Efficacy of methyl ester of conjugated linoleic acid (t10,c12 isomer) for sows and cows for reproduction

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Abstract

A mixture of methylated conjugated linoleic acid (CLA) isomers (t10,c12 and c9,t11) in equal proportions is the subject of this assessment. The active substance is considered to be CLA (t10,c12) methyl ester (ME). The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) of EFSA previously issued an opinion on the safety and efficacy of the product, in which it could not conclude on the efficacy of this additive for sows for reproduction and for cows for reproduction. The European Commission asked EFSA to deliver an opinion on the efficacy of this additive for sows and cows for reproduction, based on additional data submitted by the applicant. The FEEDAP Panel has performed the assessment of the new data following an approach in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance documents. In relation to the data on efficacy in sows for reproduction, owing to methodological shortcomings of the study submitted, including the duration of the study and the limited biological relevance of the effect observed, the FEEDAP Panel cannot conclude on the efficacy of CLA (t10,c12)-ME for sows for reproduction. The data related to dairy cows indicate that dietary CLA (t10,c12)-ME supplementation in the late dry period and/or lactation period showed an increase of the probability of pregnancy and a reduction of time to conception in the same reproductive cycle. However, considering that the minimum duration of efficacy studies for reproductive parameters is of at least two reproductive cycles, the FEEDAP Panel is not in a position to conclude on the efficacy of the additive for cows for reproduction.

Keywords: nutritional additives, conjugated linoleic acid methylster, CLA (t10, c12) isomer, cows, sows, efficacy

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Summary

Following a request from European Commission, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) of the European Food Safety Authority (EFSA) was asked to deliver a scientific opinion on the efficacy of omega-6-fatty acid as octadecadienoic acid (conjugated linoleic acid (CLA) methyl ester) as a nutritional additive for sows and cows.

The active substance under assessment is methylated CLA trans10,cis12-C18:2 (CLA (t10,c12)-ME). It is contained in two different formulations together with an approximately equal proportion of methylated CLA cis9,trans11-C18:2 (CLA (c9,t11)-ME).

The FEEDAP Panel previously issued an opinion on the safety and efficacy of the product, in which it could not conclude on the efficacy of this additive for cows for reproduction and for cows for reproduction. The European Commission asked EFSA to deliver an opinion on the efficacy of this additive for sows and cows for reproduction, based on additional data submitted by the applicant.

The FEEDAP Panel has performed the assessment of the new data following an approach in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance documents.

As per the data related to the efficacy of the additive in sows for reproduction, owing to methodological shortcomings of the study submitted, including the duration of the study and the limited biological relevance of the effect observed, the FEEDAP Panel cannot conclude on the efficacy of CLA (t10,c12)-ME for sows for reproduction.

The data related to dairy cows indicates that dietary CLA (t10,c12)-ME supplementation in the late dry period and/or lactation period showed an increase of the probability of pregnancy and a reduction of time to conception in the same reproductive cycle. However, considering that the minimum duration of efficacy studies for reproductive parameters is of at least two reproductive cycles, the FEEDAP Panel is not in a position to conclude on the efficacy of the additive for cows for reproduction.
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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1831/2003 establishes rules governing the Community authorisation of additives for animal nutrition and, in particular, Article 9 defines the terms of the authorisation by the Commission.

The Commission received a dossier from the applicant BASF SE, requesting an authorisation of Omega-6-fatty acid as octadecadienoic acid (conjugated linoleic acid-methylester) as a nutritional additive (Table 1).

Table 1: Description of the substances

| Category of additive | Nutritional additive |
|----------------------|----------------------|
| Description          | Omega-6-fatty acid as octadecadienoic acid (conjugated linoleic acid-methylester) |

On 5 January 2016, the Panel on Additives and Products or Substances used in Animal Feed of the European Food Safety Authority ("Authority"), in its opinion on the safety and efficacy of the product, concluded that CLA does not positively affect energy balance of sows and their fertility. The number of piglets and their performance are also not influenced by CLA feeding to sows.

The Commission gave the possibility to the applicant to submit complementary information in order to complete the assessment on the efficacy and to allow a revision of Authority’s opinion.

The Commission has received new data on the efficacy of Omega-6-fatty acid as octadecadienoic acid (conjugated linoleic acid-methylester).

In view of the above, the Commission asks the Authority to deliver a new opinion on the efficacy of Omega-6-fatty acid as octadecadienoic acid (conjugated linoleic acid-methylester) as a nutritional additive for sows and cows based on the additional data submitted by the applicant.

1.2. Additional information

Omega-6 essential unsaturated fatty acids, as octadecadienoic acid, are included in the European Union Register of Feed Additives following the provisions of Article 10(1) of Regulation (EC) No 1831/2003.¹

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier² following a previous application on the same product.³

2.2. Methodologies

The approach followed by the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) to assess the efficacy of isomer t10,c12 of methyl ester of conjugated linoleic acid (CLA (t10,c12)-ME) for sows and cows is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance documents: Guidance on nutritional additives (EFSA FEEDAP Panel, 2012) and the Technical guidance on tolerance and efficacy studies in target animals (EFSA FEEDAP Panel, 2011).

¹ Commission list of the authorised additives in feedingstuffs published in application of Article 9t (b) of Council Directive 79/524/EEC concerning additives in feedingstuffs, 2004/C 50/01. OJ 25.2.2004 C 50/1.
² FEED dossier reference: FAD-2016-0033.
³ FEED dossier reference: FAD-2010-0248.
3. Assessment

The current application is for the assessment of the efficacy of the active substance methyl ester of CLA (t10,c12 isomer) for sows and cows for reproduction. CLA (t10,c12)-ME is contained in two formulated additives (Lutalin® and Lutrell® Pure, a rumen protected formulation) together with an approximately equal proportion of methylated CLA cis9,trans11-C18:2 isomer (CLA (c9,t11)-ME). CLA (t10, c12)-ME is classified as a nutritional additive, functional group: vitamins, provitamins and chemically well-defined substances having similar effects. Lutalin® is intended for use in pigs and ruminants whereas Lutrell® Pure is aimed only for ruminants. More details about the mode of action and the effects of CLA in pigs for fattening, sows and dairy cows are described in a previous opinion (EFSA FEEDAP Panel, 2016).

According to a literature review conducted by the applicant, the main effects of supplemental methylated CLA would consist of a reduction in fat synthesis and consequent improvement in performance and reproduction of sows and dairy cows (EFSA FEEDAP Panel, 2016).

The FEEDAP Panel, in its previous opinion on the safety and efficacy of the additive (EFSA FEEDAP Panel, 2016), concluded that CLA (t10,c12)-ME does not positively affect energy balance of sows and their fertility. The number of piglets and their performance are also not significantly influenced by CLA (t10,c12)-ME feeding to sows. Regarding cows for reproduction, energy balance in early lactation was improved by CLA (t10,c12)-ME; reproductive parameters, however, were not significantly influenced.

The applicant has provided new information on the efficacy of the product for sows and cows for reproduction that are the subject of this assessment.

3.1. Characterisation

Linoleic acid (LA, octadecadienoic acid) is an omega-6 fatty acid with unconjugated (separated by a methylene group) double bonds at C9 and C12 positions in cis/cis conformation.

Conjugated linoleic acids are a family of geometrical isomers of LA found mostly in meat and dairy products from ruminants. The double bonds of CLA are conjugated and separated by a single bond. The most biologically relevant isomers are cis (c)9, trans (t)11-C18:2 and t10,c12-C18:2.

The active substance under assessment is the methyl ester of CLA (t10,c12) (EFSA FEEDAP Panel, 2016). Figure 1 represents the structural formula.

![Figure 1: Structural formula of CLA(t10,c12) methylester](image)

This additive has been characterised in a previous scientific opinion (EFSA FEEDAP Panel, 2016). It has two different formulations:

- Lutalin®: a liquid formulation of the additive that contains by specification a minimum of 28% of CLA (t10,c12)-ME. It also contains ≥ 28% CLA (c9,t11)-ME, < 2% free CLA (t10,c12), < 2% free CLA (c9,t11). It is intended for use in pigs and ruminants.
- Lutrell® Pure: a solid formulation intended for use in ruminants only. It contains by specification ≥ 9% CLA (t10,c12)-ME. It also contains ≥ 9% CLA (c9,t11)-ME, < 1% of CLA (t10,c12), < 1% CLA (c9,t11).

3.1.1. Conditions of use

The recommended use level for sows is 1.5 g CLA (t10,c12)-ME/kg feed (min 88% dry matter), which corresponds to 5 g of the liquid formulation of the additive (Lutalin®)/kg feed. The maximum use level is 5 g CLA (t10,c12)-ME/kg feed, corresponding to 17 g Lutalin®/kg feed.

The recommended use levels for cows are in the range of 5–10 g CLA (t10,c12)-ME per head and day, which correspond to 50–100 g of the solid formulation (Lutrell® Pure) or to 17–34 g of the liquid

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4 FAD-2010-0248/Technical dossier/Supplementary information April 2014/EFSA Sin reply/Reply to question 13.
formulation (Lutalin®) per head per day. The maximum use level is 30 g CLA (t10,c12)-ME per head and day, which corresponds to 300 g of the solid formulation or to 100 g of the liquid formulation per head per day.

3.2. Efficacy

In its previous assessment, the FEEDAP Panel concluded that the addition of CLA (t10,c12), and therefore CLA (t10,c12)-ME, did not positively affect energy balance of sows and their fertility and did not significantly improve sows’ or piglets’ performance. In addition, as regards reproductive parameters of cows, it was concluded that reproductive parameters (e.g. days to first ovulation, days to pregnancy, number of services per pregnancy and conception rate) were not significantly influenced by CLA.

The applicant has provided additional data on the effects of the additive on reproductive performance that are the subject of this assessment.

It should be noted that, for the purposes of this assessment, it is assumed that CLA-ME and free CLA are bioequivalent, and studies using the different forms of CLA have been analysed on the basis of this assumption. In fact, direct evidence of bioequivalence of the two forms of CLA (methylated and free CLA isomers) for reproductive parameters is lacking. Free CLA and CLA-ME do, however, have and it is reasonable to propose that high esterase activities in gut tissues will lead to the rapid release and absorption of CLA from CLA-ME.

It should also be noted that CLA isomers other than (t10,c12) are inevitably present in the additives used in efficacy studies. It is impractical to manufacture a product containing pure individual CLA isomers. As different CLA have different biological effects (Pariza et al., 2001), benefits attributed to the CLA (t10,c12) in the product may stem from, or be mediated by, other isomers present in the additive.

To the knowledge of the FEEDAP Panel, CLA (t10,c12)-ME deficiency in farm animals has not been recognised under experimental or field conditions. Therefore, the FEEDAP Panel considers that there is no evidence of the essentiality of CLA (t10,c12)-ME in animal nutrition. Consequently, the allocation of this additive to the category ‘nutritional additives’ (Section 1.1) seems not to be justified.

3.2.1. Efficacy for sows for reproduction

In the previous opinion, it was concluded that ‘An effect of CLA in sows has been claimed in terms of improved reproduction and litter performance. Taken all together, CLA does not positively affect energy balance of sows and their fertility (i.e. days from weaning to first oestrus). Adjusting litter size or not might have masked potentially positive results on body weight changes of sows. The number of piglets and their performance are also not influenced by CLA feeding to sows’.

Two papers reviewed in the previous opinion provided indirect evidence that CLA might improve reproductive performance in sows. Cordero et al. (2011) reported a study with 17 lactating sows receiving no CLA and 17 receiving dietary CLA (10 g CLA/kg diet), while Lee et al. (2014) described a similar trial with 9 sows per treatment. Both papers reported a statistically significant decrease in loss of backfat in the CLA group during lactation. However, no other significant effect was observed, including no effect on weaning-oestrus interval. Only one reproduction cycle was studied, thus not complying with the two cycles requested in EFSA Guidance (EFSA FEEDAP Panel, 2011).5

The applicant provided a further study on the influence of CLA on fertility parameters in sows.6 About 120 sows (Porkuss lineage) were distributed into two treatment groups (control and treated, the exact number of sows per group is unclear).7 The basal diet contained barley, wheat and soy meal. During the lactation period, 0.5% Lutalin (corresponding to 1.4 g CLA (t10,c12)-ME/kg feed) was supplemented to the treatment group. The control group received instead 0.5% soya oil. The concentration of the test item in feed during the treatment was not confirmed by analytical data. At parturition, piglets were cross-fostered to make homogeneous litters of maximum 14 piglets/litter.

Farrowing performance (duration of the gestation period, piglets born alive, piglets born dead, total number of piglets born or body weight of the piglet at birth), weaning performance (daily weight gain, number of weaned piglets, suckling piglets mortality or increase in litter weight) and sows’ body

5 EFSA Journal 2011;9(5):2175.
6 Technical dossier/Experimental report FK FE 2013 01.
condition (body weight at farrowing and weaning; body condition score at farrowing and weaning; back fat in front, middle and rear both at farrowing and weaning) were surveyed during the study (1 year). Feed intake was measured from farrowing to the end of weaning. Milk samples were taken from 10 sows per treatment group 1 day after farrowing (to analyse immunoglobulin (Ig) A and IgG concentrations in colostrum) and again from 11 sows per group during the second week after farrowing (to analyse dry matter, crude protein, crude fat and crude ash). Performance was compared between treatment groups by mixed linear models. The sow was included in the model as random effect. Sows were classified in three groups (categorical variable) according to the number of parturitions (up to 3, 4 or 5, 6 or more). The treatment and the number of parturitions of the sows were considered as fixed effects. The milk samples were compared using the Mann–Whitney U-Test (non-parametric) due to the low number of samples.

For the sows that had two consecutive litters during the study, 66 and 71 litters were obtained from the control and treatment groups, respectively. From the parameters studied, significant differences were observed in sows body weight loss during lactation (13 kg in treated sows vs 22 kg in control sows, \( p = 0.01 \)) and back fat thickness at weaning (about 1 mm thicker in treated sows compared to the control only when measured front and rear, \( p < 0.05 \); this becoming 0.6 mm when front, middle and rear measurements were considered). Feed intake in farrowing pen was higher in the treated sows (193 kg) compared to the control (186 kg), \( p = 0.03 \). In relation to the milk parameters surveyed, only crude fat was statistically lower in the treated group (68.8 g/L) compared to the control (75.8 g/L, \( p = 0.03 \)). No significant differences were observed in the rest of parameters surveyed.

The FEEDAP Panel notes that the difference observed between treatments in back fat thickness (0.6 mm) is of limited biological relevance. In addition, the higher feed intake of the treated group compared with the control group could partly justify the lower weight loss (farrowing – weaning) in the treated animals.

Considering the above and the fact that the study presented shortcomings (unclear number of sows with two consecutive litters; no indication on whether creep feed was supplied; supplemented dose not confirmed analytically; no statistical output submitted; no raw data on the performance of sows and piglets; and the effect of the additive on weaning to oestrus interval was not investigated), the FEEDAP Panel cannot conclude on the efficacy of CLA (t10,c12)-ME for sows for reproduction.

### 3.2.2. Efficacy for cows for reproduction

In the previous opinion (EFSA FEEDAP Panel, 2016), it was concluded that ‘Energy balance (body weight loss) in early lactation is improved by feeding CLA as a consequence of reduced milk fat synthesis. To obtain consistent effects, higher doses (\( \geq 6.1 \) g CLA (t10,c12)-ME per cow and day) than for reduced milk fat concentration appear necessary. Also here differences between various CLA products may become apparent. From the reduction of energy losses in the critical early lactation period in which the energy requirement of high yielding cows can mostly not be covered by feed (energy) intake, an improvement of the reproductive performance of cows could be expected. Nevertheless, reproductive parameters (e.g. days to first ovulation, days to pregnancy, number of services per pregnancy and conception rate) were not significantly influenced by giving CLA to cows’.

The applicant provided three scientific papers not considered in the previous opinion, to support the efficacy of the additive for cows for reproduction.

The papers by
Although the study provides some evidence of benefits of CLA to reproduction, it is not possible to assess the differences in energy balance because the dry matter and energy intake were not provided. In addition, the trial was not of adequate duration (minimum of two reproduction cycles) with regard to the EFSA Guidance on tolerance and efficacy studies (EFSA FEEDAP Panel, 2011).

As before, the trials were not of adequate duration (minimum of two reproduction cycles) with regard to the EFSA Guidance on tolerance and efficacy studies (EFSA FEEDAP Panel, 2011).

| Study | Form of the additive | Duration of treatment (days) | Type of oestrus | Dose (g CLA (t10,c12)/day) |
|-------|----------------------|-----------------------------|-----------------|-----------------------------|
|       | Methyl ester of conjugated linoleic acid (t10,c12 isomer) for sows and cows for reproduction |                      |                 |                             |
Overall, it appeared to demonstrate a strong concordance between the nature of the dose response and the predicted optimal dose of CLA (t10,c12) across the reproductive variables evaluated. These results thus appeared to indicate that reproductive performance of dairy cows may be improved by feeding CLA supplements during early lactation.

The applicant presented a report which assessed the relationship between dietary CLA (t10,c12) supplementation and reproductive parameters. As the minimum number of studies to be included in a meta-analysis is three, this endpoint was not considered in the assessment.

The available evidence suggests that dietary CLA (t10,c12) supplementation to dairy cows in the late dry period (from –21 days) and/or in lactation period (up to 140 days) showed benefits on reproductive parameters (probability of pregnancy and reduction of time to conception) in the same reproductive cycle.

4. Conclusions

Owing to methodological shortcomings of the study submitted, including the duration of the study and the limited biological relevance of the effect observed, the FEEDAP Panel cannot conclude on the efficacy of CLA (t10,c12)-ME for sows for reproduction.

The data related to dairy cows indicates that dietary CLA (t10,c12)-ME supplementation in the late dry period and/or lactation period showed an increase of the probability of pregnancy and a reduction of time to conception in the same reproductive cycle. However, considering that the minimum duration of efficacy studies for reproductive parameters is of at least two reproductive cycles, the FEEDAP Panel is not in a position to conclude on the efficacy of the additive for cows for reproduction.

Documentation provided to EFSA

1) Efficacy of methylester of conjugated linoleic acid (t10,c12 isomer) for sows and cows for reproduction. January 2017. Submitted by BASF SE.
2) Efficacy of methylester of conjugated linoleic acid (t10,c12 isomer) for sows and cows for reproduction. Supplementary information. June 2017. Submitted by BASF SE.
3) Efficacy of methylester of conjugated linoleic acid (t10,c12 isomer) for sows and cows for reproduction. Supplementary information. October 2017. Submitted by BASF SE.
4) Efficacy of methylester of conjugated linoleic acid (t10,c12 isomer) for sows and cows for reproduction. Supplementary information. December 2017. Submitted by BASF SE.
Chronology

| Date             | Event                                                                 |
|------------------|----------------------------------------------------------------------|
| 02/06/2016 and   | Dossier received by EFSA                                               |
| 20/12/2016       |                                                                      |
| 27/05/2016       | Reception mandate from the European Commission                        |
| 23/01/2017       | Application validated by EFSA – Start of the scientific assessment    |
| 12/05/2017       | Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. Issues: Efficacy in sows for reproduction and efficacy in cows for reproduction. |
| 08/06/2017       | Reception of supplementary information from the applicant - Scientific assessment re-started |
| 31/08/2017       | Request of additional supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. Issues: Efficacy in cows for reproduction. |
| 05/10/2017       | Request of additional supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. Issues: Efficacy in cows for reproduction. |
| 29/11/2017       | Reception of supplementary information from the applicant - Scientific assessment re-started |
| 18/12/2017       | Reception of supplementary information from the applicant - Scientific assessment re-started |
| 24/01/2019       | Opinion adopted by the FEEDAP Panel. End of the Scientific assessment |

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Pariza MW, Park Y and Cook ME, 2001. The biologically active isomers of conjugated linoleic acid. Progress in Lipid Research, 40, 283–298.

**Abbreviations**

CLA  conjugated linoleic acid  
FEEDAP  EFSA Panel on Additives and Products or Substances used in Animal Feed  
Ig  immunoglobulin  
LA  linoleic acid  
ME  Methyl ester