Assessment : Assessment of the safety of an additive consisting of synthetic vitamin K_1 (phytomenadione) for horses (JARAZ Enterprises GmbH & Co. KG)

Reference Number RP1349

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1.Executive summary

The Food Standards Agency (FSA) and Food Standards Scotland (FSS) have undertaken an assessment of application RP1349 for the use of an additive consisting of synthetic vitamin K_1 (≥97%[1]) (phytomenadione) for horses from JARAZ Enterprises GmbH & Co KG, Halligenstrasse 5, 49661 Cloppenburg, Germany (category: nutritional additives; functional group: vitamins, pro-vitamins and chemically well-defined substances having a similar effect (to be used as a daily supplement for Vitamin K_1)).

A feed additive application has been received by Great Britain (GB) where EFSA, prior to the end of the transition period, evaluated an application for the product. FSA/FSS have reviewed the EFSA opinion (EFSA Journal 2021;19(4):6538, 14 pp.) and confirm that it is adequate and relevant for GB risk analysis and used this to form the basis of GB opinion.

The FSA/FSS risk assessors concluded that the EFSA opinion is adequate and relevant for GB risk analysis. Therefore, the use of vitamin K_1 (phytomenadione), as described in this application, is safe and is not liable to have an adverse effect on the target species, worker safety, environmental safety and human health at the intended concentrations of use.

There are no specific conditions or restrictions in relation to handling, labelling, post-market monitoring requirements and use of this additive as described in this application. Maximum Residue Limits (MRLs) are not required for this additive.

2.Background and purpose of review

EFSA Journal 2021;19(4):6538 **Question number**: EFSA-Q-2020-00142

In accordance with Retained EU Regulation 1831/2003 on feed additives, the application RP1349 for the use of a feed additive consisting of vitamin K_1 (phytomenadione) in horses from JARAZ Enterprises GmbH & Co KG has been submitted for authorisation in GB.

Whilst it was a Member State of the EU, UK accepted the assessments of EFSA in respect of authorisations for regulated food and feed products. Since the end of the transition period, FSA/FSS has adopted equivalent technical guidance and quality assurance processes to be able to undertake GB risk assessments for regulated product applications.

Where EFSA, prior to the end of the transition period, evaluated an application for the product for which an application is now made to GB, FSA/FSS has decided to make use of the EFSA risk assessment, where this is appropriate, in forming its opinion. Therefore, FSA/FSS risk assessors have reviewed the EFSA opinion[2] for

[1] Purity includes the sum of *E*-phytomenadione, *E*-epoxyphytomenadione and *Z*-phytomenadione determined by liquid chromatography according to the European Pharmacopoeia 2.2.29

[2] EFSA (2021). Scientific Opinion on the safety and efficacy of an additive consisting of synthetic vitamin K_1 (phytomenadione) for horses (JARAZ Enterprises GmbH & Co. KG). EFSA Journal 2021;19(4):6538, 14 pp. https://doi.org/10.2903/j.efsa.2021.6538

the application below in the context of intended GB use and have concluded that the intended uses are safe.

In reviewing the output of the EFSA risk assessment the reviewers have verified that the standard approach as outlined in the relevant guidance[3] has been followed and the arguments made are consistent with the data summarised in the opinion. Consideration has been given to the processes undertaken to ensure the opinion is robust and whether there are any aspects that would require further review such as specific issues for the countries of GB. The result of the assessment is that the EFSA scientific opinion is also adequate for GB risk analysis. Therefore, a full risk assessment has not been performed by FSA/FSS.

3.Details of the EFSA assessment

3.1 Methodology applied in the EFSA opinion

EFSA FEEDAP guidance: Guidance on studies concerning the safety of use of the additive for users/workers (**2012**), Guidance on the identity, characterisation and conditions of use of feed additives (**2017a**), Guidance on the assessment of the safety of feed additives for the target species (**2017b**), Guidance on the assessment of the safety of feed additives for the consumer (**2017c**), Guidance on the assessment of the safety of feed additives for the environment (**2019**) and principles in Regulation (EC) No. 429/2008.

3.2 Source/organism

The additive contains vitamin K_1 produced by chemical synthesis. The details of the chemical synthesis are redacted by EFSA due to confidentiality.

3.3 Genetic modification step

Not relevant.

3.4 Specification

The vitamin K_1 produced is specified by the applicant as containing ≥75% *E*-phytomenadione and ≤4% *E*-epoxyphytomenadione. The sum of *E*-phytomenadione, *E*-epoxyphytomenadione and *Z*-phytomenadione should represent ≥97%. An analysis of five batches of the additive showed *E*-phytomenadione to average 83.3% (range 81.8–85.6%), *Z*-phytomenadione to average 16.5% (range 14.4–18.1%), and the sum of *E*-, *Z*-phytomenadione to average 99.8% (range 99.2–100%). In three batches that were analysed *E*-epoxyphytomenadione was 0.6% in each batch.

The applicant proposed the following specification for related impurities, which were based on the European Pharmacopoeia and International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guidelines:

- 2-methylnaphthalene-1,4-dione (menadione/vitamin K_3) with a maximum limit of 0.2%;

[3] See reference list for the full set of guidance applied.

- (*E*)-1a-methyl-7a-[(3,7,11,15-tetramethylhexadec-2-en-1-yl]-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione, consisting of the *E*-epoxyphytomenadione isomers with a maximum limit of 4%;
- other impurities ('total impurities' in relation to the peaks of the three main constituents) with a maximum limit of 1.2%;
- the residual solvents methanol (maximum 0.3%), diethyl ether (maximum 0.5%) and ethanol (maximum 0.5%);
- inorganic impurities that may result from the use of catalysts and other chemicals during the manufacturing are determined as sulfated ash (maximum 0.1% according to the European Pharmacopoeia).

Analysis of three batches (five batches for ether and absolute alcohol) showed compliance with the impurities listed in European Pharmacopoeia monograph 01/2014:1036.

EFSA noted that the specification does not fully meet the most recently updated monograph for phytomenadione (01/2020:30111) in the European Pharmacopoeia, which specifies a concentration of ≤0.2% *E*-epoxyphytomenadione, compared to the 0.6% measured in three batches of this additive.

The applicant provided analyses of cadmium, lead and mercury in three batches of the additive, and these were in all cases below the limit of detection (0.1 mg/kg).

The additive itself is a viscous liquid. It is marketed diluted and standardised in the form of a solid powder preparation formulated with carriers (e.g. maltodextrin, sugars), emulsifier(s) and antioxidant(s) (made up of sucrose, maize starch, polyoxyl 35 Castor oil and β-carotene) at a concentration of 42 g vitamin K_1/kg.

Since the additive is a viscous liquid, no tests are required for its dusting potential. However, the dusting potential of the marketed preparation, described above, was measured in three batches using the Stauber–Heubach method. No dust was formed, which was attributed to the hygroscopic characteristics of the preparation.

The shelf life of two batches of the additive was tested when stored at -4˚C in its original packaging (tight containers keeping the additive dry and protected from sunlight) for 7 months and 21 months. There were no losses observed at 7 months and the losses at 21 months were <1%.

The shelf life of the additive in a preparation (composition not stated) was measured in retention samples of three batches stored for 8, 20 and 31 months after manufacturing (one batch per storage time) at 15-25˚C in containers as described above. No losses were observed in any of the samples.

Information partly redacted by EFSA indicates that the stability of three batches of the additive in a complementary feed (at 140 mg vitamin K_1/kg) for horses was studied, while stored in sealed white polyethylene containers for three months at 25˚C. No losses were observed for two batches, while one showed a loss of 0.6%.

The homogeneity of distribution of the additive was studied in 10 subsamples of one of the batches of complementary feed described above. The coefficient of variation was 1%.

The additive may be placed on the market in form of a preparation. The applicant proposed its use for all horses via a complementary feed (moisture content 12%), up to a maximum concentration of 140 mg vitamin K_1/kg. The complementary feed should provide 7–14 mg vitamin K_1 per horse per day, not taking into account the background exposure to vitamin K_1 in the diet.

3.5 Exposure assessment

Vitamin K_1 is largely metabolised and rapidly excreted, and according to a previous evaluation by EMEA (1998) no residues of concern in meat or milk are expected.

No data were available on levels of vitamin K_1 in horse meat. A paper in the literature reported horse liver to contain 3.3 mg/kg of vitamin K_1 (Duello and Matschiner, 1970). In the absence of residue data in horses, EFSA considered that some assumptions could be made based on the absorption, distribution, metabolism and excretion (ADME) of the substance and available literature on occurrence.

Several tissues (e.g. pancreas, testis, blood vessel wall) can convert vitamin K_1 into menaquinone 4 (MK-4), and this can reach relatively high concentrations in animal products. No substantial differences in MK-4 concentrations in meat were seen between game (hare, deer), free-range animals and those from factory farms. However, in horses, vitamin K_1 conversion to MK-4 is likely to be low, as supplementation of diets for 7 days with vitamin K_1 led to a 2- to 2.3-fold increase in its plasma concentration within 8 h post administration and did not result in a significant increase in plasma MK-4 concentration.

EFSA concluded that it is not expected that the use of vitamin K_1 in horse nutrition at the proposed conditions of use will result in an increase in consumer exposure to vitamin K_1.

3.6 Toxicological data

The applicant provided a tolerance study in horses and a literature review to support the safety of vitamin K_1 in horses. However, EFSA concluded that the tolerance study could not be used due to serious limitations in the study design. The horses were not randomly assigned into the different groups, resulting in differences in starting body weights and blood parameters in the different groups. The literature review also had a number of limitations in the conduct and/or reporting. Exclusion criteria were not described, only 50 out of 160 hits from a database were considered, a “targeted literature search” was not fully documented, most of the studies were not related to horses and the references selected by the applicant to support the safety of the vitamin K_1 for horses were studies not designed to evaluate the safety of vitamin K_1. The applicant made a case that horses eating green leaves of forage plants usually have exposures to vitamin K_1 substantially higher than those from the recommended maximum use level proposed for the additive; however, EFSA noted uncertainties related to the bioavailability.

EFSA noted that the inclusion rate of 140 mg vitamin K_1/kg complementary feed proposed by the applicant related to a maximum daily provision of 100 g complementary feed for a 500 kg horse, corresponding to a daily dose of 14 mg per horse or an average concentration of 1.4 mg/kg complete feed. Excess intake of phytomenadione appears to be essentially innocuous, and menaquinones and

menadione also likely have low oral toxicity. NRC (1987) proposed that oral toxic levels of vitamin K are at least 1,000 times the dietary requirement. EFSA concluded that the use of vitamin K_1 under the proposed conditions of use is safe for horses, and setting a maximum content in feed is not necessary.

It should be taken into account that the complete feed will routinely be supplemented with the already authorised vitamin K_3 (menadione) so vitamin K_1 and vitamin K_3 would be administered together. Considering the very low toxicity of orally administered vitamin K, EFSA concluded that this would not be of any concern for target animal safety.

Regarding food consumers, no tolerable upper intake level has been set for vitamin K by EFSA. The UK Expert Group on Vitamins and Minerals (EVM, 2003) concluded that adverse effects were unlikely with a daily supplemental intake of 1 mg vitamin K_1/day (equivalent to 14 µg/kg bw/day in a 70 kg adult). Considering the conclusion drawn on consumer exposure (see exposure assessment), EFSA concluded that the use of vitamin K_1 in nutrition of horses under the proposed conditions of use is considered safe for the consumer.

No information was provided on the irritation/sensitisation potential of any preparations of this feed additive that may be placed on the market. In absence of such data, EFSA could not conclude on the potential of the preparations to be toxic by inhalation or on their potential as skin/eye irritants. Data from the SCCS (2010) indicate that vitamin K_1 can be categorised as a dermal sensitiser.

4. EFSA assessment and conclusions

The use of vitamin K_1 is safe for the target species when used as a feed additive for horses under the proposed conditions of use. The use of vitamin K_1 in nutrition of horses under the proposed conditions of use is considered safe for the consumer and the environment.

No exposure of users by inhalation is expected. EFSA could not conclude on the potential of the additive to be a skin and eye irritant. Vitamin K_1 is considered a moderate dermal sensitiser.

5. Caveats and uncertainties

There are no further caveats or uncertainties to highlight.

6. FSA Conclusion on reliability and applicability

The application has been assessed in line with the applicable guidance, though EFSA largely used data from previous evaluations of vitamin K_1 and from the scientific literature to draw conclusions on risks to the target species and to food consumers. FSA/FSS agrees with EFSA's assessment.

6.1 Analytical Method Review

FSA/FSS accepts the EURL analytical method evaluation report[4]. FSA/FSS determined the analytical method as appropriate for official controls for this feed additive.

7. Outcome of assessment

FSA/FSS has reviewed the EFSA opinion and consider it adequate and relevant for GB risk analysis. Therefore, the opinion was used to form the basis of the GB opinion.

FSA/FSS had access to all supporting documentation that was provided to the EFSA Panel by the applicant, and subsequently used to form the EFSA opinion. FSA/FSS agree with the safety conclusions outlined in the EFSA opinion.

The FSA/FSS opinion is that vitamin K_1 for horses as a feed additive for horses, as described in this application, is safe and is not liable to have an adverse effect on the target species, worker safety, environmental safety and human health at the intended concentrations of use.

8. References

Duello TJ, Matschiner JT, 1970. Identification of phylloquinone in horse liver. Archives of Biochemistry and Biophysics, 138, 640–645

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012. Guidancecon studies concerning the safety of use of the additive for users/workers. EFSA Journal 2012;10(1):2539, 5 pp. https://doi.org/10.2903/j.efsa.2012.2539

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2017a. 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), 2017b. 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), 2017c. Guidance on the assessment of the safety of feed additives for the consumer. EFSA Journal 2017;15(10):5022, 17 pp. pp. https://doi.org/10.2903/j.efsa.2017.5022

[4] The full report is available on the EURL website: https://joint-research-centre.ec.europa.eu/system/files/2021-02/finrep-fad-2020-0006_vitk1.pdf

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

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2019. Guidance on the assessment of the safety of feed additives for the environment. EFSA Journal 2019;17(4):5648, 78 pp. https://doi.org/10.2903/j.efsa.2019.5648

EFSA (2021). Scientific Opinion on the safety and efficacy of an additive consisting of synthetic vitamin K_1 (phytomenadione) for horses (JARAZ Enterprises GmbH & Co. KG). EFSA Journal 2021;19(4):6538, 14 pp. https://doi.org/10.2903/j.efsa.2021.6538

EMEA (European Agency for the Evaluation of Medical Products), 1998. Opinion on the Scientific Committee for Veterinary Medicinal Products on phytomenadione (vitamin K1) and menadione (vitamin K3). EMEA/MRL/447/98-Final.

EVM (Expert Group on Vitamins and Minerals), 2003. Safe Upper Levels for Vitamins and Minerals. Available online: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf

FAO (Food and Agriculture Organization), 2011. Chapter 10 Vitamin K. In Human vitamin and mineral requirements. Report of a joint FAO/WHO expert consultation, Bangkok, Thailand. p 133-147.

NRC (National Research Council), 1987. Vitamin Tolerance of Animals. The National Academies Press, Washington, DC. https://doi.org/10.17226/949

SCCS (Scientific Committee on Consumer Safety), 2010. Opinion on vitamin K1 (phytonadione), 23 March 2010. Available online: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_014.pdf