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Safety of lactic acid and calcium lactate when used as technological additives for all animal species

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Abstract

Following a request from the European Commission, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety lactic acid and calcium lactate for all animal species. In 2015 and in 2017, the Panel on Additives and Products or Substances used in Animal Nutrition (FEEDAP) delivered two opinions on the safety of lactic acid and calcium lactate. In that opinion, the panel concluded that the additive is safe for pigs and ruminants at concentrations of 50,000 mg lactic acid/kg complete feed but could not conclude on the safety for poultry and for pre-ruminants. Now the applicant is proposing a new maximum concentration of 20,000 mg lactic acid/kg feed for all other animal species, with the exclusion of pre-ruminants, and provided a new study in chickens for fattening. Based on the results of the new study, the Panel concluded that 20,000 mg lactic acid/kg complete feed is safe for chickens for fattening. The FEEDAP Panel extrapolates the lowest safe level of 20,000 mg lactic acid/kg complete feed observed in chicken for fattening to all animal species other than pigs and ruminants for which 50,000 mg lactic acid/kg is safe, with the exception of pre-ruminants for which a safe dose could not be established. The maximum content of 20,000 mg lactic acid is equivalent to 24,000 mg calcium lactate and 30,000 mg calcium lactate hydrate (hydrate, n = 4–5). The corresponding maximum content in water for drinking would be 8,000 mg lactic acid/L.

Keywords: Lactic acid, calcium lactate, chickens for fattening, safety

Requestor: European Commission

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1. Introduction

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

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition and in particular, Article 9 defines the terms of such authorisation by the Commission.

The applicant, FEFANA ASBL, is seeking a Community authorisation of Lactic acid and calcium lactate as a feed additive to be used as a preservative for all animal species (Table 1).

Table 1: Description of the substances

Category of additive	Technological additive
Functional group of additive	Preservatives
Description	Lactic acid and Ca-lactate
Target animal category	All animal species
Applicant	FEFANA ASBL
Type of request	New opinion

On 5 July 2017, 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 of the product, could not conclude on the safety of lactic acid and Ca-lactate in all animal species, under the conditions of use as proposed by the applicant.

"based on the studies submitted in chickens for fattening and laying hens, no safe concentration of lactic acid and calcium lactate in complete feed for these species could be identified. Owing the absence of data on tolerated dietary levels of D-lactic acid, no conclusions on the safety of lactic acid in milk replacer for pre-ruminant is possible. Since a safety concentration of lactic acid (and calcium lactate) was established only for pigs and cattle, and not for a third major species, no extrapolation to any other species is possible."

After the discussion with the Member States on the Standing Committee, it was suggested to check the possibility to demonstrate the safety of the additive.

The Commission gave the possibility to the applicant to submit complementary information in order to complete the assessment and to allow a revision of the Authority's opinion. The new data have been received on 14 March 2019.

In view of the above, the Commission asks the Authority to deliver a new opinion on lactic acid and Ca-lactate as a feed additive for all animal species based on the additional data submitted by the applicant.

1.2. Additional information

Lactic acid and calcium lactate are presently listed in the EU Register of Feed Additives as technological additives (functional group: preservatives) for use with feed for all animal species and categories without restrictions, and are subject to re-evaluation. Lactic acid is authorised for use as a feed flavouring up to 5 mg/kg (Regulation (EU) 2017/56).

Lactic acid (E 270) and calcium lactate (E 327) are permitted food additives used in a variety of foods (e.g. nectars, jam, jellies, marmalades, mozzarella and whey cheese, fats of animal or vegetable origin for cooking and/or frying, canned and bottled fruits and vegetables, fresh pasta, beer) according to Regulation (EC) No 1333/2008 on food additives. Specifications for purity are laid down in Directive 2008/84/EC.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) issued an opinion on lactic acid and calcium lactate (JECFA, 1974) allocating an acceptable daily intake (ADI) of 'not limited'. In 1991, this ADI was supported by the Scientific Committee of Food (EC, 1991) and in 2006 iterated in the evaluation of lactate and sodium lactate for poultry carcass treatment (EFSA, 2008a). The European Food Safety Authority (EFSA) has issued several opinions on the use of lactic acid and calcium lactate for carcass decontamination (EFSA, 2006, 2008b; EFSA BIOHAZ Panel, 2011).

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) adopted in 2015, an opinion on the safety and efficacy of lactic acid and calcium lactate as technological additives for all animal species (EFSA FEEDAP Panel, 2015). In that opinion, the FEEDAP Panel could not conclude on the safety of the additive in pre-ruminants and poultry. The same conclusion was reached in the second opinion of the FEEDAP Panel adopted in 2017 (EFSA FEEDAP Panel, 2017a).

The applicant has submitted additional information related to the safety of lactic acid and calcium lactate in poultry.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of additional information[2] to previous applications on the same product.[3]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of lactic acid and calcium lactate is in line with the principles laid down in Regulation (EC) No 429/2008[4] and the relevant guidance documents: Guidance on technological additives (EFSA FEEDAP Panel, 2012), Guidance for the preparation of dossiers for the re-evaluation of certain additives already authorised under Directive 70/524/EEC (EFSA, 2008a) and Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b).

3. Assessment

The additives under assessment are lactic acid and its calcium salt (calcium lactate). Lactic acid is produced by four strains of *Bacillus* spp. (*Bacillus coagulans* LMG S-26145 and DSM 23965, *Bacillus smithii* LMG S-27890 and *Bacillus subtilis* LMG S-27889). Lactic acid is proposed to contain a minimum of 90% of the enantiomer L(+)-lactic acid and a maximum of 10% of the enantiomer D(-)-lactic acid. The additive is provided as an aqueous solution specified to contain a minimum of 72% (w/w) lactic acid. The additive calcium lactate is produced by neutralising lactic acid with calcium hydroxide, and it is specified to contain $\geq$ 98% (as dry matter (DM), w/w) calcium lactate. Lactic acid and calcium lactate are intended to be used as technological additives, functional group preservatives in feedingstuffs for all animal species.

In its previous opinion (EFSA FEEDAP Panel, 2015), the Panel concluded that lactic acid (and its calcium salt) is safe for pigs and functional ruminants at concentrations up to 50,000 mg/kg complete feed and 30,000 mg calcium lactate/kg complete feed (and 15,000 mg lactic acid/L water for pigs), while no conclusion could be drawn for pre-ruminants, laying hens and chickens for fattening.

In its subsequent opinion (EFSA FEEDAP Panel, 2017), the Panel concluded that 'based on the studies submitted in chickens for fattening and laying hens, no safe concentration of lactic acid and calcium lactate in complete feed for these species could be identified. Owing the absence of data on tolerated dietary levels of D-lactic acid, no conclusions on the safety of lactic acid in milk replacer for pre-ruminant is possible. Since a safe concentration of lactic acid (and calcium lactate) was established only for pigs and cattle, and not for a third major species, no extrapolation to any other species is possible'.

The applicant is now proposing new maximum content in feedingstuffs for all animal species and submitting new information to support the safety for the target animals.

3.1. Conditions of use

Lactic acid and calcium lactate (anhydrous and hydrate) are proposed for use as preservatives in feedingstuffs, and in water for drinking in the case of the lactic acid, for all animal species and categories.

[2] FEED dossier reference: FAD-2019-0038.
[3] FEED dossier reference: FAD-2010-0133 and FAD-2016-0053.
[4] Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

In the original application, the proposed maximum content was 50,000 mg lactic acid/kg feed, 30,000 mg calcium lactate kg/complete feed and 30,000 mg lactic acid/L water. The applicant is proposing new conditions of use with regard to the original application. The newly proposed maximum contents are:

i) Pigs: 50,000 mg lactic acid/kg feed, 30,000 mg calcium lactate kg/complete feed and 15,000 mg lactic acid/L water.
ii) Ruminants: 50,000 mg lactic acid/kg feed, 30,000 mg calcium lactate kg/complete feed.
iii) All other animal species (except pre-ruminants): 20,000 mg lactic acid/kg feed, equivalent to 24,000 mg calcium lactate (active) or 30,000 mg calcium lactate (additive; hydrate, n = 4–5)/kg complete feed.

3.2. Safety

3.2.1. Safety for the target species

3.2.1.1. Tolerance study with chickens for fattening

A total of 880 one-day-old male chickens (Ross 308) was fed diets supplemented with 0; 10,000 (0.5× the maximum recommended dose), 20,000 (1× the maximum recommended dose) or 30,000 (1.5× the maximum recommended dose) mg lactic acid/kg feed. Group size was 10 replicates with 22 birds each. The diets (starter, from day 1 to day 21; finisher, from day 22 to day 42), consisting mainly of maize, wheat, soybean and soybean meal, were calculated to be isonitrogenous (starter: 227 g CP/kg, met + cys 9.9 g/kg; finisher: 197 g CP/kg, met + cys 8.9 g/kg) and isoenergetic (starter: 12.7 MJ AMEn/kg; finisher: 13.4 MJ AMEn/kg) among treatments. The concentration of the additive in the diets was analytically confirmed. The diets contained also titanium as an inert marker for digestibility analysis. Feeds (mash form) and water were offered for *ad libitum* intake for 42 days. Health status and mortality were monitored daily and the most probable cause of death, determined by necropsy. Body weight (pen) was recorded at start, at days 21 and 42, feed intake was measured daily, average daily body weight gain and feed to gain ratio were calculated for the corresponding intervals. At the end of the experiment (day 42), two birds per pen (20/treatment) were randomly selected for blood sampling, then killed for necropsy and tibia collection. Routine blood haematology and biochemistry[5] parameters were determined. Necropsy included weight and gross examination of tissues, and those birds showing macroscopic alterations were submitted to microscopic evaluation (histopathology). Tibiae were analysed for Ca and P concentration. Excreta were collected per pen during the last three consecutive days of the experiment and analysed for titanium, dry matter, calcium and phosphorus. An analysis of variance (ANOVA) was performed with the data considering the pen or the bird (blood and tibia analysis) as the experimental unit and group means were compared by Tukey's test. The significance level was set at $p < 0.05$.

Mortality and culling of birds were low (overall 5.7%) and not affected by treatment. Final body weight (mean 3,060 g) and body weight gain (mean 71.9 g/day), daily feed intake (mean 106.5 g/day) and feed to gain ratio (mean 1.48) were not affected by treatments. There were some significant differences in the haematological and biochemical parameters measured, which included: (i) a higher packed cell volume at the dose of 20,000 mg/kg feed compared to control and 30,000 mg/kg feed (21.3 vs. 19.0 and 18.4%, respectively), (ii) a higher mean corpuscular volume at the dose of 20,000 mg/kg feed compared to 30,000 mg/kg feed (82.2 vs. 74.3 fL), (iii) a lower total leucocyte count at the dose of 20,000 mg/kg feed compared to 10,000 and 30,000 mg/kg feed (7.51 vs. 8.13 and 8.09 $\times$ 10^3/μL, respectively), (iv) a lower cholesterol concentration at the dose of 30,000 mg/kg feed compared to 10,000 mg/kg feed (118 vs. 130 mg/dL) and (v) a higher calcium concentration at the dose of 20,000 mg/kg feed compared to 10,000 mg/kg feed (12.0 vs. 11.3 mg/dL).The modifications did not show a clear pattern, were small and not dose related. Therefore, they are not considered of concern.

No treatment effects were observed either in the tibia ash, calcium and phosphorus content or in the calcium and phosphorus retention.

[5] Haematology: Total erythrocyte count, packed cell volume, haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, total leucocyte count, differential leucocyte count, platelet count, prothrombin time and fibrinogen. Biochemistry: Sodium, potassium, chloride, calcium, phosphate, magnesium, total protein, albumin, globulin, glucose, urea/uric acid, cholesterol, creatinine, bilirubin, acute phase proteins (ovotransferrin), amylase, alanine aminotransferase activity (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and creatinine kinase.

3.2.1.2. Conclusion on the safety for chickens for fattening

The lactic acid supplementation up to 30,000 mg/kg feed did not adversely affect health and performance of chickens. The maximum use level of 20,000 mg/kg complete feed is therefore considered safe for chickens for fattening, with a margin of safety of 1.5.

3.2.1.3. Safety for all animal species

In its previous opinions, the FEEDAP Panel concluded that 50,000 mg lactic acid/kg complete feed is safe for functional ruminants and pigs.

The current opinion establishes 20,000 mg lactic acid/kg complete feed as safe for chickens for fattening. Safe dietary levels of an additive in three major species allow to extrapolate to other animal species/categories, provided a sufficient margin of safety is demonstrated. A margin of safety of > 2 for functional ruminants, of 2.5 for pigs and of 1.5 for chickens was established, which are considered sufficient for an organic acid when used as a feed additive. Consequently, the FEEDAP Panel extrapolates the lowest safe level of 20,000 mg lactic acid/kg complete feed observed in chickens to all other animal species/categories. Pre-ruminant animals (calves, kids and lambs) are exempted from this extrapolation, since they are known to be particularly sensitive to D-lactic acid which is contained in the additive lactic acid, and no specific data were provided.

The maximum content of 20,000 mg lactic acid is equivalent to 24,000 mg calcium lactate and 30,000 mg calcium lactate hydrate (hydrate, n = 4–5). The corresponding maximum content in water for drinking would be 8,000 mg lactic acid/L.

4. Conclusions

Based on the results of a newly submitted tolerance study in chickens for fattening, the Panel concludes that 20,000 mg lactic acid/kg complete feed is safe for chickens for fattening. Considering this and the fact that safety of lactic acid at 50,000 mg/kg was shown in functional ruminants and pigs, the FEEDAP Panel considers that inclusion of lactic acid at 20,000 mg/kg complete feed is safe for all animal species and categories with the exception of pre-ruminants, for which a safe dose cannot be established. The maximum content of 20,000 mg lactic acid is equivalent to 24,000 mg calcium lactate (active) and 30,000 mg calcium lactate (additive; hydrate, n = 4–5). The corresponding maximum content in water for drinking would be 8,000 mg lactic acid/L.

Documentation as provided to EFSA/Chronology

Date	Event
15/05/2019	Dossier received by EFSA. Lactic acid and calcium lactate for all animal species. FEFANA asbl
23/05/2019	Reception mandate from the European Commission
04/06/2019	Application validated by EFSA – Start of the scientific assessment
12/11/2019	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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Abbreviations

ADI	acceptable daily intake
AMEn	apparent metabolisable energy, nitrogen-corrected
ANOVA	analysis of variance
CP	crude protein
DM	dry matter
FAO	Food and Agriculture Organization
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
WHO	World Health Organization