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Safety and efficacy of the feed additive consisting of ammonium chloride (Ammonium Chloride AF) for all ruminants, dogs and cats for the renewal of its authorisation (BASF SE)

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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 assessment of the application for renewal of authorisation of the feed additive consisting of ammonium chloride (tradename: Ammonium chloride AF) as a zootechnical additive for ruminants, cats and dogs. In 2012, the FEEDAP Panel delivered an opinion on the safety and efficacy of the additive and subsequently the additive was authorised in the EU. The additive is authorised as 'ammonium chloride with a content of ammonium chloride \geq 99% and sodium chloride \leq 0.5% in the active substance' for ruminants, cats and dogs under the category 'zootechnical additives' and functional group 'other zootechnical additives'. The evidence provided by the applicant indicates that the additive currently in the market complies with the conditions of authorisation. No new evidence was found that would make the FEEDAP Panel reconsider its previous conclusions on the safety for target species, consumers and environment. The FEEDAP Panel concludes that ammonium chloride is considered an eye and skin irritant and a potential respiratory sensitiser, but is not a dermal sensitiser. 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.

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003¹ establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 14(1) of that Regulation lays down that an application for renewal shall be sent to the Commission at the latest one year before the expiry date of the authorisation.

The European Commission received a request from BASF SE² for the renewal of the authorisation of the additive consisting of ammonium chloride (Ammonium chloride AF), when used as a feed additive for ruminants, cats and dogs (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 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 2 March 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 (Ammonium chloride AF), when used under the proposed conditions of use (see Section 3.1.2).

1.2. Additional information

Ammonium chloride AF is a feed additive based on the active substance ammonium chloride. The additive was first authorised in 2012 in the European Union (EU) as a zootechnical additive, functional group other zootechnical additives, for ruminants, cats and dogs (4d8).³ Another product based on ammonium chloride is also authorised in the EU from another company as a feed additive for lambs for fattening, ruminants other than lambs for fattening, cats and dogs (category: zootechnical additive, 4d7).^{4,5}

The safety and efficacy of the additive under the current assessment were the subject of one opinion of the FEEDAP Panel (EFSA FEEDAP Panel, 2012a). The FEEDAP Panel has also assessed the safety and efficacy of another additive based on the same active substance in two previous opinions (EFSA FEEDAP Panel, 2012b, 2016).

The safety of ammonium chloride used in food has been assessed in two other opinions (EFSA, 2009; EFSA CEF Panel, 2011).

Ammonium chloride is listed as a 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 BASF SE, Carl-Bosch-Str. 38, 67056, Ludwigshafen, Germany.

³ 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 27.07.2013, p. 17.

⁴ 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.

⁵ 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.

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 dossier⁸ in support of the authorisation request for the use of ammonium chloride (Ammonium chloride AF) 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 ammonium chloride (Ammonium chloride AF) 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 (Ammonium chloride AF) is in line with the principles laid down in Regulation (EC) No 429/2008¹⁰ and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012c) and Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2021).

3. Assessment

The additive Ammonium chloride AF consisting of ammonium chloride is currently authorised for use in feed for ruminants, cats and dogs as a zootechnical additive (functional group: other zootechnical additives (reduction of urinary pH)). The applicant is requesting the renewal of the authorisation. From here onwards, the additive will be referred to as Ammonium chloride AF.

3.1. Characterisation

The additive is currently authorised with a content of ammonium chloride $\geq 99\%$ and sodium chloride $\leq 0.5\%$ in the active substance. It is further specified by the applicant to contain $< 0.7\%$ tricalcium phosphate (as an anticaking agent).

The active substance is ammonium chloride (IUPAC name: ammonium chloride) identified by Chemical Abstracts Service (CAS) No: 12125-02-9. The molecular formula of ammonium chloride is NH_4Cl and its molecular weight is 53.5 g/mol. The applicant stated that no changes in the manufacturing process, composition, purity or activity of the additive have been introduced since the additive was authorised. Compliance with the specifications set in the authorisation was provided by the analysis of five recent batches of the additive,¹¹ showing the following average values:

Levels of cadmium, lead and mercury, fluorine, arsenic and nickel were analysed in the same five batches.

Polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and coplanar dioxin-like polychlorinated biphenyls (co-planar PCBs) were analysed in three separate batches.¹²

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

⁸ FEED dossier reference: FAD-2021-0002.

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/FAD-2021-0002_SIn_150721/Annex_SIn_2, Annex_SIn_3, Annex_SIn_4.

¹² Values preceded with the sign '<' correspond to the limit of quantification (LOQ).

¹³ Technical dossier/Section II/Annexes/Annex_II_25.

3.1.1. Physical properties of the additive

The data submitted supporting the physico-chemical properties of the additive (including dusting potential and particle size) and homogeneity are the same as those provided in the previous dossier and evaluated by the FEEDAP Panel (EFSA FEEDAP Panel, 2012a). Since no changes in the manufacturing processes have been introduced, those data are still considered valid in the context of the renewal application.

The applicant provided further data on the dusting potential of one batch of the additive,¹⁴ determined using the Stauber–Heubach method, [REDACTED]. Particle size distribution was measured by laser diffraction in the same batch. The particle fractions below 1, 10 and 50 µm [REDACTED] respectively.

[REDACTED]¹⁵
No data on shelf-life and stability in premixtures or feedingstuffs were provided.

3.1.2. Conditions of use

Ammonium chloride AF is currently authorised for use in feed for ruminants at a maximum use level of 10,000 mg/kg complete feed if used for a period not exceeding three months, or 5,000 mg/kg complete feed if used for a period exceeding three months. The additive is authorised for cats and dogs at a maximum use level of 5,000 mg/kg complete feed.

The current authorisation includes the following *other provisions*:

- The additive shall be incorporated into feed in the form of a premixture.
- For safety: breathing protection, eye protection, gloves and protective clothing shall be used during handling.
- The mixture of different sources of ammonium chloride shall not exceed the permitted maximum levels in complete feedingstuffs for ruminants.

The applicant proposed to keep the same conditions of use as authorised.

3.2. Safety

In its previous opinion on ammonium chloride, the FEEDAP Panel (EFSA FEEDAP Panel, 2012a) concluded that the additive is considered as safe for ruminants at the maximum dose of 10,000 mg Ammonium chloride AF/kg for a limited period of feeding (< 3 months). For longer periods of administration, a concentration of 5,000 mg Ammonium chloride AF/kg is considered safe for ruminants. The additive was considered safe for cats and dogs at the maximum dose of 5,000 mg ammonium chloride/kg in the complete diet for an unlimited period. The Panel also concluded that the use of Ammonium chloride AF at the proposed conditions of use is safe for the consumer and the environment.

In the same opinion, the additive was considered an irritant to skin, eyes, the digestive and respiratory tract, potentially harmful if swallowed and may cause systemic toxicity by acidosis. Ammonium chloride fumes were considered as a skin sensitiser and a potential respiratory sensitiser.

The applicant also provided a literature search on the safety of Ammonium chloride AF.

The search focused on the safety for target animals, consumers, users and environment.¹⁶ The following databases were used: Cab Abstracts and Global Health, Biomedcentral, RKI, ETH Zürich, Google Scholar, Agris FAO, Index to Thesis in Great Britain and Ireland, WhiteRose, PubMed (in NCBI webpage), Open Grey, WorldWideScience, EU Clinical Trials Register. The search covered the period 2009–August 2020 and only abstracts in English and German were considered. The search protocol described the inclusion and exclusion criteria applied for the screening process. The applicant identified 110 hits which could be considered relevant for the assessment of the safety of ammonium chloride.

None of the papers found in the ELS identified a safety concern for cats and dogs, the consumers or the environment. Two studies were found which provided information on ruminants and are describe below.

¹⁴ Technical dossier/Section II/Annexes/Annex_II_37.

¹⁵ Technical dossier/Section II/Annexes/Annex_II_38.

¹⁶ Technical dossier/Section III/Annexes/Annex_III_03.1 and Annex_III_3.2.

Wang et al. (2018) investigated the effects of the ruminal infusion of ammonium chloride on the productive performance¹⁷ and serum and urine metabolic parameters¹⁸ of lactating Chinese Holstein dairy cows (N = 4; BW 556 kg; 357 days in 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 approximately 0, 6,000, 15,500 and 25,200 mg /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 content, and an increase of the milk urea nitrogen and protein content. Serum Cl⁻, phosphate, ALT, AST, GGT and urea N, and urine volume, Cl⁻, Ca²⁺, urea N, ammonium N, and phosphate showed a linear dose-dependent increase; while urine pH, serum and urine uric acid showed a linear reduction. Most of the negative effects on productive performance and metabolism were seen with infused levels of ammonium chloride equivalent to 15,500 mg/kg feed and above, which seems to be related to the negative dietary cation anion difference (DCAD, calculated as 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 approximately 0, 6,300, 15,300 and 23,100 mg ammonium chloride/kg complete feed) on the productive performance¹⁹ and serum and urine metabolic parameters²⁰ 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 the supplementation of the diets with levels of ammonium chloride above 15,300 mg/kg complete feed for 56 days showed lower dry matter intake, milk yield and urine pH in comparison with the control. Urinary K and Ca concentrations were lower and higher, respectively, at any ammonium chloride concentration. Urinary Cl and P were higher above 15,300 mg/kg, and urinary Mg and serum Cl only at the highest ammonium chloride level.

Both studies showed that levels of ammonium chloride equivalents to approximately 6,000 mg/kg complete feed, provided either via feed or ruminal infusion during short periods of time (one week or 56 days), do not show negative effects on the productive performance and metabolism of dairy cows. Therefore, none of the studies contradict the previous conclusion of the FEEDAP Panel that Ammonium chloride AF remains safe for ruminants up to a maximum use level of 10,000 mg/kg complete feed if used for a period not exceeding three months or 5,000 mg/kg complete feed if used for a period exceeding three months.

Based on the new data made available by the applicant, the FEEDAP Panel concludes that, in light of the current knowledge, the additive remains safe for ruminants, cats and dogs under the authorised conditions of use.

To support safety for the user, the applicant provided two studies on skin and eye irritation potential not compliant with OECD guidelines, which were not further considered.


²¹ The results of this study showed that ammonium chloride is not a dermal sensitiser.

Based on the above and the fact that the manufacturing and composition of the additive have not been modified, the FEEDAP Panel concludes that Ammonium chloride AF remains safe under the

¹⁷ 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.

¹⁸ Parameters analysed in the serum: K⁺, Na⁺, Cl⁻, Ca²⁺, PO₄³⁻, Mg²⁺. Parameters analysed in the urine: K⁺, Na⁺, Cl⁻, Ca²⁺, PO₄³⁻, Mg²⁺; plus urine pH, urine volume, creatinine clearance, UUN, urine ammonium allantoin, uric acid.

¹⁹ Parameters analysed: DMI, milk yield, FCM yield, ECM yield, milk fat percentage, milk protein percentage, milk protein yield, lactose percentage, lactose yield, total solid content, solid-non-fat content.

²⁰ Parameters analysed in serum: K⁺, Na⁺, Cl⁻, Ca²⁺, P⁵⁺, Mg²⁺. Parameters analysed in the urine: K⁺, Na⁺, Cl⁻, Ca²⁺, P⁵⁺, Mg²⁺ and pH.

²¹ Technical dossier/Section III/Annexes/Annex_56.

authorised conditions of use for the target animals, consumers and the environment. The additive should be considered a skin/eye irritant and a respiratory sensitiser but is not a dermal sensitiser.

3.3. Efficacy

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 is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

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 Regulation²² and Good Manufacturing Practice.

4. Conclusions

The applicant has provided evidence demonstrating that the additive currently in the market complies with the conditions of authorisation.

The FEEDAP Panel concludes that the use of Ammonium chloride AF under the current authorised conditions of use remains safe for target species (ruminants, cats and dogs), consumers and environment.

The FEEDAP Panel concludes that Ammonium chloride AF is considered an eye and skin irritant and a potential respiratory sensitiser, but it is not a dermal sensitiser.

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.

5. Documentation provided to EFSA/Chronology

Date	Event
14/01/2021	Dossier received by EFSA. Ammonium chloride (Ammonium Chloride AF) for all ruminants, dogs and cats. Submitted by BASF SE
20/01/2021	Reception mandate from the European Commission
02/03/2021	Application validated by EFSA – Start of the scientific assessment
06/06/2021	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: characterisation</i>
03/07/2021	Comments received from Member States
17/07/2021	Reception of supplementary information from the applicant - Scientific assessment re-started
23/03/2022	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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²² Regulation (EC) No 1831/2005 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

CV	coefficient of variation
DCAD	dietary cation anion difference
DM	dry matter
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LOD	limit of detection
LOQ	limit of quantification
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
WHO	World Health Organization