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Safety of an essential oil from *Origanum vulgare* subsp. *hirtum* (Link) letsw. var. Vulkan when used as a sensory additive in feed for all animal species

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Abstract

An essential oil from *Origanum vulgare* subsp. *hirtum* var. Vulkan (DOS 00001) is intended to be used as a sensory additive in feed for all animal species. In a previous opinion of the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), the Panel concluded that the recommended use level of 150 mg additive/kg feed was safe for chickens for fattening and weaned piglets and this conclusion was extended to all poultry and porcine species grown for meat production. The Panel also concluded that the dose of 500 mg additive/head and day (equivalent to ~25 mg/kg complete feed) was safe for dairy cows. Since the recommended use level differs between the dairy cow and the non-ruminants tested, the lower use level of 25 mg additive/kg feed was applied to all target animals not included above. The Panel also concluded that the additive was safe for the consumers and the environment, but should be considered as an irritant to skin and eyes and a potential skin and respiratory sensitiser in susceptible individuals. In the present application, the applicant has provided a new tolerance study in dairy cows to support the safety of a higher use level of 150 mg/kg for all animal species. Data on residues in milk from dairy cows fed the additive at the maximum recommended use level where also provided to assess consumer exposure. The Panel concluded that the essential oil under assessment is safe for cows at the recommended use level of 150 mg additive/kg feed. Since safety has been demonstrated in three major species with a comparable margin of safety, this conclusion on safety is extrapolated to all animal species. No concerns for consumer safety were identified following the application of the additive at the proposed use level in animal nutrition.

Keywords: *Origanum vulgare*, essential oil, carvacrol, consumer safety, target animal safety

Requestor: European Commission

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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 defined the term of the authorisation by the Commission.

The applicant Dostofarm GmbH is seeking a Community authorisation of the product natural essential oil from *O. vulgare* L. subsp. *hirtum* var. Vulkan (DOS 00001) as a feed additive to be used as a flavouring for all animal species (Table 1).

Table 1: Description of the substances

Category of additive	Sensory additive
Functional group of additive	Flavourings
Description	Natural essential oil from *Origanum vulgare* L. subsp. *hirtum* var. Vulkan (DOS 00001)
Target animal category	All animal species
Applicant	Dostofarm GmbH
Type of request	New opinion

On 29 November 2017, the Panel on Additives and Products or Substances used in Animal Feed of the European Food Safety Authority ("Authority"), in its opinion on the safety and efficacy of the product could not conclude on the safety of the recommended use level 150 mg additive/kg feed for all animal species due to the limitations identified in the studies provided.

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 28 February 2019.

In view of the above, the Commission asks the Authority to deliver a new opinion on natural essential oil from *O. vulgare* L. subsp. *hirtum* var. Vulkan (DOS 00001) as a feed additive for all animal species based on the additional data submitted by the applicant.

1.2. Additional information

The FEEDAP Panel issued an opinion on the safety and efficacy of the essential oil from *O. vulgare* L. subsp. *hirtum* var. Vulkan (DOS 00001) as a feed additive for all animal species (EFSA FEEDAP Panel, 2017). The Panel could not conclude on the safety of the recommended use level 150 mg additive/kg feed for all animal species. The applicant has provided new data to address the limitations previously identified regarding the safety and the efficacy for the target species.

2. Data and methodologies

2.1. Data

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

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 oregano essential oil in animal feed are valid and applicable for the current application.[4]

[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] FEED dossier reference: FAD-2019-0018.
[3] FEED dossier reference: FAD-2016-0004.
[4] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/finrep-fad-2016-0004_origanum_oil.pdf

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of an essential oil form *O. vulgare* L. subsp. *hirtum* is in line with the principles laid down in Regulation (EC) No 429/2008[5] and the relevant guidance documents: Guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), Technical guidance: Tolerance and efficacy studies in target animals (EFSA FEEDAP Panel, 2011) and Guidance for establishing the safety of additives for the consumer (EFSA FEEDAP Panel, 2012b).

3. Assessment

The product under assessment is an essential oil derived by steam distillation from a single registered variety (Vulkan) of *O. vulgare* subsp. *hirtum* (Link) letsw. The product is a yellow-green to dark brown clear liquid with a density of 0.935–0.950 g/cm^3. The product is specified to contain carvacrol (60–65%), thymol (1–3%), γ-terpinene (4–9%), *p*-cymene (5–10%), linalool (< 5%), β-caryophyllene (2–5%), α-terpinene (< 1.5%), terpinen-4-ol (< 2%) and *trans*-sabinene hydrate (0.3–1%).

The additive is intended to be used as a sensory additive (functional group: flavourings) in feed for all animal species at a concentration of 15–150 mg/kg complete feed.

In a previous opinion of the FEEDAP Panel, the additive was characterised in full; also the safety and the efficacy of the product were evaluated (EFSA FEEDAP Panel, 2017). In that assessment, the Panel concluded that the recommended use level of 150 mg additive/kg feed is safe for chickens for fattening and weaned piglets and this conclusion was extended to all poultry and porcine species grown for meat production. A dose of 500 mg additive/head and day (equivalent to ~ 25 mg/kg complete feed) was also demonstrated safe for the dairy cow. The Panel concluded that since the recommended use level differs between the dairy cow and the non-ruminants tested the lower use level of 25 mg additive/kg feed could be applied to all target animals not included above.

The Panel also concluded that the additive is safe for the consumers of food products obtained from animals fed with the additive and that the additive would pose no risks to the environment. Regarding the safety for the users, the Panel concluded that the additive should be considered as an irritant to skin and eyes and a potential skin and respiratory sensitiser in susceptible individuals.

In the above-mentioned opinion, five tolerance studies in three species (chicken for fattening, weaned piglets and dairy cows) were assessed. The studies in chickens for fattening and weaned piglets showed no adverse effects when animals were fed the additive up to four or five times the maximum recommended use level (150 mg/kg complete feed). During the assessment, the conditions of use for dairy cows were modified, and the highest recommended dose was reduced to 500 mg additive/head and day, corresponding to about 25 mg/kg complete feed.

The applicant has provided a new tolerance study in dairy cows to support the safety of a higher use level of 150 mg/kg for all animal species. Data on residues in milk from dairy cows fed the additive at the maximum recommended use level were also provided to assess consumer exposure.

3.1. Safety

3.1.1. Safety for the target species

A total of 40 Holstein cows (age: 41.3 months, initial body weight: 649 kg, initial average days in milk: 120 days) were distributed to four treatment groups each of 10 animals.[6] Animals were assigned on the basis of a randomised complete block design with blocking by parity, calving date and start of lactation. All animals were fed a total mixed ration based mainly on ryegrass silage, corn silage, barley, wheat and soybean meal (total mixed ration (TMR): 51.6% dry matter (DM); net energy of lactation (NEl) 1.63 Mcal/kg DM; crude protein (CP) 14.1% DM; neutral detergent fibre (NDF) 40.2% DM). The essential oil in the form of DOSTO® Rumen-Pearls 200 containing 18 mL oregano oil/100 g (corresponding to 169 g/kg) was added to the TMR (via a premixture with soybean meal) to give 0, 3,300, 9,900 or 16,500 mg essential oil/head and day. Based on the assumed DM intake of 22 kg, these concentrations would equate to around 140 (1× maximum recommended level), 405 (3×) and

[5] 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.

[6] Technical dossier/Annex 1: Report.

690 (5×) mg/kg complete feed (88% DM). These concentrations were confirmed by analysis of the content of carvacrol in the concentrate at days 1, 28 and 56. The lactating dairy cows (electronically tagged) were individually fed the TMR for 56 days and feed offered and refused was recorded daily. Animals were weighed daily and individual milk production and milk fat and protein were recorded after each milking. Somatic cell counts, lactose, total solid and urea were analysed weekly in sample from two consecutive days. Samples of milk were taken from the control and the recommended dose group (five animals each) at day 56 for the analysis of residues and metabolites derived from the essential oil. Blood samples were taken from five animals per treatment on days 1, 28 and 56 for haematology[7] and clinical biochemistry.[8]

Data were analysed by a mixed-effects model for repeated measures. The model accounted for the fixed effects of treatment, week of study and its interaction, plus the random effects of animal within treatment. Time entered the model as a repeated measure using the variance-covariance matrix. Days in milk at the beginning of the study entered the model as a covariate.

No mortality was reported. No statistically significant differences were observed in any of the performance parameter between the groups. In the control group, daily DM intake was 20.3 kg/day, daily milk yield 32.4 kg/day, milk protein 3.37%, fat content 3.74%, protein and fat energy corrected milk yield 34.0 kg/day. No significant treatment-related effects were seen in haematological data or clinical chemistry except for some differences in non-esterified fatty acids (NEFA), urea and Mg, which seemed to be not treatment related.

Feeding the cows with the additive up to fivefold the recommended dose did not have any negative effects on the performance parameters. Therefore, the FEEDAP Panel concludes that the product is safe for cows at the recommended dose.

3.1.1.1. Conclusions on safety for the target species

Safety has been demonstrated in three major species with a comparable margin of safety between the maximum proposed use level and the highest tolerated use level tested, allowing a conclusion on safety to be extrapolated to all animal species.[9]

3.1.2. Safety for the consumer

Milk samples collected from the control and the recommended dose group (five animals each) at day 56 (see Section 3.1.1) were analysed for residues and metabolites derived from the essential oil. Carvacrol, thymol and linalool were below the limit of detection (LOD)[10] in all samples. Comparable concentrations of γ-terpinene were detected in one sample from control animals (20 μg/L) and in three samples from treated animals (20–35 μg/L). The concentration of *p*-cymene was similar in controls (9–15 μg/L) and treated animals (12–24 μg/L).

In the previous opinion, the FEEDAP Panel estimated the exposure of consumers to carvacol and thymol based on the residue data from pig tissues. The estimated daily intakes of 50 μg carvacrol and 5 μg thymol were compared to the daily safe exposure of 1,800 μg carvacrol/person derived from the application of the threshold of toxicological concern (TTC) for Cramer class I compounds and were considered of no concern. Additional exposure from milk/eggs was considered negligible, as carvacrol was detected in trace amount in milk and eggs and thymol was not detectable. No residue data were provided for the other terpenoids present in the essential oil. However, since their concentration was considerably lower than that of carvacrol, they were not expected to be detectable in tissues and products and their contribution to consumer exposure was considered negligible (EFSA FEEDAP Panel, 2017).

The residue data confirm that the consumer exposure to carvacrol and thymol from milk would be negligible even when the additive is supplemented at 150 mg/kg complete feed.

[7] Erythrocytes, leucocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, neutrophils, lymphocytes, monocytes, eosinophyls, basophils, platelets, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration and mean platelet volume.

[8] Albumin, globulin, total protein, fibrinogen, alanine aminotransferase, amylase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase, creatinine kinase, glucose, urea, lactate, cholesterol, total bilirubin, non-esterified fatty acids, creatinine, as well as for electrolytes (sodium, potassium, magnesium, chloride, calcium, and inorganic phosphate).

[9] The conclusions on safety in three major species are exceptionally extrapolated to all animal species following the provisions of the guidance on sensory additives (EFSA FEEDAP Panel, 2012a), following the same approach as the original application.

[10] Technical dossier/Annex 2: Residue analysis milk_AR. Limit of detection (LOD): carvacrol 6 μg/L, thymol 4 μg/L, γ-terpinene 12 μg/L, *p*-cymene 7 μg/L and linalool 5 μg/L.

New data have been provided for linalool (not detectable), γ-terpinene and *p*-cymene in milk. Assuming a daily consumption of 1.5 L milk for adults, the daily intake of γ-terpinene and *p*-cymene would result in 53 and 36 μg/person. These values are considerably lower than the TTC for Cramer Class I compounds (1,800 μg/person and day) and would be comparable for unsupplemented and supplemented animals.

3.1.2.1. Conclusions on safety for the consumer

No concerns for consumer safety were identified following the application of the additive at the proposed use level in animal nutrition.

4. Conclusions

The essential oil from *Origanum vulgare* subsp. *hirtum* is safe for cows at the recommended use level of 150 mg additive/kg feed. Since safety has been demonstrated in three major species with a comparable margin of safety between the maximum proposed use level and the highest tolerated use level tested, this conclusion on safety is extrapolated to all animal species.

No concerns for consumer safety were identified following the application of the additive at the proposed use level in animal nutrition.

5. Documentation as provided to EFSA/Chronology

Date	Event
01/03/2019	Dossier received by EFSA. Natural essential oil from *Origanum vulgare* L. subsp. *hirtum* var. Vulkan (DOS 00001) for all animal species. Submitted by Dostofarm GmbH
19/03/2019	Reception mandate from the European Commission
10/05/2019	Application validated by EFSA – Start of the scientific assessment
04/07/2019	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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Abbreviations

CP	crude protein
DM	dry matter
EURL	European Union Reference Laboratory
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
LOD	limit of detection
NDF	neutral detergent fibre
NEFA	non-esterified fatty acids
NEl	net energy of lactation
TMR	total mixed ration
TTC	threshold of toxicological concern