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Assessment of the feed additive consisting of ammonium chloride (Amoklor™) for all ruminants, dogs and cats for the renewal of its authorisation and its extension of use to sows (Latochema Co Ltd)

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Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the assessment of the application for the renewal of authorisation of ammonium chloride (Amoklor™) as a zootechnical additive for all ruminants, dogs and cats and its extension of use in sows for urinary health. The applicant provided evidence that the additive currently in the market complies with the existing conditions of authorisation. There is no new evidence that would lead the FEEDAP Panel to reconsider its previous conclusions. Thus, the Panel concludes that the additive remains safe for ruminants other than lambs for fattening, lambs for fattening, cats and dogs, consumers and the environment under the current authorised conditions of use. Inhalation exposure of the additive is considered very likely. Amoklor™ should be considered a potential respiratory sensitiser but not a skin sensitiser. The additive is not irritant to the skin, but the Panel could not conclude on its eye irritation potential. The present application for renewal of the authorisation does not include a proposal for amending or supplementing the conditions of the original authorisation that would have an impact on the efficacy of the additive. Therefore, there was no need for assessing the efficacy of the additive in the context of the renewal of the authorisation. Regarding the extension of use in sows, the FEEDAP Panel concludes that the additive is safe and efficacious for sows at the inclusion level of 5,000 mg/kg feedingstuffs from week 9th to 11th of gestation and from week 15th of gestation to 1st of lactation.

Keywords: zootechnical additives, other zootechnical additives, ammonium chloride, Amoklor™, safety, efficacy

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1. Introduction

1.1. Background and terms of reference

Regulation (EC) N° 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of feed additive shall submit an application in accordance with Article 7. In particular, Article 14(1) of that Regulation lays down that an application for renewal shall be sent to the Commission at the latest 1 year before the expiry date of the authorisation.

The European Commission received a request from Latochema Co Ltd[2] for the renewal of the authorisation of the additive consisting of ammonium chloride (Amoklor™), when used as a feed additive for all ruminants, dogs and cats and for the authorisation when used as a feed additive for sows for urinary health (category: zootechnical additive; functional group: other zootechnical additive).

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 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 14(1) (renewal of the authorisation). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 17 February 2021.

According to Article 8 of Regulation (EC) No 1831/2003, 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. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the feed additive consisting of ammonium chloride (Amoklor™), when used under the condition of use (see Section 3.1.3).

1.2. Additional information

Amoklor™ is a feed additive based on the active substance ammonium chloride. EFSA has issued two opinions on the safety and efficacy of this additive (EFSA FEEDAP Panel, 2012a, 2016). The safety of ammonium chloride used with foodstuffs has been assessed in two other opinions (EFSA, 2009; EFSA CEF Panel, 2011).

The additive is authorised in the European Union (EU) to be used as a zootechnical additive (4d7), functional group other zootechnical additives (reduction of urinary pH), for lambs for fattening[3] and for ruminants (other than lambs for fattening), cats and dogs.[4]

This additive is applicable to feed intended for the reduction of the risk of renal calculi and milk fever (hypocalcaemia) in ruminants including pregnant cows and dissolution or reduction of the occurrence of struvite stones in animals.

Another product based on ammonium chloride is also authorised in EU from another company as a feed additive for ruminants, cats and dogs (category: zootechnical additive, 4d8).[5]

Ammonium chloride is listed as food flavouring substance according to Commission Decision No 2232/96.[6]

Ammonium chloride is listed as a pharmacologically active substance in veterinary medicinal products and is not subject to maximum residue levels when used in food-producing animals (Commission Regulation (EC) No 37/2010).[7]

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2] Latochema Co Ltd, 2 Riga Fereou & Griva Digeni 3,091, Limassol, Cyprus.
[3] Commission implementing regulation (EU) No 832/2012 of 17 September 2012 concerning the authorisation of a preparation of ammonium chloride as a feed additive for lambs for fattening (holder of authorisation Latochema Co. Ltd) OJ L 251, 18.9.2012, p. 27.
[4] Commission implementing regulation (EU) No 2016/1007 of 22 June 2016 concerning the authorisation of ammonium chloride as a feed additive for ruminants other than lambs for fattening, cats and dogs (holder of authorisation Latochema Co. Ltd) OJ L 165, 23.6.2016, p. 10.
[5] Commission Implementing Regulation (EU) No 725/2013 of 26 July 2013 concerning the authorisation of ammonium chloride as a feed additive for ruminants, cats and dogs (holder of the authorisation BASF SE); OJ L 202 27.7.2013, p. 17.
[6] Commission Decision of 23 February 1999 adopting a register of flavouring substances used in or on foodstuffs drawn up in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council of 28 October 1996 (notified under number C(1999) 399) (1999/217/EC) OJ L 84, 27.3.1999, p. 1.
[7] Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. OJ L15, 20.1.2010, p. 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 dossier[8] in support of the authorisation request for the use of ammonium chloride (Amoklor™), as a feed additive.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment regarding the methods used for the control of the ammonium chloride (Amoklor™) in animal feed are valid and applicable for the current application.[9]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of ammonium chloride (Amoklor™) is in line with the principles laid down in Regulation (EC) No 429/2008[10] and the relevant guidance documents: Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012b), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018) and Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2021).

3. Assessment

The additive (Amoklor™) consisting of ammonium chloride is currently authorised as a zootechnical additive (functional group: other zootechnical additives (reduction of urinary pH)) for ruminants, cats and dogs. The assessment regards the renewal of the authorisation of the feed additive for the species listed before and for the extension of the authorisation to sows. From here onwards, the additive will be referred to as Amoklor™.

3.1. Characterisation

The active substance is ammonium chloride (IUPAC name: ammonium chloride) identified by Chemical Abstracts Service (CAS) No: 12125-02-9, European Chemical Agency (ECHA) InfoCard: 100.031.976 and EC number: 235-186-4. The molecular formula of ammonium chloride is NH_4Cl and its molecular weight is 53.5 g/mol.

The additive is currently authorised as a minimum of 99.5% ammonium chloride and a maximum of 0.5% of sodium chloride. It is further specified by the applicant to contain $\leq$ 0.7% of tricalcium phosphate (as an anticaking agent). The applicant states that no changes in the manufacturing process or composition of the additive have been introduced since the last authorisation.

Analytical data to confirm the specifications were provided for five recent batches of the additive,[11] showing the following average values: 99.7% ammonium chloride (range 99.6%–99.7%), < 0.4% sodium chloride, < 0.7% tricalcium phosphate, 0.1% moisture (range 0.08%–1.2%), < 0.02% sulfate, 0.01% water-insoluble part and a pH of 5.3 (range 5.3–5.4 in 200 g/L at 25°C).

The applicant submitted three further certificates of analysis,[12] showing the following average values: 99.7% ammonium chloride (99.5%–99.8%), 0.02% moisture (0.01%–0.04%), 5.6% iron (4.8%–6.1%), water-insoluble part 0.42 (0.38%–0.5%) and a pH of 6.2 (6%–6.3, 1% solution). Levels of nitrite, analysed in the same three batches, were found below the limit of quantification (LOQ).[13] Levels of cadmium, lead and mercury, arsenic and fluorine were analysed in the same three batches.

[8] FEED dossier reference: FAD-2020-0093.
[9] The full report is available on the EURL website: https://ec.europa.eu/jrc/en/eurl/feed-additives/evaluation-reports.
[10] 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.
[11] Technical dossier/SIn_170222/Annex_II_1, Annex_II_2, Annex_II_3, Annex_II_4, Annex_II_5.
[12] Technical dossier/SIn_170222/Annex_II_13, Annex_II_14, Annex_II_15.
[13] LOQ: nitrite 1 mg/kg.

The results reported for arsenic, cadmium, lead and mercury were not detected in all samples tested and the mean value for fluorine was 52.9 mg/kg (44.3–66.7 mg/kg).[14]

Polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and coplanar dioxin-like polychlorinated biphenyls (co-planar PCBs) were analysed in three independent batches.[15] Dioxins and the sum of dioxins plus dioxin-like PCBs concentrations/levels were 0.062 ng WHO-PCDD/F-TEQ/kg (0.055–0.066) and 0.15 ng WHO-PCDD/F-PCB-TEQ/kg.

The detected amounts of the above described chemical impurities do not raise safety concerns.

3.1.1. Physical properties of the additive

The additive is an odourless white crystalline powder with a density of 1,519 kg/m^3 and a solubility in water of 383 g/L at 25°C. Considering the results on solubility, there is no need to further characterise the fraction of small particles potentially present in the additive (EFSA Scientific Committee, 2021).

The dusting potential of three recent batches of the additive was tested using the Stauber–Heubach method and averaged a value of 1,008 mg/m^3 (range 975–1,050 mg/m^3 air).[16]

The particle size distribution of six recent batches, analysed by laser diffraction, showed an average of 8.3% (range: 4%–11%) of particles smaller than 105 μm in diameter, a 5.6% (range: 3%–8%) of particles smaller than 88 μm in diameter and 1.6% (range: 0.5%–3%) of particles smaller than 44 μm in diameter.[17]

A second set of two batches was analysed by laser diffraction,[18] which showed an average of 80.4% particles less than 440 μm in diameter (range: 78.1%–82.4%), 51.8% of particles less than 310 μm in diameter (range: 48.3%–54.5%) and a 30.5% of particles less than 240 μm in diameter (range: 27.1%–32.9%). No particles below 10 μm in diameter were found.

3.1.2. Stability and homogeneity

No new data were provided regarding the shelf-life, stability and homogeneity of the additive. The data described in the previous opinion (EFSA FEEDAP Panel, 2016) still apply.

No further data supporting stability and homogeneity of the additive are considered necessary for the extension of the authorization in sows.

3.1.3. Conditions of use

The additive is currently authorised for use in (i) lambs for fattening at a maximum content of 10,000 mg/kg complete feed for a feeding period not exceeding 3 months; (ii) ruminants other than lambs for fattening at 10,000 mg/kg complete feed for a feeding period not exceeding 3 months, or 5,000 mg/kg complete feed for a feeding period exceeding 3 months; (iii) cats and dogs at a maximum content of 5,000 mg/kg complete feed. Under other provisions of the authorisation, it is specified that:

1) The additive shall be incorporated into feed in the form of a premixture.
2) The mixture of different sources of ammonium chloride shall not exceed the permitted maximum levels in complete feedingstuffs for ruminants, cats and dogs.
3) For users of the additive and premixtures, feed business operators shall establish operational procedures and appropriate organisational measures to address the potential risks by inhalation, dermal contact or eyes contact. Where risks cannot be reduced to an acceptable level by these procedures and measures, the additive and premixtures shall be used with appropriate personal protective equipment.

The applicant has requested to maintain the same conditions of use as authorised for lambs for fattening, ruminants other than lambs for fattening, cats and dogs.[19]

[14] LOQ: arsenic 0.01 mg/kg, cadmium 0.01 mg/kg, lead 0.05 mg/kg, mercury 0.005 mg/kg, fluorine 1 mg/kg.
[15] Technical dossier/SIn_170222/3. Dioxins/Annex_II_32, Annex_II_33, Annex_II_34, Annex_II_35, Annex_II_36.
[16] Technical dossier/Supplementary information request_260922/Safety for the user/ Dusting_potential_Report_No_3.897.
[17] Technical dossier/Section II/Annex_II_19, Annex_II_20, Annex_II_21, Annex_II_22, Annex_II_23, Annex_II_24.
[18] Technical dossier/Supplementary information request_260922/Safety for the user/Particle_size_analysis_Report_22_1108 and Particle_size_analysis_Report_22_1131.
[19] Technical dossier/Section II/Annex_II_25 and Annex_II_26.

The applicant is also asking for the use of the additive in feed for sows. The additive is intended to be used at 5,000 mg ammonium chloride /kg in complete feed for sows for 2 periods of 3 weeks each: 9th–11th weeks pregnancy and 15th–16th weeks pregnancy and 1st lactation.

3.2. Safety

For the renewal of the authorisation of the additive for use in feed for lambs for fattening, ruminants other than lambs for fattening, cats and dogs, the applicant provided two literature searches on the safety of Amoklor™ that are described below. In addition, new data on safety for the user has been submitted.

To support the new authorisation for sows, a tolerance study was submitted.

3.2.1. Literature search

One search focused on the safety for target animals, consumers, workers, the environment, and interactions (e.g. with drugs, feed components etc.).[20] The search covered the period 2010–2020 with no language restriction. The search terms used were related to ammonium chloride, Amoklor™, ruminants, cats, dogs and sows, residues, user/worker, consumer and environmental safety.[21] The following databases were used: Cab Abstracts and Global Health,[22] Veterinary Science Database[23] and PubMed[24] (in NCBI webpage). The search protocol described the inclusion and exclusion criteria applied for the screening process. In total 658 articles were considered for the screening and after applying the inclusion/exclusion criteria, a total of six scientific papers were considered eligible; two of these articles were EFSA opinions. Only two of the remaining four papers contained information relevant for the safety of the ruminants other than lambs for fattening, which are described below.

The second literature search focused only on the safety for the target species.[25] The search covered the period 2012–2020. The species of interest were all ruminants, cats, dogs and pigs, including sows. The following databases were used: Scopus, CAB Abstracts, Science Direct, Google Scholar and Toxline in Pubmed. In total, 22 articles were considered for the screening. A total of three scientific papers were considered eligible. Two of these articles were EFSA opinions and the third one was not considered relevant for the assessment of the safety of the additive.

No papers were found in the two literature searches related to the safety concern for lambs for fattening, cats and dogs. None of the hits found in the literature searches identified a safety concern for consumers and the environment.

3.2.2. Safety for the target species

In its previous opinions on Amoklor™ (EFSA FEEDAP Panel, 2012a, 2016), the FEEDAP Panel evaluated studies in lambs for fattening, goats, dairy cows and cattle for fattening fed diets supplemented with ammonium chloride at increasing concentrations (approximately 5,000; 10,000; 15,000; 20,000 mg/kg) and concluded that the additive is considered safe for lambs for fattening at a maximum content of 10,000 mg/kg complete feed for a feeding period not exceeding 3 months, and for ruminants other than lambs for fattening at 10,000 mg/kg complete feed for a feeding period not exceeding 3 months, or 5,000 mg/kg complete feed for a feeding period exceeding 3 months.

In the literature search, two studies in dairy cows were found, which provided information on the safety of the additive. The applicant also submitted a new tolerance study in sows that is assessed in Section 3.2.2.2.

3.2.2.1. Safety for ruminants

Wang et al. (2018) investigated the effects of ruminal infusion of ammonium chloride on the *productive performance*[26] and serum and urine metabolic parameters[27] of lactating dairy cows (N = 4;

[20] Technical dossier/Section III/Annex_III_9 and Annex_III_3.
[21] Technical dossier/Section III/Annexes/Annex_III_9_McCartney_search summary.
[22] Technical dossier/Section III/Annexes/Annex_III_4_CABAbstracts.ris.
[23] Technical dossier/Section III/Annexes/Annex_III_8_VSD.RIS.
[24] Technical dossier/Section III/Annexes/Annex_III_5_PubMed.RIS, Annex_III_6_PubMed.RIS, Annex_III_7_PubMed.RIS.
[25] Technical dossier/Section III/Annexes/Annex_2_toxicity.
[26] Parameters analysed: DMI, milk yield, FCM, ECM, fat percentage, fat yield, protein percentage, protein yield, lactose percentage, lactose yield, MUN, total solids content, solids-not-fat content.
[27] Parameters analysed in the serum: K^+, Na^+, Cl^-, Ca^{2+}, PO_4^{3-}, Mg^{2+}. Parameters analysed in the urine: K^+, Na^+, Cl^-, Ca^{2+}, PO_4^{3-}, Mg^{2+}; plus urine pH, urine volume, creatinine clearance, UUN, urine ammonium allantoin, uric acid.

BW 556 kg; 357 in days of milk). The study followed a crossover design, in which, each week during a 4-week period, half of the fistulated cows were infused (3 times a day after 30 min feeding) with one increasing level of ammonium chloride (0, 150, 300, 450 g/day; equivalent to 0, 5,900, 15,500 and 28,700 mg ammonium chloride/kg complete feed), while the other half was infused with water as control during the whole period. After a 2-week washout period, in which all cows received the water infusion, the cows receiving the ammonium chloride during the first period received the water infusion, and vice versa. Feed and water were provided ad libitum.

The ruminal infusion of lactating cows with increasing levels of ammonium chloride showed a linear reduction of dry matter intake, milk yield and milk lactose, and an increase of the milk urea nitrogen and protein. Serum Cl^{-}, phosphate, ALT, AST, GGT and urea N, and urine volume, Cl^{-}, Ca^{2+}, urea N, ammonium NH_4^+, and phosphate PO_4^{3-} showed a linear dose-dependent increase; while urine pH, serum and urine uric acid showed a linear reduction. No negative effects were observed at 5,900 mg ammonium chloride/kg feed. The supplementation of the diets with *infused levels* of ammonium chloride at level of 15,500 mg/kg feed and above affected negatively the productive performance and metabolism which seems to be related to the negative dietary cation anion difference (DCAD, calculated as milliequivalents of Na + K – Cl – S) induced in the feed by the presence of levels of ammonium chloride above that threshold.

Wang et al. (2016) investigated the effects of dietary ammonium chloride (> 99% purity) at levels of 0 (control), 150, 300 or 450 g/day (corresponding to 0, 6,500, 15,300 and 23,100 mg ammonium chloride/kg complete feed) on the productive performance[28] and serum and urine metabolic parameters[29] of lactating dairy cows (N = 48; BW 550 kg; 170 days in milk). Ammonium chloride was provided mixed with the total mixed ration twice a day. The study included an adaptation period to the basal diets of 14 days, and the diets were supplemented with the additive for 56 days. Feed and water were provided *ad libitum*. The results showed that no adverse effects were observed at 6,500 mg ammonium chloride/kg feed. The supplementation of the diets with levels of ammonium chloride above 15,300 mg/kg complete feed for 56 days led to lower dry matter intake, milk yield and urine pH in comparison with the control. Urinary potassium and calcium concentrations were lower and higher, respectively, at any ammonium chloride concentration. Urinary chlorine and phosphorus were higher above 15,300 mg/kg, and urinary magnesium and serum chlorine only at the highest ammonium chloride level.

In both studies where levels of ammonium chloride of approximately 6,000 mg/kg complete feed, provided either via feed or ruminal infusion during short periods of time (1 week or 56 days), no negative effects on the productive performance and metabolism of dairy cows were observed, confirming the findings described in the previous FEEDAP Panel opinions. Considering all the information available, including the two studies described above, the Panel considers reiterates that ammonium chloride (Amoklor™) is 'safe for ruminants other than lambs for fattening up to a maximum use level of 10,000 mg/kg complete feed if used for a period not exceeding 3 months or 5,000 mg/kg complete feed if used for a period exceeding 3 months'.

3.2.2.2. Safety for sows

A total of 32 female pregnant hybrid sows[30] from ≥ 2nd parity (average BW 245.9 kg) were distributed in four treatments with eight replicate pens of one sow each and were fed mash diets (based on barley, wheat bran, maize and soya bean meal).

The experimental diets were administered in two periods of the reproductive cycle of the sows: from week 9 to week 11 of gestation (period 1) and from week 15 of gestation to the end of week 1 of lactation (period 2). Each experimental period lasted 21 days. These experimental diets were supplemented with 0, 5,000 (maximum proposed level), 7,000 (1.4×), or 9,000 (1.8×) mg ammonium chloride/kg feed (confirmed by analysis). Sows were fed 2.6 kg/day and 3.4 kg/day during weeks 9–11 and 15–16 of gestation, respectively. During lactation, feed allowance increased from 2.5 kg (day 1) to 6 kg (day 7) with water being offered *ad libitum*.

[28] Parameters analysed: DMI, milk yield, FCM yield, ECM yield, milk fat percentage, milk fat yield, milk protein percentage, milk protein yield, lactose percentage, lactose yield, total solid content, solid-non-fat content.
[29] Parameters analysed in serum: K^+, Na^+, Cl^-, Ca^{2+}, P^{5+}, Mg^{2+}. Parameters analysed in the urine: K^+, Na^+, Cl^-, Ca^{2+}, P^{5+}, Mg^{2+} and pH.
[30] Topigs Norsvin (TN70).

The first 4 weeks of the trial in the farm took place in the gestation building. Sows were transferred to the farrowing house approximately 1 week before the expected farrowing date for acclimatisation. Light was provided with tubular fluorescent lights for 14 h/day.

Health status and mortality were monitored daily. BW was recorded at the beginning and at the end of each experimental period (Period 1: 9th–11th week; Period 2: 15th week of gestation–1st week of lactation). Average daily feed intake, body weight gain (only for period 1), and feed to gain ratio (F/G, only for period 1) were calculated.

Blood samples were taken from four animals from each experimental group at the beginning and at the end of each experimental period. In total, 64 blood samples (16 from the beginning of the 9th week, 16 from the end of the 11th week, 16 from the beginning of the 15th week and 16 from the end of the 1st week of lactation) were taken for haematology[31] and biochemistry.[32]

Urinary pH was measured every 4 days from all the sows starting from the first day of the 9th week of gestation until the end of 11th of gestation (period 1) and from the first day of the 15th week of gestation until the end of 1st week of lactation (period 2). Two urine pH samples were collected for an extra week after the end of each experimental period to see the effect of withdrawal (corresponding to week 12th of gestation and of 2nd week of lactation, respectively).

The following data were recorded for each sow's progeny: piglets born alive, piglets born dead, litter weight at birth and at weaning, piglets weaned, weaning-oestrus interval. Piglets were weaned 28 days post-farrowing, thus 3 weeks after the end of the second experimental period.

Data on performance (feed intake, period 1 and 2; BW and body weight gain, period 1 and F/G, period 1), blood and urine pH were statistically analysed by one-way ANOVA and for multiple comparisons with Tukey as a post hoc test for performance and blood parameters and with Bonferroni as a post hoc test for urine pH. The significance level was set at $p < 0.05$.

No mortality or culling in sows occurred. The measured sows' performance parameters did not show any treatment-related effects at any measured time point (control group results: BW – gestation week 9: 257.50 kg; gestation week 15: 283.13 kg; lactation week 1: 266.25 kg; average daily feed intake – period 1: 2.6 kg, period 2: 3.6 kg; F/G Ratio – period 1: 7.50). No statistical differences in any of the blood haematology parameters were observed at 11th week of gestation (end of the period 1). Regarding the biochemical parameters[33] measured in the sows, differences were recorded at 15th week of gestation (begin of period 2) in the case of haptoglobin and C-reactive protein between control and 1.8×. No statistical differences between treatments were observed at 1st week of lactation (end of period 2).

Concerning the haematological parameters,[33] significant differences were observed at 15th week of gestation in haemoglobin between control and 1.8× and between 1.4× and 1.8×; in mean cell volume and mean corpuscular haemoglobin between control and 1.8×. Haemoglobin and mean cell volume were statistically different at 1st week of lactation, between control and 1.8×. The observed differences were generally of small magnitude and were not considered biologically relevant.

The results of the urine analysis showed that urinary pH decreased by increasing the amount of ammonium chloride in the feed. The overall results of the analysis of urinary pH during the two experimental periods are reported in Table 1.

Table 1: Effect of ammonium chloride in diet on urinary pH values over period 1, period 2 and overall period (from week 9 of gestation to end of week 1 of lactation)

pH	Groups (mg ammonium chloride/kg feed)			
	0	**5,000**	**7,000 (1.4×)**	**9,000 (1.8×)**
pH period 1	$6.86^{(a)}$	$6.16^{(b)}$	$6.23^{(b)}$	$5.41^{(c)}$
pH period 2	$6.74^{(a)}$	$6.04^{(b)}$	$5.87^{(b)}$	$5.50^{(c)}$
pH overall	$6.80^{(a)}$	$6.07^{(b)}$	$6.07^{(b)}$	$5.46^{(c)}$

(a), (b), (c): Mean values within a trial and within a column with a different superscript are significantly different $p < 0.05$.

[31] Haematological parameters analysed: leucocytes, neutrofils, lymphocytes, mononuclei, eosinophils, basophils, red blood cells, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, red cell distribution width, Platelets, Mean platelet volume, Mean platelet Width, Platelet large cell ratio.

[32] Biochemical parameters analysed: glucose, urea, creatinine, uric acid, cholesterol, SGOT, SGPT, γ-GT, LDH, CPK, alkaline phosphatase, total bilirubin, bilirubin direct, total protein, albumin, globulins, sodium, potassium, calcium total, phosphorus, magnesium, chloride, Hp, CRP, PT, fibrinogen.

[33] Technical dossier/Supplementary information request_260922/Blood_1, Blood_2, Blood_3, Blood_4.

None of the reproduction related parameters showed treatment related effects (control group results: piglets born alive – 13.6; piglets still dead –1.50; litter weight at birth – 19.29 kg; litter weight at weaning – 91.74 kg; number of piglets weaned per sow – 12.38; sows' weaning-oestrus interval – 5.13 days).

3.2.2.3. Conclusion on the safety for the target species

The FEEDAP Panel reiterates its former conclusion that a feed concentration of 10,000 mg Amoklor™/kg is considered safe for ruminants other than lambs for fattening for a restricted period of time (approximately 3 months). For an unlimited period of administration, 5,000 mg Amoklor™/kg in the complete feed for ruminants other than lambs for fattening should not be exceeded, particularly considering the variety of feedingstuffs with different anion–cation ratios. For lambs for fattening a concentration of 10,000 mg/kg feed is considered safe for a feeding period not exceeding 3 months. For cats and dogs at a maximum concentration of 5,000 mg/kg complete feed is considered safe.

Based on the data of the tolerance trial in sows, in which the animals were fed the additive from week 9th to 11th of gestation and from week 15th of gestation to 1st week of lactation, the FEEDAP Panel concludes that the additive is safe for sows at the inclusion level of 5,000 mg/kg feedingstuffs.

3.2.3. Safety for the user

In the previous assessment (EFSA FEEDAP Panel, 2012a), the Panel concluded that the additive should be considered an irritant to skin, eyes, the digestive and respiratory tract. Ammonium chloride fumes were considered as skin sensitiser and a potential respiratory sensitiser.

In the current assessment, no specific inhalation toxicity studies investigating the effects of the additive on the respiratory system were submitted. Considering the high dusting potential of the additive (up to 1,050 mg/m^3), the exposure by inhalation is considered very likely.

The applicant submitted new studies on the effects of the additives on skin and eyes.

The skin irritation potential of Amoklor™ was investigated in an *in vitro* skin irritation study according to OECD TG 439 and following the principles of GLP.[34] The results indicated that the additive should be classified as non-irritant to the skin (UN GHS 'No Category').

The eye irritation potential of Amoklor™ was established in an *in vitro* eye irritation study according to OECD TG 438 and following the principles of GLP.[35] The results of the study lead to the category 'no prediction can be made': the test item did not cause serious eye damage ('Category 1') but cannot be classified for eye irritation ('No Category'). Therefore, the FEEDAP Panel is not in the position to conclude on the eye irritation potential of the additive.

The skin sensitisation potential of Amoklor™ was assessed in mice using the local lymph node assay according to OECD TG 442-B following the principles of GLP.[36] The results of the study showed that the additive is not a skin sensitiser.

3.2.4. Conclusion on the safety for the user

The FEEDAP Panel concluded that the inhalation exposure of the additive is considered very likely. Amoklor™ should be considered a potential respiratory sensitiser but is not a skin sensitiser. The additive is not irritant to the skin, but the Panel could not conclude on its eye irritation potential.

3.3. Efficacy

The present application for renewal of the authorisation does not include a proposal for amending the conditions of the original authorisation that would have an impact on the efficacy of the additive. Therefore, there is no need for assessing the efficacy of the additive for ruminants, dogs and cats in the context of the renewal of the authorisation.

3.3.1. Efficacy for sows

The applicant provided five studies, similar in design, performed in five different farrow-to-finish swine farms. These studies aimed to support efficacy of Amoklor™ for sows.

[34] Technical dossier/Supplementary information request_260922/ Safety for the user/LLNA BrdU_22_0415_final.
[35] Technical dossier/Supplementary information request_260922/ Safety for the user/HSMI_22_0415_final.
[36] Technical dossier/Supplementary information request_260922/ Safety for the user/ICE_22_0415_final.

[redacted]

No outliers were removed prior to statistical analysis. [redacted]

No adverse effects and no mortality in sows were reported.

[redacted]

[37] [redacted]
[38] [redacted]
[39] Technical dossier/Section IV/Annex_10.
[40] Technical dossier/Section IV/Annex_11.
[41] Technical dossier/Section IV/Annex_12.
[42] Technical dossier/Section IV/Annex_13.
[43] Technical dossier/Section IV/Annex_14.

The results of the five trials showed that the additive Amoklor™ added to the diet has the potential to significantly reduce the urinary pH relative to the control diet.

3.3.1.1. Conclusions on efficacy in sows

The administration of ammonium chloride to sows at 5,000 mg Amoklor™/kg complete diet, from week 9th to 11th of gestation and from week 15th of gestation to 1st of lactation, decreased urinary pH.

3.4. 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[44] and Good Manufacturing Practice.

4. Conclusions

The additive currently on the market complies with the conditions of authorisation.

The FEEDAP Panel concludes that the use of Amoklor™ under the current authorised conditions of use remains safe for target species (ruminants other than lambs for fattening, lambs for fattening, cats and dogs), consumers and the environment.

The FEEDAP Panel concludes that the inhalation exposure of the additive is considered very likely. Amoklor™ should be considered a potential respiratory sensitiser but is not a skin sensitiser. The additive is not irritant to the skin, but the Panel could not conclude on its eye irritation potential.

The present application for renewal of the authorisation does not include a proposal for amending the conditions of the original authorisation that would have an impact on the efficacy of the additive.

Regarding the extension of use in sows, the FEEDAP Panel concludes that the additive is safe and efficacious for sows at the inclusion level of 5,000 mg/kg feedingstuffs from week 9th to 11th of gestation and from week 15th of gestation to 1st of lactation.

5. Documentation provided to EFSA/Chronology

Date	Event
13/11/2020	Reception mandate from the European Commission
24/11/2020	Dossier received by EFSA. Amoklor™ (Ammonium Chloride) for all ruminants, sows for urinary health, cats and dogs. Submitted by Latochema Co Ltd
17/02/2021	Application validated by EFSA – Start of the scientific assessment
26/04/2021	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterisation/safety for the target species*
18/05/2021	Comments received from Member States
17/02/2022	Reception of supplementary information from the applicant – Scientific assessment re-started
20/05/2022	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: condition of use/safety for the target species/safety for the user*
26/09/2022	Reception of supplementary information from the applicant – Scientific assessment re-started
22/11/2022	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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[44] 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

AFC	EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
BW	body weight
CAS	Chemical Abstracts Service
CPK	Creatine Phosphokinase
CRP	C-Reactive Protein
DMI	dry matter intake
ECM	Extracellular Matrix
ECHA	European Chemicals Agency
EURL	European Union Reference Laboratory
FAO	Food Agricultural Organization
FCM	Fat–corrected Milk
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
Hp	Haptoglobin

IUPAC	International Union of Pure and Applied Chemistry
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LDH	Lactate dehydrogenase
LOQ	limit of quantification
mbw	metabolic body weight
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
OECD	Organisation for Economic Co-operation and Development
PT	Prothrombin
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
WHO	World Health Organization
γ-GT	Gamma glutamil transferasi