™ LHS appears to be tolerated at the level of 5.0% (analysed value). Therefore, the FEEDAP Panel considers Formi™ LHS to be safe for use in sows at a maximum dose of 1.2%, with a margin of safety of approximately four.

Although Formi™ LHS has a potential antimicrobial effect in the gastrointestinal tract, the nature of the product makes selection for bacteria resistant to clinically relevant antibiotics unlikely.

## 3.2. Safety for the consumer

All of the data presented in this dossier, with the exception of the residue study presented below, were evaluated by SCAN (EC, 2001). All the studies were performed to current standards and according to GLP.

### 3.2.1. Metabolism and residues

The consequence of the chemical characteristics of potassium diformate, namely the hydrogen bond between the hydroxyl group of the potassium formate molecule and the carbonyl group of the formate, is that the complex remains in the diformate form under acidic conditions and dissociates into formate and potassium ions under neutral or alkaline conditions. Therefore, diformate, present as the salt in the

[18] Technical dossier/Section III/V04_REG04_III-04

stomach, is likely to dissociate in the neutral conditions prevailing in the intestine and after eventual absorption, in plasma and tissues. Formate is a normal endogenous metabolite.

A residue study with young pigs (mean weight, 10 kg) was performed.[19] The animals were fed a control feed (n=8) or the same feed supplemented with Formi™ LHS at 1.2% (n=10) until a mean weight of 27 kg. The concentration of formate in the different tissues is given in Table 4.

**Table 4.** Effect of Formi™ LHS on the concentration of formate (µg/g) in different edible tissues of pigs

| | Formi™ LHS (%) | | | |
|---|---|---|---|---|
| | 0 | | 1.2 | |
| | Mean (µg/g) | Standard deviation | Mean (µg/g) | Standard deviation |
| Muscle | 14.6 | 6.8 | 14.4 | 3.6 |
| Skin | 7.4[b] | 1.3 | 12.6[a] | 1.4 |
| Fat | 11.1 | 0.6 | 11.8 | 1.5 |
| Spleen | 10.1[b] | 6.1 | 15.1[a] | 1.4 |
| Lung | 9.5[b] | 0.7 | 17.5[a] | 1.9 |
| Liver | 20.9 | 5.2 | 16.9 | 3.2 |
| Kidney | 13.6[b] | 2.9 | 22.2[a] | 2.0 |

[a, b]: Values with different superscript letters within a row are significantly different (P< 0.05; Students-t test).

The data from Table 4 can be used for the calculation of human exposure, using the worst case scenario (300 g muscle, 100 g liver, 50 g kidney and 50 g fat). The calculated values, 7.7 mg/day in the control group and 7.7 mg/day in the treated group are not different. Hence, it is concluded that use of Formi™ LHS in pig diets at 1.2% will not result in an increase of background exposure. The FEEDAP Panel sees no reason to assume that this product will behave differently in sows.

### 3.2.2. Studies in laboratory animals

The data submitted in the dossier was previously assessed by SCAN (EC, 2001). The FEEDAP Panel has made a full review of these data which is summarised below.

#### 3.2.2.1. Genotoxicity, including mutagenicity

The studies included bacterial mutagenicity tests (*Salmonella* Typhimurium, *Escherichia coli*),[20] *in vitro* mouse lymphoma assay[21] and chromosome aberration test in human peripheral blood lymphocytes,[22] and an *in vivo* bone marrow micronucleus test in rats.[23] None of the studies showed indications for potential genotoxicity.

#### 3.2.2.2. Laboratory animal toxicity studies

An acute oral toxicity study in mouse and rats produced a $LD_{50}$ of approximately 3000 and >2000 mg/kg bw, respectively.[24]

A subchronic toxicity study was performed in mice, producing no adverse effects even in the highest dose tested (3000 mg/kg diet).[25] Chronic studies were performed in mice[26] and rats.[27] No treatment

[19] Technical dossier/Section III/V3_REG13_III-13
[20] Technical dossier/Section III/V3_REG24_III-24
[21] Technical dossier/Section III/V3_REG26_III-26
[22] Technical dossier/Section III/V3_REG26_III-26
[23] Technical dossier/Section III/V3_REG27_III-27
[24] Technical dossier/Section III/V3_REG18_III-18
[25] Technical dossier/Section III/V4_REG30_III-30

related increase in tumours was seen in either species, and the NOAEL was based on the only treatment related effect being some evidence of irritation in the forestomach, and yielding a NOAEL of 400 and 50 mg/kg bw/day in mice and rats, respectively.

Toxicity for the reproductive system was not directly studied. The FEEDAP Panel does not consider that there is a requirement for these studies as the carry-over of potassium diformate in the tissues does not occur.

### 3.2.3. Conclusions on consumer safety

Considering the absence of genotoxicity, the low toxicity of potassium diformate and the lack of an increased consumer exposure to formate, the FEEDAP Panel considers that the use of Formi™ LHS as a feed additive in sows under the proposed conditions of use is safe for the consumer.

## 3.3. Safety for the user

The data submitted in the dossier to assess user safety was previously assessed by SCAN (EC, 2001) on the basis of skin[28] and eye[29] irritation studies (rabbit), skin sensitisation test (Magnusson-Kligman test with Guinea pigs)[30] and an acute inhalation toxicity test (rats).[31] The FEEDAP Panel has reviewed the data and reached the same conclusions as SCAN. Except for ocular irritation potential, no effects requiring specific user protection measures were found.

## 3.4. Safety for the environment

The data submitted in the dossier to assess safety for the environment was previously assessed by SCAN (EC, 2001). The FEEDAP Panel concludes, as did SCAN, that since the excretion products formic acid and formate are naturally occurring metabolites, and the use of potassium diformate would not substantially increase excretion of formate (and potassium ions) in the environment, no further environmental assessment is necessary.

# 4. Efficacy

Four studies, carried out at three different locations, have been presented in the dossier to support efficacy in sows.

*First study*

A performance trial was made with 74 multiparous sows (Danish Landrace x Yorkshire).[32] Individual sows were the experimental unit. Sows were allotted to one of two dietary treatments according to parity and live weight one week before expected farrowing. The dietary treatments consisted of a lactation control diet and a basal diet containing 1.0% Formi™ LHS. The concentration of Formi™ LHS in the experimental diet was confirmed by analysis.

The experimental period was from one week before expected farrowing and throughout the lactation until weaning when the piglets were about four weeks of age. Individual feed intake of sows was

[26] Technical dossier/Section III/V7_REG32_III-32
[27] Technical dossier/Section III/V5_REG31_III-31
[28] Technical dossier/Section III/V3_REG19_III-19
[29] Technical dossier/Section III/V3_REG20_III-20
[30] Technical dossier/Section III/V3_REG23_III-23
[31] Technical dossier/Section III/V3_REG21_III-21
[32] Technical dossier/Section IV/ V01_REG06_IV-1a_Efficacy_Study 1

registered during lactation period. The litter size was standardised within 1 - 2 days after farrowing. Litter weight was registered on day 5 after farrowing and at weaning at four weeks.

The addition of 1.0% (1000 mg/kg) Formi™ LHS to sows' diets significantly increased litter weight gain and daily feed intake of sows during the lactation period (Table 5).

**Table 5.** Effect of Formi™ LHS on performance of sows and piglets during lactation

| | Formi™ LHS (%) | |
|---|---|---|
| | 0 | 1.0 |
| Number of sows | 37 | 37 |
| Number of piglets after standardizing the litter | 11.1 | 11.3 |
| Piglets (with litter size after standardisation) | | |
| Initial litter weight (kg) | 20.9 | 22.1 |
| Daily litter weight gain (kg) | 2.34[b] | 2.53[a] |
| Average piglet weight at weaning (kg) | 7.00 | 7.35 |
| Mortality (%) | 4.4 | 4.0 |
| Sows | | |
| Initial weight of sow (kg) | 242.7 | 252.8 |
| Sows' weight change during lactation (kg) | -20.9 | -22.1 |
| Daily feed intake of the sow during lactation (kg) | 5.76[b] | 6.04[a] |

[a, b:] Values in a row with different superscripts differ significantly (P≤0.05)

*Second study*

A second performance trial was made with 130 multiparous sows (Danish Landrace x Yorkshire).[33] This trial was carried out in two periods, period 1 was in 1999 and period 2 was in 2001. Individual sows were the experimental unit. Sows were allotted to two dietary treatments according to parity and live weight one week before expected farrowing. There were a total of 69 (control group) or 61 (0.8% Formi™ LHS group) sows per treatment. The dietary treatments consisted of a lactation control diet and a diet containing 0.8% Formi™ LHS (confirmed by analysis). The experimental period was from one week before expected farrowing and throughout the lactation until weaning at when the piglets were about four weeks of age. Individual feed intake of sows was registered during lactation period. The litter size was standardized within 1 - 2 days after farrowing. Litter weight was registered on day 5 after farrowing and at weaning at four weeks.

There was no significant period effect; therefore, the results from period 1 and period 2 were combined. The addition of 0.8% Formi™ LHS to diet led to a significant increase in average daily litter weight gain (Table 6). Sows' daily feed intake and weight loss during lactation were no different between groups.

**Table 6.** Effect of Formi™ LHS on the performance of sows and piglets during lactation

| | Formi™ LHS (%) | |
|---|---|---|
| | 0 | 0.8 |
| Number of sows | 69 | 61 |
| Number of piglets after standardizing the litter | 11.3 | 11.3 |
| Piglets (with litter size after standardisation) | | |
| Initial litter weight (kg) | 25.4 | 25.5 |

[33] Technical dossier/Section IV/ V01_REG09_IV-2a_Efficacy_Study 2

| | | |
|---|---|---|
| Daily litter weight gain (kg) | 2.36 [b] | 2.48[a] |
| Average piglet weight at weaning (kg) | 6.90 | 7.04 |
| Mortality (%) | 4.7 | 4.0 |
| Sows | | |
| Initial weight of sow (kg) | 266.4 | 267.3 |
| Sows' weight changes during lactation (kg) | -18.3 | -17.7 |
| Daily feed intake of the sow during lactation (kg) | 6.17 | 6.26 |

[a, b:] Values in a row with different superscripts differ significantly (P≤0.05)

*Third study*

The third growth performance trial was made with 156 sows (Dutch Landrace x Scandinavian Landrace).[34] The treatments were 0, 0.8 and 1.2% Formi™ LHS (confirmed by analysis) in the diet during one reproductive cycle including gestation, lactation and the successive interval from weaning to mating. Litter size was standardised before day 3 post-farrowing.

The addition of 1.2% Formi™ LHS led to an increase in feed intake of sows during the lactation period (Table 7). Body weight changes in gestation and lactation were small and not significant. There was a significant dose-dependent increase in backfat thickness with increasing levels of Formi™ LHS during the gestation period. There was also a significant dose-dependent increase in the weaning weight. No significant improvements in performance were seen with the minimum proposed dose.

**Table 7.** Effects of Formi™ LHS on the performance of sows and piglets during lactation

| | Formi™ LHS (%) | | |
|---|---|---|---|
| | 0 | 0.8 | 1.2 |
| Number of sows | 50 | 54 | 52 |
| Number of piglets after standardizing the litter | 11.2 | 11.6 | 11.2 |
| Piglets (with litter size after standardisation) | | | |
| Initial piglet weight (kg) | 1.47 | 1.50 | 1.55 |
| Litter weight gain (kg/day) | 2.52 | 2.62 | 2.59 |
| Weaning weight (kg) | 7.98[a] | 8.26[ab] | 8.32[b] |
| Mortality (%) | 7.8 | 7.2 | 8.8 |
| Sows | | | |
| Weight at mating (kg) | 187 | 183 | 185 |
| Weight loss during lactation (kg) | -19 | -22 | -19 |
| Feed intake of sows during lactation (kg/day) | 5.52[ab] | 5.45[a] | 5.75[b] |

[a, b:] Values in columns with different superscripts differ significantly (P≤0.05)

Milk composition (fat, protein, lactose) from ten sows per treatment was examined on day 4, 12 and 24 post-farrowing. There were no significant effects of Formi™ LHS on milk composition.

Faecal digestibility of proximate components was determined using eight sows from each treatment with 0 and 1.2% Formi™ LHS in the diet. Although the increase in digestibility was not significant for the individual proximate components, the sum of the effects resulted in a significant increase in estimated net energy of 2.3% with the addition of 1.2% Formi™ LHS.

*Fourth study*

The fourth trial was carried out during one cycle at a research farm with 77 sows (Landrace), selected out of a group of 140 and distributed to five treatments with 14-17 sows per treatment.[35] The sows were fed restrictedly a pelleted diet during gestation and lactation, based on barley, maize, alfalfa and

[34] Technical dossier/Section IV/V01_REG12_IV-3a_Efficacy_ Study 3
[35] Technical dossier/Section IV/V01_REG12_IV-4

soybean meal. The five dietary treatments during gestation and lactation resulted from the supplementation of a control diet with Formi™ LHS at 0, 0.8, 1.2, 3.6 or 6.0%. Creep feed was offered to the piglets after the second week of lactation. Performance of the sows was evaluated using the following parameters: weight at service, weight before and after farrowing, weight at weaning, days of gestation, weaning to fertile service, interval between cycles, number of piglets born alive, total number born, number born dead, individual weight at birth, number of piglets weaned, mortality during lactation and individual weight at weaning. Sows in gestation and lactation were observed daily for abnormalities and clinical signs of sickness.

There were no significant effects of Formi™ LHS at any tested concentration on any of the parameters examined on sows and piglets. Water consumption during lactation was not different between treatments.

### 4.1. Effects on quality of animal products

Studies on the quality of animal products, organoleptic analysis, as well as formate residue in edible tissue of pigs fed Formi™ LHS were reported for pigs for fattening and evaluated by SCAN (EC, 2002). These results shown that no residues from Formi™ LHS were detected in animal produce from piglets or pigs for fattening given feed added Formi™ LHS at recommended rates. Formi™ LHS did not affect the sensory quality (odour, flavour, firmness, tenderness and juiciness) of pork. It is assumed that feeding sows with Formi™ LHS would not have a different effect.

### 4.2. Conclusions on efficacy in sows

The results show that adding Formi™ LHS at doses ranging 0.8 - 1.2% to sows' diets has some effects directly on sows (increase in feed intake in studies 1 and 3) or indirectly on litter's performance (increase in daily litter weight gain in studies 1 and 2 and an increase in weaning weight in study 3). The data support a potential for efficacy at the highest proposed level (1.2%) over the period from one week before farrowing until weaning of piglets. The efficacy of the product at the lowest proposed dose (0.8%) is not demonstrated.

No negative effects on meat quality would be expected from the use of Formi™ LHS in sows' feed at the recommended dose range.

## 5. Post-market monitoring

No risks associated with the use of the product are foreseen. It is considered that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation[36] and Good Manufacturing Practice.

[36] OJ L 35, 8.2.2005, p.1

## CONCLUSIONS AND RECOMMENDATIONS

### CONCLUSIONS

The FEEDAP Panel considers Formi™ LHS to be safe for use in sows at a maximum dose of 1.2%, with a margin of safety of approximately four.

Although Formi™ LHS has a potential antimicrobial effect in the gastrointestinal tract, the nature of the product makes selection for bacteria resistant to clinically relevant antibiotics unlikely.

Considering the low toxicity and the absence of genotoxicity of potassium diformate as well as the lack of any additional consumer exposure to formate, the FEEDAP Panel concludes that the use of Formi™ LHS as a feed additive in sows under the proposed conditions of use is safe for the consumer.

Formi™ LHS is an eye irritant. No other effects requiring specific user protection measures were identified.

The FEEDAP Panel concludes that use of Formi™ LHS would not pose a risk for the environment.

The data support a potential for efficacy at the highest proposed level (1.2%) over the period from one week before farrowing until weaning of piglets. The efficacy of the product at the lowest proposed dose (0.8%) is not demonstrated.

No negative effects on meat quality would be expected from the use of Formi™ LHS in sows' feed at the proposed dose range.

### RECOMMENDATIONS

The product should be described as: potassium diformate, minimum 97%.

Given the eye irritation potential, the product should be labelled accordingly and appropriate protection measures taken by users.

## DOCUMENTATION PROVIDED TO EFSA

1. Dossier Formi™ in sows. July 2008. Submitted by BASF SE.
2. Supplementary information request on the product Formi™ LHS (Potassium diformate) as feed additive for sows. April 2009. Submitted by BASF SE.
3. Evaluation report of the Community Reference Laboratory for Feed Additives on the methods(s) of analysis for Formi™ LHS for sows.
4. Comments from Member States received through the ScienceNet.

## REFERENCES

EC (European Commission), 2001. Report of the Scientific Committee on Animal Nutrition on the use of potassium diformate (Formi™ LHS) as feed additive. http://ec.europa.eu/food/fs/sc/scan/out83bis_en.pdf

EC (European Commission), 2002. 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 http://ec.europa.eu/food/fs/sc/scan/out83_en.pdf

EFSA (European Food Safety Authority), 2004. Opinion of the Scientific Panel on additives and products or substances used in animal feed on the safety and efficacy of Formi LHS for sows. *The EFSA Journal* (2004) 139, 1-9 http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/feedap_opinion34_formilhs_adopted1.pdf?ssbinary=true

EFSA (European Food Safety Authority), 2006. Opinion of the Scientific Panel on additives and products or substances used in animal feed on the safety and efficacy of the product "Formi™ LHS" as a feed additive for weaned piglets and pigs for fattening in accordance with Regulation (EC) No 1831/2003. *The EFSA Journal* (2006) 325, 1-16 http://www.efsa.europa.eu/EFSA/Scientific_Opinion/feedap_op_ej325_formi_en1.pdf?ssbinary=true

## APPENDIX

### Executive Summary of the Evaluation Report of the Community Reference Laboratory for Feed Additives on the Method(s) of Analysis for Formi™ LHS

In the current application authorisation is sought for *potassium diformate (Formi LHS)* under the category "zootechnical additives", group 4(d) - "other zootechnical additives", according to the classification system of Annex I of Regulation (EC) No 1831/2003. Specifically, authorisation is sought to use Formi LHS as an additive for sows. The additive is intended to be marketed as a crystalline dry product containing 98% *potassium diformate*, 1.5% silica and water up to 0.5%.

The active agent of *Formi LHS* is *potassium diformate*. The product is intended to be incorporated into premixtures and/or complete feedingstuffs. The minimum and maximum content of *potassium diformate* in complete feedingstuffs for sows is 8000 and 12000 mg/kg, respectively.

For the determination of *potassium diformate* in the *feed additive*, the applicant proposes a method based on the quantification of total formate. The measured formate content allows the calculation of potassium diformate content in the sample. The method is based on oxidation with potassium permanganate followed by iodometric titration. The following acceptable performance characteristics for the determination of total formate content obtained from the in-house validation study were reported: - a recovery rate ranging from 99 to 101 % and a relative standard deviation of repeatability ($RSD_r$) of 0.1 %.

Based on acceptable performance characteristics, the proposed method is recommended for official control purposes for the determination of *potassium diformate* in *feed additives* in the frame of authorisation.

For the determination of *potassium diformate* in *premixtures* and *feedingstuffs*, the applicant proposes an ion chromatography method equipped with electrical conductivity detection (IC/ECD). The method is based on the principle that *potassium diformate* dissociates into formate under the conditions of the analysis. From the measured formate content the potassium diformate content is then calculated. On request of the CRL the applicant provided in-house validation results for the determination of *potassium diformate* in *feedingstuffs* only. As no results were reported for *premixtures* the CRL could not evaluate the suitability of the proposed method for official control purposes.

The following acceptable performance characteristics obtained from the in-house validation study were reported for *feedingstuffs*: - a limit of detection (LOD) of 100 mg/kg; - a limit of quantification (LOQ) of 500 mg/kg; - a recovery rate close to 100 %; and - $RSD_r$ ranging from 3.2 to 3.5 %. The validation experiments were performed with a set of different feed samples covering a formate content ranging from 3600 to 10000 mg/kg. These samples were also analysed by a second independent expert laboratory and all the reported results were in good agreement. Furthermore, the validation report included summary information related to a proficiency test (PT) organised by VDLUFA in 2006. Upon request from the CRL, the organiser of the PT provided the raw data together with the statistical assessment of the trial, showing a relative standard deviation of reproducibility of 16%.

Based on the acceptable performance characteristics mentioned above, the CRL recommends the proposed method for official control purposes for the determination of *potassium diformate* in *feedingstuffs* in the frame of authorisation.

Further testing or validation is not considered necessary.