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Safety of Lancer (lanthanide citrate) as a zootechnical additive for weaned piglets

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)

Abstract

Lancer (lanthanide citrate) is a feed additive mainly consisting of two rare earth elements, lanthanum (La) and cerium (Ce), in their citrate forms. Lancer has not been previously authorised in the European Union. In 2013, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) issued an opinion on the safety and efficacy of Lancer as a zootechnical feed additive for weaned piglets. In its opinion the FEEDAP Panel could not conclude on the safety of the additive for the target species, on the safety for the consumer and on the safety for the environment. As a result of the additional information provided by the applicant, the FEEDAP Panel concluded that the additive Lancer is safe for weaned piglets when used at the maximum recommended dose of 250 mg/kg complete feed. In view of concerns over the possible developmental neurotoxicity of La, the many gaps in the available toxicological information on Ce and La, the absence of studies of long-term toxicity, carcinogenicity, reproductive toxicity and developmental toxicity of Lancer, and the absence of residue data in edible tissues, the FEEDAP Panel cannot conclude on the safety of Lancer for the consumer. In the absence of adequate data the FEEDAP Panel cannot conclude on the safety of Lancer for the environment.

Keywords: Lancer, lanthanide citrate, zootechnical additive, weaned piglets, safety

Requestor: European Commission

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Amendment: This scientific opinion has been amended following the adoption of the decision of the Commission on confidentiality claims submitted by the applicant, in accordance with Article 8(6) and Article 18 of Regulation (EC) No 1831/2003.

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Summary

Following a request from the European Commission, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety of Lancer (lanthanide citrate) as a zootechnical additive (other zootechnical additives) for weaned piglets.

Lancer is a feed additive mainly consisting of two rare earth elements, lanthanum (La) and cerium (Ce), in their citrate forms. Lancer has not been previously authorised in the European Union.

In 2013, the FEEDAP Panel issued an opinion on the safety and efficacy of the additive. In that opinion, the FEEDAP Panel could not conclude on the safety of the additive for the target species because of serious flaws found in the tolerance studies provided. The Panel did not conclude on consumer safety as a no observed adverse effect level (NOAEL) could not be set and it could not be excluded that there would be consumer exposure to residues derived from the additive. Finally, in the absence of data on the toxicity of the additive to terrestrial organisms in the environment, a full environmental assessment could not be completed.

The applicant submitted additional information related to the safety of the additive for the target species, the consumer and the environment and this new information is the subject of this opinion.

The FEEDAP Panel concluded that the additive Lancer is safe for weaned piglets when used at the maximum recommended dose of 250 mg/kg complete feed.

As no new information is available to indicate the extent to which ingested Lancer and its component chemicals may be absorbed from the gastrointestinal tract, may accumulate in the body or leave residues in edible tissues of the target animals, the level of exposure of consumers is still not known.

In the re-evaluation of the results of the 90-day rat toxicity study, a no observed effect level (NOEL) of 300 mg/kg bw day was identified for forestomach hyperplasia. This lesion was considered of no relevance for consumer safety.

In view of concerns over the possible developmental neurotoxicity of La, the many gaps in the available toxicological information on Ce and La, the absence of studies of long-term toxicity, carcinogenicity, reproductive toxicity and developmental toxicity of Lancer, and the absence of residue data in edible tissues, the FEEDAP Panel cannot conclude on the safety of Lancer for the consumer.

Information needed for the assessment of the exposure of the soil to La and Ce and adequate data on plant and earthworm ecotoxicity has not been provided. Predicted environmental concentration (PEC) and predicted no effect concentration (PNEC) values have not been provided and therefore, no risk quotient can be determined. Consequently, in the absence of adequate data, the FEEDAP Panel cannot conclude on the safety of Lancer for the environment.

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

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 thereof defines the terms of such authorisation by the Commission.

The applicant Treibacher Industrie AG is seeking an authorisation of its lanthanide citrate (Lancer), to be used as zootechnical additive in weaned piglets (Table 1).

Table 1: Description of the substance

Category of additive	Zootechnical additives
Functional group of additive	Other zootechnical additives
Description	Lanthanide citrate (cerium citrate and lanthanum citrate) (IUPAC nomenclature), yellow, crystalline powder
Target animal category	Weaned piglets
Applicant	Treibacher Industrie AG
Type of request	New Opinion

On 16 April 2013, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) of the European Food Safety Authority ('Authority'), in its opinion on the safety and efficacy of the product, raised concerns on animal health and consumer safety, because of the absence of an adequate tolerance study for weaned piglets and of an appropriate study of consumer exposure. In addition, the safety for terrestrial organisms in the environment was not tested, so the FEEDAP Panel could not conclude a full assessment on the environment.

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

The Commission has now received an additional dossier from the applicant on Lancer, with supplementary information concerning safety studies of the additive.

In view of the above, the Commission asks the Authority to deliver a new opinion on the safety of Lancer as a zootechnical additive in feed for weaned piglets based on the additional data submitted by the applicant.

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 a previous application on the same product.[3]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of Lancer is in line with the principles laid down in Regulation (EC) No 429/2008[4] and the relevant guidance documents: Guidance on zootechnical additives (EFSA FEEDAP Panel, 2012a),Technical guidance: Tolerance and efficacy studies in target animals (EFSA FEEDAP Panel, 2011), Technical Guidance for assessing the safety of feed additives for the environment (EFSA, 2008), Guidance for establishing the safety of additives for the consumer (EFSA FEEDAP Panel, 2012b).

[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.
[2] FEED dossier reference: FAD-2015-0041.
[3] FEED dossier reference: FAD-2011-0050.
[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.

3. Assessment

The additive Lancer mainly consists of two rare earth elements, lanthanum (La) and cerium (Ce), in their citrate forms. It is intended to be used as a zootechnical additive (functional group: other zootechnical additives) in feed for weaned piglets. This additive has not previously been authorised in the European Union.

Lancer is intended for use in weaned piglets up to 120 days of age at a dose of 250 mg/kg complete feedingstuffs either by direct addition to feed or via a premixture (EFSA FEEDAP Panel, 2013).

The European Food Safety Authority (EFSA) FEEDAP Panel adopted, in 2013, an opinion on the safety and efficacy of the product as a zootechnical additive for weaned piglets (EFSA FEEDAP Panel, 2013). In that opinion, the FEEDAP Panel could not conclude on the safety of the additive for the target species because of serious flaws found in the tolerance studies provided. The Panel did not conclude on consumer safety as a no observed adverse effect level (NOAEL) could not be set and it could not be excluded that there would be consumer exposure to residues derived from the additive. Finally, in the absence of data on the environmental toxicity of the additive to terrestrial organisms, a full environmental assessment could not be completed.

The applicant has submitted additional information related to the safety of the additive for the target species, the consumer and the environment and this new information is the subject of this opinion.

3.1. Safety

3.1.1. Safety for the target species

A tolerance study was performed to evaluate the tolerance of weaned piglets to Lancer.[5]

In total, 56 weaned piglets of 4 weeks of age (Piétrain × Large White, 28 males and 28 females) were used in this experiment. Piglets were physically examined and weighed on arrival and blood samples were taken. All piglets were found to be healthy.

After a 7-day acclimation period, piglets were assigned to one of four treatment groups based on body weight and sex. The experimental set-up was a randomised block design with four dietary treatments: control (non-supplemented diet), supplementation with Lancer at 250 mg/kg complete feed (1× maximum recommended use level), 1,250 mg/kg complete feed (5×) and 2,500 mg/kg (10×). There were seven replicates (pens) per treatment with two piglets (one male and one female) per replicate. Doses of the additive were confirmed by analysis. Experimental diets were provided *ad libitum* for 6 weeks. Animals were observed (including behaviour, clinical status, signs of illness, consistency and colour of faeces) every day and mortality was recorded daily. Piglets were weighed weekly, feed intake was registered twice per week and feed to gain calculated. Clinical examinations[6] were performed weekly. Four pens (four males and four females) per treatment were selected for blood sampling and necropsy. Blood samples were taken from those 32 piglets (eight per treatment) at days 1 and 42 for measurement of haematological[7] and serum biochemistry parameters.[8] On days 42–43, the same 32 piglets were killed and subjected to a complete necropsy. Histology was performed on selected organs (kidneys, liver, spleen, heart, lung, pancreas, gall bladder, stomach, jejunum, ileum, colon, caecum, spinal cord, brain, ovaries (when applicable), testes (when applicable), bone and marrow, urinary bladder, lymph nodes and thymus). Heart, kidneys, liver and spleen were also weighed.

In the statistical analysis, the individual animal was considered as the experimental unit except for feed intake and feed conversion where the pen was considered as the experimental unit. Data from supplemented animals were compared with the control group. Clinical examination and gross

[5] Technical dossier/Tolerance study Lancer.

[6] Rectal temperature, general behaviour, breathing pattern, abnormal body shape, abnormal swellings on the body surface, skin abnormalities, pruritus, lameness and joint abnormalities, neurological signs, abnormalities of the eyes and diarrhoea.

[7] Red blood cell (RBC) counts, reticulocyte count, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), haemoglobin (Hb), haematocrit/packed cell volume (PCV), white blood cell counts: total (WBC) and differential counts, platelet count.

[8] Sodium, potassium, chloride, calcium, phosphorous, magnesium, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), creatine kinase (CK), total proteins, albumin, globulin, glucose, amylase, total bilirubin, direct bilirubin, cholesterol.

pathology frequency values were compared among groups using the chi-squared test. Body weight, body weight gain, feed intake, feed conversion ratio, haematology and blood chemistry data were subjected to ANOVA with repeated measures in time. Statistical significance was declared at $p < 0.05$.

No mortalities were observed during the study. Dietary treatments did not have any effect on the frequency of abnormalities from the clinical examination and on the haematology and biochemical parameters. No treatment-related lesions were observed in the gross pathology. Weights of heart, liver, spleen and kidneys were similar for controls and all treatment groups (no statistics done) and no treatment-related microscopic findings were observed. Average final body weight (48–50 kg), average daily body weight gain (0.94–0.98 kg) and average daily feed intake (1.32–1.39 kg) were not significantly different in treated and control groups during the study (42 days).

Based on the results of the tolerance study, the use of the additive at up to 10 times the recommended use level did not have any adverse effect on piglet performance, haematology and blood chemistry parameters, gross pathology or microscopic findings.

The FEEDAP Panel concludes that the additive Lancer is safe for weaned piglets when used at the maximum recommended dose of 250 mg/kg complete feed.

3.1.2. Safety for the consumer

In the previous opinion (EFSA FEEDAP Panel, 2013), one study suggested that neither La nor Ce deposited in tissues of piglets. However, as this was not consistent with data found in other species (cattle and rats), the FEEDAP Panel was reluctant to conclude that there was no potential for consumer exposure. In addition, as a level of exposure that would not cause adverse effects had not been identified, the Panel was unable to relate any possible exposure to a safe dose.

3.1.2.1. Toxicology

The toxicology of Lancer was reviewed in the previous FEEDAP Opinion (EFSA FEEDAP Panel, 2013). Lancer had been shown to be of low acute oral toxicity in rats. A 28-day oral toxicity study in rats showed changes in some serum biochemistry parameters (increased activities of ALP and ALT) at 250 mg/kg bw per day or more, with no NOAEL identified. A 90-day oral toxicity study in rats was reported to show increased incidences of hyperplasia of the forestomach epithelium at all doses tested (100 mg Lancer/kg bw per day (8.5 mg La/kg bw per day; 16.3 Ce/kg bw per day); 300 and 600 mg Lancer/kg bw per day or more). No chronic toxicity or carcinogenicity studies were available. The results of mutagenicity studies (a bacterial reverse mutation test, an *in vitro* mammalian chromosome aberration test and an *in vitro* mammalian micronucleus test) indicated that Lancer is not genotoxic. No reproduction studies were available for Lancer.

Following the previous opinion of the FEEDAP Panel, the applicant submitted a peer review of the histopathology results of the 90-day rat study on Lancer that had been described in the previous opinion (EFSA FEEDAP Panel, 2013). The study had used dose levels of 0, 100, 300 and 600 mg Lancer/kg bw per day. A second pathologist had reviewed the histopathology of the lungs, mesenteric lymph nodes and the stomach. The two pathologists produced a consensus opinion, which reclassified some of the lesions.[9] The pathologists' assessment was reviewed by the FEEDAP Panel.

Lung changes were found in some males from the 100 mg Lancer/kg bw per day group and in some males and females from the 600 mg Lancer/kg bw per day group, but they were considered to be local reactions due to accidental aspiration of the test material and therefore, not of relevance for the assessment of the systemic toxicity of Lancer.

An apparent increase of microgranulomas in mesenteric lymph nodes was noted at the highest dose (600 mg Lancer/kg bw per day) only in males. However, it was not clear that the effect was caused by treatment with Lancer, because of the high prevalence of this lesion in all groups including controls and the absence of a response in males at lower doses or in females at any dose.

A minimal to mild epithelial hyperplasia of the limiting ridge in the forestomach was observed in both sexes at 600 mg/kg bw per day. This effect was not seen in any control animals and was seen only in one male from each of the other two dose groups (100 and 300 mg Lancer/kg bw per day). A NOAEL of 300 mg/kg bw per day was identified for this effect. It should be noted that this organ is highly and non-specifically reacting to locally irritating compounds. Moreover, the forestomach and its particular sensitivity to local irritants has no equivalent in humans, hence the effects described are considered irrelevant to human risk assessment.

[9] Technical dossier/Lanthanide_Expert_statement_90_day_rat_study.

The effects seen in this study were lung lesions attributed to aspiration accidents, an equivocal increase in the prevalence of lymph node microgranulomas in only top-dose males and mild hyperplasia at the top-dose only in a non-glandular forestomach area, which is not representative of humans. The FEEDAP Panel identified a no observed effect level (NOEL) of 300 mg Lancer/kg bw per day, but considered that the NOAEL for the study was the top-dose of 600 mg Lance/kg bw per day. Therefore, the FEEDAP Panel concludes that no effects of relevance for consumer risk assessment were seen in the 90-day rat toxicity study at repeated doses up to 600 mg Lancer/kg bw per day.

Some studies of compounds of La other than the citrate were available. In a three-generation rat study, a mixture of oxides incorporating La oxide at concentrations of 0.4–400 mg La/kg diet (equivalent to up to 36 mg La/kg bw per day) had no effect on any parameter other than a slight reduction in bodyweight gain of young rats at all dose levels (as compared with controls). A poorly described rat developmental toxicity study of 'rare earth nitrates' showed decreased survival of offspring at 80–400 mg/kg bw, but no effect at 16 mg/kg bw (information on La doses was not available). A mouse developmental toxicity study of lanthanum chloride ($LaCl_3$) found various effects on neurobehavioural development (differences in the emergence of swimming and walking behaviour, eye and ear opening, and differences in touch response and visual placing response) at drinking water concentrations of 125 mg/L (equivalent to 25 mg $LaCl_3$/kg bw per day or 9.3 mg La/kg bw per day) or more, with no NOAEL identified. Neurotoxicological effects of $LaCl_3$ were evaluated in rats exposed throughout gestation and lactation (mothers dosed by gavage with 0, 0.1, 2 or 40 mg/kg bw per day) and up to 6 months of age (same doses as given to mothers). Adverse effects on learning (Morris water maze) were observed at 2 and 40 mg $LaCl_3$/kg bw per day (0.73 mg La/kg bw per day or more), increasing with dose. The NOAEL was 0.1 mg $LaCl_3$/kg bw per day, 0.037 mg La/kg bw per day (He et al., 2008).

3.1.2.2. Conclusions on toxicology

The toxicological studies that have been performed using Lancer showed no effects of relevance for consumer safety at oral doses of up to 600 mg Lancer/kg bw per day, other than the changes in serum enzyme activities reported at doses of 250 mg Lancer/kg bw per day or more in the 28-day rat study. However, these effects did not appear to be associated with any toxicity to the liver or other tissues, and the findings were not confirmed in the 90-day rat study which showed no changes to blood biochemistry parameters at up to 600 mg Lancer/kg bw per day. Lancer has not been tested in any reproduction/developmental toxicity, chronic toxicity or carcinogenicity studies, but it was shown to be non-genotoxic.

The FEEDAP Panel notes that another La compound induced adverse effects on neurobehavioural development in mice at doses of 25 mg $LaCl_3$/kg bw per day (9.3 mg La/kg bw per day) or more. The same compound caused neurotoxicological effects at doses of 2 mg $LaCl_3$/kg bw per day (0.73 mg La/kg bw per day) or more in rats exposed throughout gestation and lactation and the first 6 months of life. This raises a concern about whether Lancer could cause similar effects (Briner et al., 2000). This highlights the need for an investigation of the possible reproduction/developmental toxicity of Lancer, including a consideration of possible neurodevelopmental effects.

No information was provided on the toxicology of Ce citrate, but the FEEDAP Panel notes that Ce toxicology has been assessed by the US Environmental Protection Agency (EPA, 2009). The toxicological data available to the EPA did not allow the establishment of an average daily intake (ADI) because of paucity or absence of relevant data on genotoxicity, carcinogenicity, reproductive toxicity and target organ toxicity.

3.1.2.3. Conclusions on safety for the consumer

No new information was available to indicate the extent to which ingested Lancer and its component chemicals may be absorbed from the gastrointestinal tract. There was no information available on whether La or Ce may accumulate in the body or leave residues in edible tissues of the target animals. Consequently, the level of exposure of consumers is still not known.

In the re-evaluation of the results of the 90-day rat toxicity study, a NOEL of 300 mg Lancer/kg bw day was identified for forestomach hyperplasia. This lesion was considered of no relevance to consumer safety. No effects of relevance to consumer risk assessment were seen at any dose tested (i.e. up to 600 mg Lancer/kg bw per day).

However, in view of concerns over (i) the possible developmental neurotoxicity of La, (ii) the many gaps in the available toxicological information on Ce and La, (iii) the absence of studies of long-term toxicity, carcinogenicity, reproductive toxicity and developmental toxicity of Lancer, and (iv) the

absence of residue data in edible tissues, the FEEDAP Panel cannot conclude on the safety of Lancer for the consumer.

3.1.3. Safety for the environment

In its previous opinion, the FEEDAP Panel concluded that *Lanthanum is potentially toxic to environmental relevant species, but its toxicity is highly dependent on speciation. Because of the low solubility of La and Ce in most situations, the additive would probably not cause a concern for the aquatic environment. There are no data on toxicity of the additive to terrestrial organisms. In the absence of such data, a full environmental assessment cannot be completed* (EFSA FEEDAP Panel, 2013). The applicant has provided some additional data to support the safety of Lancer for the environment.

The applicant provided additional information summarising the occurrence of La and Ce in the soil and surface water in Europe to justify that the use of Lancer would not increase the environmental levels of La and Ce.[10] No clear information on measured concentrations of La and Ce in the ground water of EU Member States was provided.

In ecosystems, species may adapt to higher concentrations of naturally occurring elements (such as lanthanides). Therefore, the assessment of environmental risk for La and Ce should be based on the concentrations which will be added to the environmental concentrations. The background concentrations of La and Ce in soil in EU Member State geographic area varies between 1–109 and 1.6 and 266 mg/kg, respectively; however, no calculation on the expected increase of the environmental concentration (predicted environmental concentrations – PEC) of La and Ce was provided.

No prediction of environmental concentrations of La and Ce in ground water based on use of Lancer was provided.

The applicant did not provide adequate data on plant ecotoxicity according to OECD 208 (Terrestrial Plants, Growth Test) and on earthworm ecotoxicity according to OECD 207 (Earthworm, Acute Toxicity Test) or according to OECD 222 (Earthworm Reproduction Test). Consequently, the safe concentrations for soil (calculated as predicted no effect concentration – PNEC) cannot be set.

No PECs and no PNEC values are provided and therefore, no risk quotient can be determined. Consequently, in the absence of adequate data, the FEEDAP Panel cannot conclude on the safety of Lancer for the environment.

3.2. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation[11] and Good Manufacturing Practice.

4. Conclusions

The FEEDAP Panel concludes that the additive Lancer is safe for weaned piglets when used at the maximum recommended dose of 250 mg/kg complete feed.

In view of concerns over (i) the possible developmental neurotoxicity of La, (ii) the many gaps in the available toxicological information on Ce and La, (iii) the absence of studies of long-term toxicity, carcinogenicity, reproductive toxicity and developmental toxicity of Lancer, and (iv) the absence of residue data in edible tissues, the FEEDAP Panel cannot conclude on the safety of Lancer for the consumer.

In the absence of adequate data, the FEEDAP Panel cannot conclude on the safety of Lancer for the environment.

Documentation provided to EFSA

1) Lanthanide citrate (LANCER) for weaned piglets. Supplementary Information. November 2015. Submitted by Treibacher Industrie AG.

[10] Technical dossier/Environmental Risk Assessment Lancer.

[11] Regulation (EC) No 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

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Abbreviations

ADI	average daily intake
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Ce	cerium
CK	creatine kinase
EPA	US Environmental Protection Agency
FEEDAP Panel	EFSA Panel on Additives and Products or Substances used in Animal Feed
GGT	gamma-glutamyl transferase
Hb	haemoglobin
IUPAC	International Union of Pure and Applied Chemists
La	lanthanum
Lancer	lanthanide citrate
LDH	lactate dehydrogenase)
MCHC	mean corpuscular haemoglobin concentration
MCH	mean corpuscular haemoglobin
MCV	mean corpuscular volume
NOEL	no observed effect level
NOAEL	no observed adverse effect level
OECD	Organization for Economic Cooperation and Development
PCV	packed cell volume
PEC	predicted environmental concentration
PNEC	predicted no effect concentration
RBC	red blood cell
WBC	white blood cell