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SCIENTIFIC OPINION

Assessment of the feed additive consisting of Patent Blue V for all non-food-producing animal species for the renewal of its authorisation (Versele-Laga NV)

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Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of Patent Blue V as a sensory feed additive for non-food-producing animals. The additive is already authorised for use with non-food-producing animals. The applicant has not provided evidence that the additive currently on the market complies with the existing conditions of authorisation. The FEEDAP Panel cannot conclude whether the additive remains safe for the target species due to the non-compliance with the specifications and the lack of adequate data on the potential aneugenicity of the additive. In the absence of data, the FEEDAP Panel cannot conclude on the potential of the additive to be a dermal and eye irritant nor a dermal and respiratory sensitiser. Since the potential genotoxicity of the additive was not ruled out, the exposure to the additive of the unprotected users should be minimised. The Panel retains that the previously made conclusion on the efficacy remains valid.

KEYWORDS

colouring, efficacy, non-food-producing animals, patent blue V, safety, sensory additives

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1 | INTRODUCTION

1.1 | Background and Terms of Reference

Regulation (EC) No 1831/2003[1] 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 1 year before the expiry date of the authorisation.

The European Commission received a request from Versele-Laga NV[2] for the renewal of the authorisation of the additive consisting of Patent Blue V, when used as a feed additive for all non-food-producing species (category: sensory additive; functional group: colourants, substances that add or restore colour in feedingstuffs).

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 06 March 2023.

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 Patent Blue V, when used under the proposed conditions of use (see **Section 3.1.2**).

1.2 | Additional information

The additive Patent Blue V is currently authorised for use in feed for all non-food-producing animals (2a131).[3]

The FEEDAP Panel issued one opinion on the safety and efficacy of this product when used in feed for non-food-producing animals (EFSA FEEDAP Panel, 2013).

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 Patent Blue V as a feed additive. The dossier was received on 27 July 2022 and the general information and supporting documentation is available at https://open.efsa.europa.eu/questions/EFSA-Q-2022-00478.

The confidential version of the technical dossier was subject to a target consultation of the interested Member States from 6 March 2023 to 6 June 2023 for which the received comments were considered for the assessment.

In accordance with Article 38 of the Regulation (EC) No 178/2002[5] and taking into account the protection of confidential information and of personal data in accordance with Articles 39 to 39e of the same Regulation, and of the Decision of EFSA's Executive Director laying down practical arrangements concerning transparency and confidentiality,[6] a non-confidential version of the has been published on Open.EFSA.

According to Article 32c(2) of Regulation (EC) No 178/2002 and to the Decision of EFSA's Executive Director laying down the practical arrangements on pre-submission phase and public consultations, EFSA carried out a public consultation on the non-confidential version of the technical dossier from 27 July 2023 to 17 August 2023 for which no comments were received.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers, other scientific reports and experts' knowledge, to deliver the present output.

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 active substance in animal feed are valid and applicable for the current application.[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]Versele-Laga NV, Kapellestraat 70, 9800 Deinze, Belgium – Belgium.

[3]Commission Implementing Regulation (EU) No 643/2013 of 4 July 2013 concerning the authorisation of Patent Blue V as a feed additive for non-food producing animals and amending Regulation (EC) No 358/2005. OJ L 187, 4.07.2013, p. 3.

[4]Dossier reference: FEED-2022-7754.

[5]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–48.

[6]Decision https://www.efsa.europa.eu/en/corporate-pubs/transparency-regulation-practical-arrangements

[7]Evaluation report available on the EU Science Hub https://joint-research-centre.ec.europa.eu/eurl-fa-eurl-feed-additives/eurl-fa-authorisation/eurl-fa-evaluation-reports_en

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of Patent Blue V is in line with the principles laid down in Regulation (EC) No 429/2008[8] and the relevant guidance documents: Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2021).

3 | ASSESSMENT

The product consisting of Patent Blue V is currently authorised for use as a sensory additive (functional group: colourants, substances that add or restore colour in feedingstuffs) in feed for all non-food-producing species.

This assessment regards the renewal of the authorisation of Patent Blue V for the above-mentioned animal species.

3.1 | Characterisation

3.1.1 | Characterisation of the additive

Patent Blue V (dark blue powder) consists essentially of the calcium or sodium compound of [4-(α- (4-diethylaminophenyl)-5-hydroxy-2,4-disulfophenyl-methylidene)2,5-cyclohexadien-1-ylidene] diethylammonium hydroxide inner salt and subsidiary colouring matters together with sodium chloride and/or sodium sulfate and/or calcium sulfate as the principal uncoloured components. The potassium salt is also permitted.

Patent Blue V (calcium salt) has a CAS (Chemical Abstracts Service) number of 3536-49-0, IUPAC (International Union of Pure and Applied Chemistry) name calcium salt of 5-hydroxy-4′,4″-bis (diethylamino)-triphenylcarbinol-2,4-disulfonic acid, molecular formula $C_{27}H_{31}N_2O_7S_2½Ca$ and a molecular weight of 579.14 g/mol.

Patent Blue V (sodium salt) has a CAS number of 20262-76-4, IUPAC name sodium salt of 2-[(4-diethylaminophenyl) (4-diethylimino-2,5-cyclohexadien-1-ylidene)methyl]-4-hydroxy-1,5-benzene-disulfonate, molecular formula $C_{27}H_{31}N_2O_7S_2Na$ and a molecular weight of 582.15 g/mol.

Patent Blue V is authorised in feed for all non-food-producing animals with the following specifications:

- Purity criteria: minimum of 90% of total colouring matters, calculated as the sodium, calcium or potassium salts;
- Leuco base: not more than 1.0%.

According to the applicant, the production process has not been changed since the previous authorisation.

Analytical data were provided for five batches of the additive, showing an average purity of 86.8% (range: 86%–89%).[9]

The applicant provided additional analytical data[10] from other five batches of the additive, reporting the following average values: purity, 88.9% (range: 88.7%–89.9%); sum of chlorides, sulfates and humidity, 11.06% (range: 10.1%–11.3%); and not soluble matter, 0.005% (for all the batches).

Based on the analytical data provided, the compliance with the authorised specifications for the use of the additive in feed is not demonstrated. No further information was made available by the applicant.

The additive consists of a dark blue powder. The applicant reported a solubility in water as 50 g/L (at 20°C), but it is not indicated whether this value refers to the sodium, calcium or potassium salt and no analytical evidence was provided.[11]

3.1.2 | Conditions of use

The additive is currently authorised for use in feed for all non-food-producing animal species up to a maximum level of 250 mg/kg complete feed.

Under 'other provisions', it is stated:

- For user safety: breathing protection, safety glasses and gloves should be worn during handling.

The applicant did not request any changes in the current conditions of authorisation.

[8]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.

[9]Annex_2.1.2.

[10]Annex 2.1.3 Certificates of analysis (manufacturer).pdf.

[11]Annex_2.1.6.

3.2 | Safety

The additive is authorised for use only in feed for non-food-producing animals, and therefore, there is no need to perform an assessment of the safety for the consumer and the environment.

The safety of Patent Blue V was previously evaluated by the FEEDAP Panel (EFSA FEEDAP Panel, 2013) that re-evaluated the same toxicological data set available to the ANS Panel in 2013 for its assessment on the use of Patent Blue V as a food additive (EFSA ANS Panel, 2013).

The ANS Panel identified a no observed adverse effect level (NOAEL) of 500 mg/kg body weight (bw) per day based on haematological changes observed in a chronic toxicity study in mice. Genotoxicity studies comprised bacterial reverse mutation assays, a mouse lymphoma assay, in vitro and in vivo (in rat liver, intestine and blood) comet assays, three in vivo micronucleus assays in mice and rats (target tissue bone marrow) and a cytogenetic assay in mouse bone marrow. The results of most of the above-mentioned genotoxicity studies were equivocal, but reliable recent in vivo tests (micronucleus and comet assays) gave negative results both at the site of contact and at systemic targets. Therefore, the ANS Panel excluded any concern about the genotoxicity of Patent Blue V (EFSA ANS Panel, 2013).

The FEEDAP Panel, in its previous assessment (EFSA FEEDAP Panel, 2013), considered that no tolerance data in the target species were available. Thus, the safe feed concentration for target animals was derived from the NOAEL of 500 mg/kg bw per day identified by the ANS Panel. The maximum safe feed concentration of Patent Blue V was set at 250 mg/kg complete feed for all non-food-producing animals.

The FEEDAP Panel shared the conclusions reached by the ANS Panel on the absence of genotoxicity concern for Patent Blue V, however noted that the in vivo comet assay, considered the most critical study, was conducted with a test item with a purity of 90% active substance and ≤ 1% leuco base and complying with Regulation (EU) No 231/2012 concerning other thresholds. Consequently, the FEEDAP Panel considered that all conclusions on the safety of Patent Blue V (E 131) referred to a product with the above specifications (90% active substance and ≤ 1% leuco base). Similarly, the ANS Panel concluded that the established acceptable daily intake (ADI) of 5 mg/kg bw per day applied to Patent Blue V with a purity of at least 90%.

Regarding the users' safety, the FEEDAP Panel concluded that, in the absence of data on irritancy, sensitisation and inhalation toxicity, it would be prudent to treat the additive as an irritant and a skin sensitiser and as toxic by inhalation (EFSA FEEDAP Panel, 2013).

The FEEDAP Panel re-evaluated the genotoxicity data set already assessed in 2013, in the light of the updated requirements (EFSA FEEDAP Panel, 2017; EFSA Scientific Committee, 2021) and confirmed the reliability of the in vivo comet assay and concluded on the absence of concern for gene mutation and structural chromosomal aberrations. However, the FEEDAP Panel noted that the investigation of the potential of the additive to cause numerical chromosomal damage was not covered by the previous data set. No additional genotoxicity studies conducted with the additive under assessment were provided.

For the current application, the applicant did not provide any additional experimental studies but statements declaring that no adverse effects were observed in the target animals[12] and in the users[13] since the authorisation was granted.

The applicant performed a literature search to identify new data related to the safety of the additive for the target species[14] and for the users[15] which were made available since the previous authorisation. Medline/PubMed and Google Scholar databases were used covering the period from 2013 to 2022.[16] The exclusion and inclusion criteria were described.

Eight papers were retrieved by the literature search: three in relation to the safety for the target species and five to the safety for the users. Only one paper was considered relevant for the safety assessment of Patent Blue V when used as feed additive in non-food-producing animals (Husunet et al., 2022).[17] This paper, investigating the in vitro clastogenic, aneugenic and cytotoxic effects of Patent Blue V (purity not specified) using human peripheral lymphocytes through different experimental systems (e.g. micronucleus assay, comet assay, plasmid DNA interaction and AMES test), reported some positive effects. However, the relevance of the test item used in the paper for the additive under assessment was not fully clarified in terms of characterisation (e.g. purity, leuco base concentration, impurities). Therefore, the results of this publication were not considered further for the assessment.

In the absence of new data and considering that the data set available does not allow to conclude on the potential of the additive to induce numerical chromosomal damage, the FEEDAP Panel is not in the position to rule out the potential of the additive to induce aneugenicity. In addition, the panel notes that the previous conclusions were limited to Patent Blue V with a purity of > 90% active substance and ≤ 1% leuco base. However, the data submitted for the additive under assessment did not confirm the compliance with the specifications.

No information, which would address the gaps identified by the FEEDAP Panel in its previous assessment regarding the safety for the user, was provided in the current application.

[12] Annex 3.1.3 Patent-Blue-V_statement_noadverseevents_targetspecies_conf.pdf.

[13] Annex 3.3.4 Patent-Blue-V_statement_noadverseevents_users_conf.pdf.

[14] Annex 3.1.1 Literature Review Target animal safety v2_conf.pdf.

[15] Annex 3.3.1 Literature Review Users-workers safety_PS v2_conf.pdf.

[16] Annex_3.3.1.

[17] Husunet (2022) Investigation of the genotoxic effects of patent blue V (E131).pdf.

3.2.1 | Conclusions on safety

Due to the lack of data on aneugenic potential of the additive and the non-compliance with the current specifications (min 90%), the FEEDAP Panel cannot conclude on the safety of Patent Blue V when used in feed for all non-food-producing animals.

In the absence of data, the FEEDAP Panel cannot conclude on potential of the additive to be a dermal and eye irritant nor a dermal and respiratory sensitiser. Since, the potential genotoxicity of the additive was not ruled out, the exposure to the additive of the unprotected users should be minimised.

3.3 | Efficacy

The present application for renewal of the authorisation does not include a proposal for amending or supplementing the original conditions that would have an impact on the efficacy of the additive. Therefore, the previously made conclusion on the efficacy remains valid.

4 | CONCLUSIONS

The applicant has not provided evidence that the additive currently on the market complies with the existing conditions of authorisation.

The FEEDAP Panel cannot conclude whether Patent Blue V remains safe for the target species due to the non-compliance with the specifications and the lack of data for the assessment of the potential aneugenicity of the additive.

In the absence of data, the FEEDAP Panel cannot conclude on the potential of the additive to be a dermal and eye irritant nor a dermal and respiratory sensitiser. Since the potential genotoxicity of the additive was not ruled out, the exposure to the additive of the unprotected users should be minimised.

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

ABBREVIATIONS

ADI	Acceptable daily intake
ANS	EFSA Scientific Panel on Additives and Nutrient Sources added to Food
BW	body weight
CAS	Chemical Abstracts Service
EURL	European Union Reference Laboratory
FAO	Food and Agriculture Organization of the United Nations
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
MW	molecular weight
NOAEL	no observed adverse effect level
SC	Scientific Committee
WHO	World Health Organization

CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

European Commission

QUESTION NUMBER

EFSA-Q-2022-00478

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