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Safety and efficacy of natural mixture of illite, montmorillonite and kaolinite for all animal species

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Abstract

The additive under assessment is a natural mixture mainly composed of illite (~ 53%), montmorillonite (~ 16%) and kaolinite (~ 17%). In 2016, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) delivered an Opinion on the safety and efficacy of a natural mixture of illite, montmorillonite and kaolinite (MIMK). The FEEDAP Panel concluded that the additive is safe for piglets and pigs for fattening at a maximum concentration of 20,000 mg/kg, and for cattle for fattening at a maximum concentration of 50,000 mg/kg. However, no conclusion could be drawn for all other species/categories. The Panel also concluded that the additive is efficacious at a minimum concentration of 50,000 mg/kg. Following this opinion, the European Commission gave the possibility to the applicant to submit complementary information in order to complete the assessment on the safety for all animal species and on its efficacy at a minimum concentration of 20,000 mg/kg. The applicant submitted a new tolerance study in piglets and an analysis of the previous EFSA opinion regarding poultry and milk-producing animals. The FEEDAP Panel concluded that the additive is safe for piglets and pigs for fattening at 50,000 mg/kg. The Panel concluded that the safe level (50,000 mg/kg) found for cattle for fattening could be extrapolated to minor growing ruminants. The conclusion could be extrapolated to dairy cows and minor ruminant species for milk production. The FEEDAP Panel confirmed that no safe concentration of MIMK in feed for chickens for fattening could be identified. No conclusions could be drawn for all the other animal species/categories. The additive is effective as a pellet binder and an anticaking agent at the lowest level tested of 5,000 mg/kg feed.

Keywords: dolomite, magnesite, magnesium-phyllosilicates, technological additives, anticaking agents, safety, target 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 and, in particular, Article 9 defines the terms of the authorisation by the Commission.

The applicant, Argile Du Velay - Arvel, is seeking a Community authorisation of natural mixture of illite, montmorillonite and kaolinite (Argile Verte du Velay), when used as a technological additive for all animal species (Table 1).

Table 1: Description of the substances

Category of additive	Technological additives
Functional group of additive	Binders, anticaking agents
Description	Mixture of illite, montmorillonite and kaolinite
Target animal category	All animal species
Applicant	Argile Du Velay - Arvel
Type of request	New opinion

On 5 January 2016, the Panel on Additives and Products or Substances used in Animal Feed on the European Food Safety Authority ('Authority'), in its opinion on the safety and efficacy of the product, could not conclude on the safety of natural mixture of illite, montmorillonite and kaolinite in animal species/categories other than in cattle for fattening at maximum concentration of 50,000 mg/kg and at a maximum concentration of 20,000 mg/kg for piglets and pigs for fattening. Although suggested use levels in premixtures and feedingstuffs of max 50,000 mg/kg has been approved by EFSA, after the discussion with the Member States on the last Standing Committee, it was suggested to check for the possibility to demonstrate the efficacy at the minimum proposed dose – 20,000 mg/kg.

The Commission gave the possibility to the applicant to submit complementary information in order to complete the assessment and to allow a revision of Authority's opinion. The new data have been received on 6 December 2016.

In view of the above, the Commission asks the Authority to deliver a new opinion of natural mixture of illite, montmorillonite and kaolinite as a technological additive for all animal species based on the additional data submitted by the applicant.

1.2. Additional information

The FEEDAP Panel, in 2016, delivered an Opinion on the safety and efficacy of a natural mixture of illite, montmorillonite and kaolinite (Argile Verte du Velay) as a feed additive for all animal species (EFSA FEEDAP Panel, 2016). The additive is not authorised in the European Union.

2. Data and methodologies

2.1. Data

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

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of natural mixture of illite, montmorillonite and kaolinite (Argile Verte du Velay) is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance documents: Guidance on technological additives (EFSA FEEDAP Panel, 2012a), Technical guidance: Tolerance and efficacy studies in target animals (EFSA FEEDAP Panel, 2011a), Technical Guidance for assessing the safety of feed additives for the environment (EFSA, 2008a), Guidance for the preparation of dossiers for the re-evaluation of

[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] Dossier reference: FAD-2016-0080.
[3] Dossier reference: FAD-2012-0025.

certain additives already authorised under Directive 70/524/EEC (EFSA, 2008b), Guidance for the preparation of dossiers for additives already authorised for use in food (EFSA FEEDAP Panel, 2012b) and Guidance on the assessment of additives intended to be used in pets and other non food-producing animals (EFSA FEEDAP Panel, 2011b).

3. Assessment

The product under assessment is a natural mixture mainly composed of illite (~ 53%), montmorillonite (~ 16%) and kaolinite (~ 17%), subsequently referred to as MIMK. The product has been fully characterised in the previous opinion (EFSA FEEDAP Panel, 2016).

The additive is intended to be used as a technological additive (functional groups: (g) binders; (i) anticaking agents) in premixtures and feedingstuffs for all animal species and categories, with no minimum and maximum content. The applicant suggested use levels in premixtures and feedingstuffs of 20,000–50,000 mg/kg.

The applicant submitted a new tolerance study in piglets, and an analysis of the previous EFSA opinion with regard to the safety for poultry and ruminants. Moreover, the applicant submitted new studies to support the efficacy at the lowest recommend dose.

3.1. Safety

In its previous opinion (EFSA FEEDAP Panel, 2016), the FEEDAP Panel assessed three tolerance studies (one with piglets, one with chickens for fattening and one with cattle for fattening), and concluded that '20,000 mg MIMK/kg complete feed is safe for piglets (weaned); and extends this conclusion to pigs for fattening. For cattle for fattening a concentration of 50,000 mg MIMK/kg complete feed is considered safe with a margin of safety of two. No conclusion can be drawn on the safety for poultry or any other species/categories'.

The applicant provided a tolerance study with piglets in order to support the safety of the additive for piglets and pigs for fattening at 50,000 mg MIMK/kg complete feed.

In addition, the applicant also provided a different interpretation of the results of two tolerance studies (one with chickens for fattening and one with cattle for fattening) assessed in the previous opinion (EFSA FEEDAP Panel, 2016) allowing, in his view, the potential authorisation of the additive for all animal species.

3.1.1. Safety for the target species

3.1.1.1. Safety for piglets

A total of 100 piglets of both sexes (Landrace × Large White) of about 25 days of age was fed pelleted diets supplemented with 0, 20,000, 50,000 (1 × maximum recommended use level), 70,000 (1.4 ×) or 100,000 (2 ×) mg MIMK/kg for 42 days.[4] Group size was five replicates with four piglets each (two males and two females, initial body weight: 5.9 kg). The diets consisting mainly of barley, maize, soybean meal and whey were isonitrogenous (about 19% crude protein (CP)) and isocaloric (about 10 MJ net energy (NE)/kg, by an increase in full fat extruded soybeans and animal fat with increasing content of the additive). The concentrations of the additive were analytically confirmed (by analysis of aluminium as the marker). Body weight and feed intake were recorded fortnightly. Feed-to-gain ratio was calculated for the corresponding periods. At the end of the experiment, a blood sample was taken from one piglet per pen for haematology[5] and clinical chemistry.[6] The experiment was statistically considered as a randomised complete block design with the pen as experimental unit. The effects of the additive were evaluated by a set of linear contrasts. Group differences were analysed by Duncan's multiple range test. Differences were considered significant at the $p < 0.05$ level.

Two piglets died during the study (both from 50,000 mg MIMK/kg group) and one piglet from the 20,000 mg MIMK/kg group was removed from the study due to chronic diarrhoea. The average daily feed intake was not affected by the treatment (595, 560, 573, 550 and 547 g/day). Moreover, other

[4] Technical dossier/Annexes 8 to 10.

[5] Haemoglobin (Hb), red blood count (RBC), hematocrit, mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), platelets, leukocytes, white blood cell differentials (segmented neutrophils, banded neutrophils, lymphocytes, monocytes, eosinophils, basophils).

[6] Albumin (Alb), alanine amino transferase (GPT), aspartate amino transferase (GOT), creatine kinase (CK), alkaline phosphatase (Alk Phos), gamma-glutamyl-transferase (GGT), globulin (Glob), glucose (Glu), lactate dehydrogenase (LDH), total protein (Prot), urea, calcium, phosphorus, iron, magnesium, potassium, sodium.

performance data did not show statistically significant differences among groups up to 70,000 mg MIMK/kg, presenting similar values for final body weight (23.6, 22.9, 22.9 and 22.3 kg, respectively), average daily gain (422, 404, 405 and 388 g/day, respectively), and feed-to-gain ratio (1.41, 1.39, 1.42 and 1.42, respectively). However, final body weight (21.2 kg), average daily gain (363 g/day), and feed-to-gain ratio (1.51) of the high-dose group (100,000 mg MIMK/kg) were inferior to the corresponding figures of the control and the minimum and maximum use level groups.

There were no significant differences among treatments for most of the endpoints of clinical chemistry except for an increase of albumin (at levels $\geq$ 50,000 mg MIMK/kg, ranges within reference values) and a decrease of phosphate (at levels $\geq$ 70,000 mg MIMK/kg); calcium was significantly ($p \leq 0.05$) increased in all level groups (12.4, 12.8, 12.8 and 14.0 mg/100 mL, respectively) compared to the control (11.5 mg/100 mL). Serum phosphate was significantly ($p \leq 0.05$) reduced in the two highest level groups (7.32 and 6.60 mg/100 mL, respectively) compared to the control and the minimum and maximum use level groups (8.54, 8.26 and 7.92 mg/100 mL, respectively). This is considered as an adverse effect indicating reduced intestinal absorption of dietary phosphorus by increasing dietary calcium. Haematological parameters showed minor although significant differences, mainly an increase in erythrocytes (at levels $\geq$ 70,000 mg MIMK/kg) and a decrease of related parameters (mean corpuscular volume (MCV) at levels $\geq$ 70,000 mg MIMK/kg and mean corpuscular haemoglobin (MCH) at 100,000 mg MIMK/kg) compared to the control; no differences were found for total haemoglobin, haematocrit and mean corpuscular haemoglobin concentration (MCHC) among the treatments.

Overall, 50,000 mg MIMK/kg complete feed did not produce significant adverse effects and could therefore considered safe for piglets, without a margin of safety. This conclusion is extended to pigs for fattening.

3.1.1.2. Safety for cattle for fattening

The applicant suggested that the conclusion raised on the safety for cattle for fattening could be extended to all meat-producing animals and all milk-producing animals, considering that animal rumen physiology is similar among ruminants, and the feeding system and feed formulation for dairy cows and cattle for fattening are not different.

The FEEDAP Panel considers that any extrapolation of results from one animal species or category carries a certain degree of uncertainty. This uncertainty is considered to be reduced by the requirement for a (wide) margin of safety of the safe use level of the test item. The margin of safety of two derived from the cattle for fattening study is considered to be low and cannot be applied in dairy cows, since high yielding dairy cows are considered the more sensitive category. Consequently, an extrapolation to dairy cows and minor ruminant species for milk production is not possible; however the margin of safety is considered sufficient for an extrapolation of the safety of 50,000 mg MIMK/kg feed to minor growing ruminants.

3.1.1.3. Safety for chicken for fattening

In its previous opinion, the FEEDAP Panel concluded that 'No safe level of MIMK for chickens for fattening could be identified since feed-to-gain ratio was higher in all treated groups compared to control'.

The applicant considered that, although the differences in feed-to-gain ratio are significantly different, they are minimal, and are to be attributed to unbalanced diet formulation.

A scientific assessment uses generally for this decision statistical parameters, a significant difference is taken as a difference to be considered. Feed-to-gain ratio was affected in a dose dependant manner, with even the lowest dose (20,000 mg MIMK/kg feed) showing a significant difference. In case of dose-related changes, the difference (even if small or not statistically significant) observed at the lowest dose is of concern.

The applicant also argued that an effect on feed-to gain ratio could by 'very likely due to the high amount of fat we added in order to make the diets isocaloric'. In fact, high amounts of fat (necessary for isocaloric diets with high ash content) may not be fully utilised by the animal (e.g. because of soap formation in the intestine and the fatty acids contained escape absorption). These findings support the requirement for tolerance studies to keep dietary changes as small as possible. The FEEDAP Panel reiterates its previous conclusion that no safe concentration of MIMK in feed for chickens for fattening could be identified.

3.2. Efficacy

3.2.1. Anticaking agent

The efficacy of the additive as an anticaking agent was tested in 10 subsamples each of typical pelleted diets for poultry and pigs (complete feed) and for dairy cows (complementary feed).[7] After incorporating the additive at concentrations of 0, 5,000, 10,000, 20,000, 30,000 and 50,000 mg/kg feed, samples of 500 g of each feed were loaded into a standard cone with an orifice of 25 mm (poultry and pig feed) or 43 mm (cattle feed) and left to fall from a standard height of 120 mm (poultry and pig feed) or 80 mm (cattle feed). Below the cone, the sample formed a small pile, forming an angle of repose α, calculated as a quotient of the height (h) and the diameter (D) of the pile ($\tan \alpha = h/0.5D$). The angle (α) gives the tendency of the material to be cohesive or free-flowing, with lower values (25–30°) for very flowing materials and higher values (> 66°) for cohesive materials (Carr, 1965). The speed of flow through the cone (*S,* expressed as seconds) gives an indication of the flowability; the data were statistically analysed using Student's t-test to compare the series. The outcome is expressed in absolute values and as a percentage improvement by the additive.

Significant improvements in the speed of flow were seen for the poultry and pig feed at the lowest tested dose, and for cattle feed at 10,000 mg MIMK/kg feed. Significantly lower angles of repose were found in pig and cattle feed at the lowest dose tested, and for poultry feed at 10,000 mg MIMK/kg feed. The results indicate that MIMK is efficacious as an anticaking agent at a minimum level of 5,000 mg/kg feed.

3.2.2. Binder

The efficacy of the additive as a pellet binder was tested in typical diets for poultry and pigs (complete feed) and for cattle for fattening (complementary feed) supplemented with 0, 5,000, 10,000, 20,000, 30,000 or 50,000 mg MIMK/kg.[8] The feeds were mixed for five minutes, and then pelleted at 75°C (poultry feed), 72°C (pig feed) and 64°C (cattle feed) to obtain 4 × 24 mm pellets. After cooling, the durability of the pellets was evaluated with 100 pellets for each sample with an electronic controlled dynamometer (KAHL Pellet Hardness Tester), measuring the pressure (expressed in Newton (N)) required to break a pellet. The data were statistically analysed using Student's t-test.

In the three feedingstuffs tested, the addition of MIMK at all the level tested improved significantly pellet hardness.

3.2.2.1. Conclusions on efficacy

MIMK is effective as pellet binder and an anticaking agent at the lowest level tested of 5,000 mg/kg feed.

4. Conclusions

MIMK is considered safe for piglets at 50,000 mg/kg complete feed. This conclusion is extended to pigs for fattening. The FEEDAP Panel confirms its previous conclusion that safe level of 50,000 mg MIMK/kg complete feed found for cattle for fattening cannot be extrapolated to dairy cows and minor ruminant species for milk production. However, the margin of safety is considered sufficient for an extrapolation of the safety of 50,000 mg MIMK/kg feed to minor growing ruminants. The FEEDAP Panel does not see any reason to modify its former position that no safe concentration of MIMK in feed for chickens for fattening could be identified. No conclusions can be drawn for all the other animal species/categories.

MIMK is effective as a pellet binder and an anticaking agent at the lowest level tested of 5,000 mg/kg feed.

Documentation provided to EFSA

1) Natural mixture of illite, montmorillonite and kaolinite (Argile Verte du Velay) for all animal species. December 2016. Submitted by Argile Verte du Velay – Arvel.

[7] Technical dossier/Annexes 2A–2C.
[8] Technical dossier/Annexes 4A–4C.

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Abbreviations

CP	crude protein
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MIMK	Natural mixture of illite, montmorillonite and kaolinite
NE	net energy