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Safety and efficacy of a feed additive consisting of a preparation of benzoic acid, calcium formate and fumaric acid (AviMatrix® Z) for all avian species other than laying birds (Novus Europe S.A. / N.V)

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Abstract

The additive AviMatrix® Z is a preparation of benzoic acid, calcium formate and fumaric acid and is authorised as a feed additive in chickens for fattening and reared for laying. The applicant has requested to extend the use of the additive to all avian species other than laying birds at a concentration range from 500 to 1,000 mg/kg of complete feed. The safety of the additive was previously assessed by the FEEDAP Panel that concluded that there were no concerns for the consumers and no risks for the environment. Given the particle size distribution and low dusting potential of the additive, the exposure of workers by inhalation and the subsequent health risks were expected to be low. AviMatrix® Z is not considered to be a skin/eye irritant or a skin sensitiser. The FEEDAP Panel is not aware of any new information that would lead to reconsider the conclusions drawn previously. The results of a new tolerance study showed that the additive is tolerated by turkeys for fattening at threefold the highest recommended dose (1,000 mg/kg feed). Therefore, the FEEDAP Panel concluded that the additive is safe for turkeys for fattening at the maximum recommended dose and this conclusion was extended to turkeys reared for breeding. Due to the absence of a margin of safety in a trial in chickens for fattening previously evaluated, the FEEDAP Panel could not extrapolate this conclusion to all other avian species up to the point of lay. The FEEDAP Panel concluded that the additive has the potential to be efficacious in all avian species other than laying and breeding birds.

Keywords: zootechnical, AviMatrix®, safety, efficacy, feed additive, avian species

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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. 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 a feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from Novus Europe S.A./N.V.[2] for authorisation of a preparation of benzoic acid, calcium formate and fumaric acid (AviMatrix® Z), when used as a feed additive for all avian species other than laying birds (category: zootechnical; functional group: other zootechnical additives).

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). The particulars and documents in support of the application were considered valid by EFSA as of 8 October 2020.

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 product a preparation of benzoic acid, calcium formate and fumaric acid (AviMatrix® Z), when used under the proposed conditions of use (see Section 3.1.1).

1.2. Additional information

EFSA issued two opinions on the safety and efficacy of AviMatrix® Z (preparation of benzoic acid, calcium formate and fumaric acid) in chickens for fattening, chickens reared for laying, minor avian species for fattening and minor avian species reared to point of lay (EFSA FEEDAP Panel, 2015, 2017a).

AviMatrix® Z (preparation of benzoic acid, calcium formate and fumaric acid) is authorised as a feed additive in chickens for fattening and chickens reared for laying at a content ranging from 500 to 1,000 mg of additive/kg of complete feed with a moisture content of 12%.[3]

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[4] in support of the authorisation request for the use of AviMatrix® Z 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 Avimatrix® Z (preparation of benzoic acid, calcium formate, fumaric acid) in animal feed are valid and applicable for the current application.[5]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of AviMatrix® Z (preparation of benzoic acid, calcium formate and fumaric acid) is in line with the principles laid down in Regulation (EC) No 429/2008[6] and the relevant guidance documents: Guidance on the identity,

[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] Novus Europe S.A. / N.V Woluwe Atrium - 5th Floor, Rue Nerveldstraat 101–103, Brussels (Belgium).
[3] Commission implementing Regulation (EU) 2018/982 of 11 July 2018 concerning the authorisation of the preparation of benzoic acid, calcium formate and fumaric acid as feed additive for chickens for fattening and chickens reared for laying (holder of the authorisation Novus Europe N.A./S.V.), OJ L 176, 12.7.2018, p. 4.
[4] FEED dossier reference: FAD-2020-0057.
[5] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2012-0037-Avimatrix-Corrected_Version_Ares.pdf
[6] 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.

characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017b), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017c) and Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018).

3. Assessment

AviMatrix® Z (benzoic acid, calcium formate and fumaric acid) is authorised as a zootechnical additive (functional group: other zootechnical additives) in chickens for fattening and chickens reared for laying. The applicant is requesting the extension of the authorisation to all avian species other than laying birds. The additive will be referred to in this opinion as 'AviMatrix®'.

3.1. Characterisation

AviMatrix® is a granulated preparation of benzoic acid, calcium formate and fumaric acid encapsulated in a lipid matrix. The additive is specified to contain 42.5–50.0% benzoic acid, 2.5–3.5% calcium formate and 0.8–1.2% fumaric acid. Other components are 3% precipitated silica and 45% palm stearin. The additive was characterised in one of the previous EFSA opinions (EFSA FEEDAP Panel, 2015). New data have been submitted on the batch-to-batch variation and purity of the additive which are described below.

The applicant provided results on batch-to-batch variation of the active substances performed on eleven batches of the additive.[7] The concentration of benzoic acid, calcium formate and fumaric acid ranged from 46 to 50% (mean: 47.7%), from 3.1 to 3.5% (mean: 3.3%) and from 0.9 to 1.2% (mean: 0.99%), respectively. The results demonstrated that the product is manufactured in compliance with the proposed specifications.

The presence of arsenic (< 0.5 mg/kg), lead (< 0.5 mg/kg), cadmium (< 0.2 mg/kg), mercury (< 0.02 mg/kg)[8] and fluorine (< 40 mg/kg) was evaluated in four batches of the product. Dioxins (polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F), the sum of dioxins and dioxin-like polychlorinated biphenyls (DL-PCBs) and the non-DL-PCBs were also analysed; the following values were reported: for dioxins, 0.19 ng WHO-PCDD/F-TEQ/kg; for the sum of dioxins and DL-PCBs, 0.34 ng WHO-PCDD/F-DL-PCB-TEQ/kg; for non-DL-PCBs, 1.7 μg/kg.[9]

The same batches were also analysed for microbial contamination; *Salmonella* spp. was absent in 25 g and *Escherichia coli* was < 10 CFU/g.

Based on the results, no concerns arise from the presence of impurities and the microbial contamination in the final product.

3.1.1. Conditions of use

The additive is currently authorised for its use in feed for chickens for fattening and reared for laying at a minimum level of 500 mg additive/kg of complete feed and a maximum level of 1,000 mg additive/kg of complete feed. The applicant is asking for the extension of the authorisation to all avian species other than laying birds, with the same conditions of use.

3.2. Safety

Safety aspects regarding the use of this additive in feed, including the safety for consumers, users and the environment, have been previously evaluated (EFSA FEEDAP Panel, 2015). The FEEDAP Panel concluded that there were no concerns for consumers safety and no risks for the environment derived from the use of the product as a feed additive for chickens for fattening and chickens reared for laying. Considering the safety for the user, the FEEDAP Panel concluded that 'Given the particle size distribution and low dusting potential of AviMatrix®, the exposure of workers by inhalation and the subsequent health risks are expected to be low. AviMatrix® is not considered to be a skin/eye irritant or a skin sensitiser' (EFSA FEEDAP Panel, 2015).

The FEEDAP Panel is not aware of any new information that would lead to reconsider the conclusions drawn previously. Moreover, the FEEDAP Panel considers that the new use requested by the applicant would not introduce hazards not already considered in the previous assessments. There is the need, however, to consider the safety of the additive for the new target species.

[7] Technical Dossier/Section III/Supplementary_Information/Appendix_1.
[8] Limit of quantification (LOQ): arsenic 0.5 mg/kg, lead: 0.5 mg/kg, cadmium : 0.2 mg/kg, mercury: 0.02 mg/kg.
[9] Technical Dossier/Section III/Supplementary_Information/Appendix_2.

3.2.1. Safety for the target species

In 2017, the FEEDAP Panel evaluated a tolerance trial in chickens for fattening which showed that the additive was tolerated at the maximum recommended dose of 1,000 mg/kg feed. However, no margin of safety could be established because of the changes observed in the counts of white blood cells at 3,000 mg/kg feed. Consequently, the Panel concluded that the additive was safe for chickens for fattening and reared for laying at the level of 1,000 mg/kg feed. Owing to the lack of evidence for a margin of safety no conclusions could be drawn for other minor poultry species at the same physiological stages.

In the current dossier, the applicant submitted a new tolerance trial performed in turkeys for fattening.

A total of 480 one-day-old female turkeys for fattening (Aviagen BUT Premium) were distributed in 24 pens in groups of 20 animals and allocated to 3 dietary treatments (8 replicates per treatment).[10,11] Two basal diets (starter and grower) based on maize, soybean meal and soya oil/fat were either not supplemented (control) or supplemented with AviMatrix® to provide 500 mg (0.5× maximum recommended dose, or 3,000 mg (3× maximum recommended dose) per kg feed (confirmed by analysis). Diets were offered on *ad libitum* basis for a total of 43 days in crumble (starter) or pelleted (grower) form.

Mortality and health status were checked every day and dead animals were necropsied. Animals were weighed on days 1, 28 and 42 (pen basis), feed intake was registered per pen and feed to gain ratio calculated. Blood samples were obtained from 2 birds per pen (16 samples/treatment group) on day 43 for haematology and blood biochemistry.[12] The same animals were also killed and subject to gross pathology, carcasses and organ (liver, spleen and kidney) weights were measured.

Performance data were statistically analysed using the analysis of variance (ANOVA) (the pen was the statistical unit) and considering the treatment as a fixed effect and the block (position in the room) as a random effect. Group means were compared with Tukey's test. Mortality was analysed by non-parametric methods. Significance level was set at $p < 0.05$.

Mortality including culling was 2.29% and no differences were found among treatments. No significant differences between treatments were observed in any of the zootechnical parameters measured/calculated (control group values: daily feed intake 77.7 g; final body weight, 2.17 kg; feed to gain ratio 1.55). The performance values reached the commercial standards of the breed used. The results of the biochemical parameters (for control, 0.5× and 3× maximum recommended dose, respectively) showed significant differences in phosphorus (8.2, 8.4 and 8.7 mg/dL) and in sodium (149, 150 and 152 mEq/L) concentrations: the 3× group had higher values compared to control ($p < 0.05$), while the 0.5× had intermediate values ($p > 0.05$). There were also significant differences in the haemoglobin (13.3, 13.9 and 13.6 g/dL for control, 0.5 and 3×) and the erythrocytes (2.47, 2.59 and 2.55 × $10^6/\mu L$): the 0.5× group showed higher values ($p < 0.05$) than those of the control group while 3× group showed intermediate values ($p > 0.05$). However, the FEEDAP Panel considered that the changes observed in the blood cells were not dose-related and those related to biochemistry were of small magnitude and of limited biological relevance. None of the other parameters were affected by treatments.

The necropsy did not show any relevant sign and most of the animals showed no apparent lesions at the gross inspection (the most frequent observation was redness of mucosa and/or petechial in caecum in four animals in the control group). The relative weights of the liver, spleen and kidney showed no differences between the treatments.

The results of this study showed that no adverse effects were observed in turkeys fed AviMatrix® 3-fold the maximum proposed dose.

3.2.2. Conclusions on safety for the target species

The additive is tolerated by turkeys for fattening at threefold the highest recommended dose (1,000 mg/kg complete feed). Therefore, the FEEDAP Panel concludes that the additive is safe for

[10] Technical Dossier/Section III/Annex_III.1.1.4

[11] Technical Dossier/Section III/Supplementary_Information/Appendix_3.

[12] Haematocrit, haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, erythrocytes count, platelets count, leucocytes count and differentials as well (eosinophil, basophil, lymphocyte, monocyte, heterophils), alkaline phosphatase, alanine aminotransferase, glutamic pyruvate transaminase, aspartate amino transferase, gamma glutamyl transpeptidase, creatine kinase, lactate dehydrogenase, amylase, bilirubin, cholesterol, creatinine, total proteins, albumin, globulin, uric acid, glucose, Ca, P, Na, K, Cl, Mg, prothrombin time.

turkeys for fattening at the maximum recommended dose and this conclusion is extended to turkeys reared for breeding. In the absence of a margin of safety in chickens for fattening, in a study previously assessed (EFSA FEEDAP Panel, 2017a), the FEEDAP Panel cannot extrapolate this conclusion to all other avian species up to the point of lay.

3.3. Efficacy

In the current application dossier, the applicant is requesting to extend the use of the additive to all avian species other than laying and breeding birds.

In the EFSA opinion issued in 2017, the FEEDAP Panel concluded that the additive is efficacious in chickens for fattening at 500 mg/kg complete feed, and the conclusion was extended to chickens reared for laying and extrapolated to minor avian species for fattening and minor avian species reared to point of lay (EFSA FEEDAP Panel, 2017a).

Following the approach described in the FEEDAP Panel guidance (EFSA FEEDAP Panel, 2018), the conclusion on the efficacy for chickens for fattening, in studies previously assessed (EFSA FEEDAP Panel, 2017a), can be extrapolated to turkeys for fattening and all other minor poultry species for fattening (to the point of lay) and ornamental birds. Therefore, the FEEDAP Panel concludes that the additive has the potential to be efficacious at 500 mg/kg complete feed in all avian species other than laying and breeding birds.

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[13] and Good Manufacturing Practice.

4. Conclusions

The FEEDAP Panel concludes that AviMatrix® would not pose any safety concerns for consumers or the environment. The additive is not considered to be a skin/eye irritant or a skin sensitiser; the exposure of workers by inhalation and the subsequent health risks are expected to be low.

The FEEDAP Panel concludes that the additive is safe for turkeys for fattening at the maximum recommended dose and this conclusion is extended to turkeys reared for breeding. Due to the absence of a margin of safety in a trial in chickens for fattening previously evaluated, the FEEDAP Panel cannot extrapolate this conclusion to all other avian species up to the point of lay.

The FEEDAP Panel concludes that the additive has the potential to be efficacious in all avian species other than laying and breeding birds.

5. Documentation as provided to EFSA/Chronology

Date	Event
16/07/2020	Dossier received by EFSA. Preparation of benzoic acid, calcium formate and fumaric acid (4d14). Submitted by Novus Europe S.A./N.V.
30/07/2020	Reception mandate from the European Commission
08/10/2020	Application validated by EFSA – Start of the scientific assessment
02/12/2020	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*
21/12/2020	Reception of supplementary information from the applicant - Scientific assessment re-started
11/01/2021	Comments received from Member States
17/03/2021	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

[13] 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.

References

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2015. Scientific Opinion on the safety and efficacy of AviMatrix® (benzoic acid, calcium formate and fumaric acid) for chickens for fattening, chickens reared for laying, minor avian species for fattening and minor avian species reared to point of lay. EFSA Journal 2015;13(5):3794, 17 pp. https://doi.org/10.2903/j.efsa.2015.3794

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, Lopez-Alonso M, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Martelli G, Renshaw D and Lopez Puente S, 2017a. Scientific opinion on the safety and efficacy of AviMatrix® (benzoic acid, calcium formate and fumaric acid) for chickens for fattening, chickens reared for laying, minor avian species for fattening and minor avian species reared to point of lay. EFSA Journal 2017;15(10):5025, 8 pp. https://doi.org/10.2903/j.efsa.2017.5025

EFSA FEEDAP Panel (EFSA Panel on additives and products or substances used in animal feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, Lopez-Alonso M, Lopez Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Galobart J and Innocenti ML, 2017b. Guidance on the identity, characterisation and conditions of use of feed additives. EFSA Journal 2017;15(10):5023, 12 pp. https://doi.org/10.2903/j.efsa.2017.5023

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Galobart J, Innocenti ML and Martino L, 2017c. Guidance on the assessment of the safety of feed additives for the target species. EFSA Journal 2017;15(10):5021, 19 pp. https://doi.org/10.2903/j.efsa.2017.5021

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, Chesson A, Cocconcelli PS, Flachowsky G, Gropp J, Kolar B, Kouba M, López-Alonso M, López Puente S, Mantovani A, Mayo B, Ramos F, Saarela M, Villa RE, Wallace RJ, Wester P, Anguita M, Galobart J, Innocenti ML and Martino L, 2018. Guidance on the assessment of the efficacy of feed additives. EFSA Journal 2018;16(5):5274, 25 pp. https://doi.org/10.2903/j.efsa.2018.5274

Abbreviations

ANOVA	analysis of variance
CFU	colony forming unit
DL-PCB	dioxin-like polychlorinated biphenyl
EURL	European Union Reference Laboratory
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
LOQ	Limit of quantification
PCDD/F	polychlorinated dibenzo-*p*-dioxins and dibenzofurans