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## Safety and efficacy of 'dry grape extract 60-20' when used as feed flavouring for dogs

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### Abstract

The feed additive 'dry grape extract 60-20' is a mixture of two extracts, one from the seed and the other from the skin of *Vitis vinifera* subsp. *vinifera*. It is intended to be used as a sensory additive (functional group: flavouring compound) in dogs. The additive 'dry grape extract 60-20' is specified to contain [REDACTED]

The applicant proposes a maximum use level of 100 mg 'dry grape extract 60-20'/kg of complete feedingstuffs for dogs without a withdrawal period. The FEEDAP Panel was aware of case reports indicating acute toxicity for some dogs consuming grapes or raisins at exposure levels relevant to the use of 'dry grape extract 60-20'. The FEEDAP Panel considered that rare idiosyncratic effects could be possibly responsible for the reported cases of fatality in dogs due to acute renal failure following exposure to different types of grapes. The FEEDAP Panel considered that the additive is poorly characterised. Based on the data available, the FEEDAP Panel was not able to conclude on the safety of 'dry grape extract 60-20' when used as a feed additive for dogs. In the absence of studies to assess the safety for the user, the FEEDAP Panel could not conclude on the safety for the user when handling the additives. Since grape seed extract is used in food as flavouring, and its function in feed is essentially the same as that in food no further demonstration of efficacy was necessary.

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## 1. Introduction

### 1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1831/2003<sup>1</sup> 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 ACTIV'INSIDE and Spécialités Pet Food (SPF - DIANA PET FOOD)<sup>2</sup> for authorisation of the product 'dry grape extract 60-20', when used as a feed additive for dogs and cats (category: sensory additive; functional group: flavouring compound). During the assessment, the applicant expressed the intention to withdraw the application for cats.<sup>3</sup> Therefore, this species is no longer considered in the present opinion.

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 1 March 2019.

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, user and the environment and on the efficacy of the product dry grape extract 60-20, when used under the proposed conditions of use (see Section 3.2.2).

### 1.2. Additional information

In 2016, the EFSA FEEDAP Panel delivered an opinion on the safety and efficacy of another dry grape extract, a mixture of two extracts from seeds and skin of *Vitis vinifera* subsp. *vinifera*, when used as feed flavouring for all animal species (EFSA FEEDAP Panel, 2016a) and another opinion on the use of the same extract in water for drinking (EFSA FEEDAP Panel, 2016b).

A dry grape extract of *Vitis vinifera* subsp. *vinifera*, a mixture of skin and seed extracts with a specified concentration of marker compounds is authorised as sensory additive (functional group: flavouring compound) for use in feed for all animal species except for dogs.<sup>4</sup>

The product under assessment, 'dry grape extract 60-20', intended for use as feed flavouring for dogs, is not authorised in the European Union (EU).

## 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 in support of the authorisation request for the use of 'dry grape extract 60-20' as a feed additive.

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of 'dry grape extract 60-20' in animal feed. The Executive Summary of the EURL report can be found in Annex A.<sup>5</sup>

### 2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of dry grape extract 60-20 is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance documents: Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), Guidance on studies concerning the safety of use of the additive

<sup>1</sup> 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.

<sup>2</sup> 12 Zone du Lapin - ZA du Grand Cazau, Beychac-et-Caillau, France.

<sup>3</sup> On 10 December 2019, EFSA was informed about the intention to withdraw the application for cats.

<sup>4</sup> Commission Implementing Regulation (EU) No 2017/307 of 21 February 2017 concerning the authorisation of dry grape extract of *Vitis vinifera* subsp. *vinifera* as a feed additive for all animal species except for dogs. OJ L 44/1, 22.2.2017, p. 5.

<sup>5</sup> The full report is available on the EURL website: <https://ec.europa.eu/jrc/en/eurl/feed-additives/evaluation-reports>

for users/workers (EFSA FEEDAP Panel, 2012) and Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018).

### 3. Assessment

The feed additive 'dry grape extract 60-20' is a mixture of two extracts, one from the seed and the other from the skin of *Vitis vinifera* subsp. *vinifera*. It is intended to be used as a sensory additive (functional group: flavouring compound) in dogs.

*Vitis vinifera* L. (grape vine) belongs to the Vitaceae family and is cultivated worldwide.

#### 3.1. Manufacturing process

The manufacturing process is fully described in the dossier provided by the applicant. [REDACTED]

#### 3.2. Characterisation of the additive

The additive 'dry grape extract 60-20' is specified to contain [REDACTED]

Data on batch-to-batch variation have been provided for five batches of the additive. [REDACTED]

[REDACTED] These values comply with the proposed specifications for the additive. [REDACTED]

The applicant provided a typical polyphenol profile of 'dry grape extract 60-20'. According to this information, [REDACTED]

[REDACTED] However, the applicant did not provide analytical data to support this. Moreover, no information was provided on the composition of the two individual components (the grape skin extract and the grape seed extract), even after request. Due to the lack of analytical data on the composition of the polyphenols and monomers of flavanol fractions and on the two individual components, the FEEDAP Panel considered that the additive is poorly characterised.

Three batches of the additive were analysed for chemical and microbiological impurities. [REDACTED]

[REDACTED]

Analysis of microbial contamination of the same three batches indicated that [REDACTED]

Based on the data provided, no concern relating to impurities was identified for the additive under assessment.

Three batches of the additive were analysed for particle size distribution. [REDACTED] However, no certificates of analysis were provided by the applicant and no further characterisation of the different fractions was provided.

In the same batches, the dusting potential measured according to [REDACTED]

### 3.2.1. Stability and homogeneity

The shelf-life of the additive is declared by the applicant to be at least 24 months. [REDACTED]

### 3.2.2. Conditions of use

The additive is intended to be used in feed for dogs at a maximum level of 100 mg/kg complete feed.

## 3.3. Safety

Following the provisions of the Regulation (EC) No 429/2008, there is no requirement for the assessment of the safety of an additive when used in pets, for the consumers and the environment.

The applicant provided a pharmacokinetic study made [REDACTED]

[REDACTED] However, this study is not considered relevant by the FEEDAP Panel since it does not evaluate the safety of the feed additive under application.

### 3.3.1. Safety for the target species

The applicant provided results of a literature search made in support of the safety of 'dry grape extract 60-20' when used as feed additive for dogs. The methodology used to perform the literature search is reported in the dossier. [REDACTED]

[REDACTED] The FEEDAP Panel notes that the purpose of some of these studies was to demonstrate possible beneficial effects rather than establishing safety. Of the submitted studies, the Panel considered two of them, performed in dogs administered PEGB, as the most relevant. The constituents of PEGB were [REDACTED]

In the first study, 24 Beagle dogs were assigned to four different treatment groups for a period of 24 weeks (Martineau et al., 2016). [REDACTED] The groups were a control and three treatment groups given PEGB administered daily in gelatine capsules at 4, 20 or 40 mg/kg body weight (bw) per day. Blood and urine samples were collected the week before the beginning of the study and at the end of the [REDACTED]

treatment. There were no adverse clinical signs and no alterations were observed in any of the analysed blood and urine parameters.

The second study (Fragua et al., 2017) aimed at evaluating some beneficial effects on the cognitive function on 35 Beagle dogs (aged between 8 and 14.5 years) fed experimental diets contained PEGB included in the diet at 0, 240 and 480 mg/kg of PEGB for 75 days. No statistically significant effects were reported on feed intake or body weight between treatments.

According to the applicant,

In the absence of the full characterisation of the two extracts, it is not possible to establish a clear relationship between the additive under assessment ('dry grape extract 60-20') and the item (PEGB) tested in the studies with Beagle dogs. In addition, the FEEDAP Panel notes that interactions between the two extracts are likely to occur when they are administered together (as PEGB) and could have influenced the outcome of the studies. Consequently, in the view of the Panel these studies cannot be used for the evaluation of the safety for the target species.

The FEEDAP Panel is aware of case reports indicating acute toxicity in some dogs consuming grapes or raisins at exposure levels comparable to the use of 'dry grape extract 60-20' (Eubig et al., 2005; Son-II, 2013; Bates et al., 2015). The FEEDAP Panel considered that rare idiosyncratic effects could be possibly behind the reported cases of fatality in dogs, due to acute renal failure following exposure to different types of grapes. Therefore, the FEEDAP Panel requested from the applicant information on the mechanisms underlying these adverse effects.

The FEEDAP Panel considers that there is high uncertainty in identifying a lowest observed adverse effect level (LOAEL)/no observed adverse effect level (NOAEL) value from sporadic events as proposed by the applicant. In view of the Panel, considering the limited data of case reports and the severity of the adverse effects observed, the proposed approach is not acceptable. No convincing data are given on a possible threshold of the induction of acute renal failures in dogs exposed to grapes. In addition, the chemical characterisation of the additive ('dry grape extract 60-20') is limited and does not allow a read across approach with data on fresh grapes.

### 3.3.1.1. Conclusions on safety for the target species

Considering the uncertainties present in the information provided by the applicant, the FEEDAP Panel cannot establish a safe concentration for 'dry grape extract 60-20' when used as feed additive for dogs.

### 3.3.2. Safety for user

The applicant did not provide any study in support of the safety of the additive for the user. In the absence of data, the FEEDAP Panel cannot conclude on the potential of the additive to be harmful to skin, eyes or respiratory system.

## 3.4. Efficacy

Flavouring preparations produced from food, such as extracts of grapes, are not required to undergo an approval procedure before being placed on the European market (Regulation (EC) No 1334/2008) for food use.<sup>22</sup> Consequently, there is no specific EU authorisation for any grape extract when used to provide flavour in food. Grape seed extract is listed in Fenaroli's Handbook of Flavour Ingredients (Burdock, 2009) and by the Flavour and Extract Manufacturers Association (FEMA) with the reference number 4045. Since grape seed extract is recognised to provide flavour in food and its function in feed would be essentially the same, no further demonstration of efficacy is considered necessary (EFSA FEEDAP Panel, 2018).

## 4. Conclusions

The FEEDAP Panel considers that the additive is poorly characterised.

<sup>22</sup> Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Regulation (EC) No 1601/91 of the Council, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34.

Based on the data available, the FEEDAP Panel is not able to conclude on the safety for dogs of ‘dry grape extract 60-20’ when used as a feed additive.

In the absence of studies to assess the safety for the user, the FEEDAP Panel cannot conclude on the safety for the user when handling the additives.

Since grape seed extract is used in food as flavouring, and its function in feed is essentially the same as that in food no further demonstration of efficacy is necessary.

## 5. Chronology

Date	Event
03/01/2019	Dossier received by EFSA. Dry grape extract 60-20 – Dogs & Cats. ACTIV’INSIDE and Spécialités Pet Food (SPF - DIANA PET FOOD)
18/01/2019	Reception mandate from the European Commission
01/03/2019	Application validated by EFSA – Start of the scientific assessment
14/05/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: characterization of the additive, manufacturing process, safety for the target species</i>
17/01/2020	Reception of supplementary information from the applicant - Scientific assessment re-started
03/06/2019	Comments received from Member States
06/11/2019	Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives
18/03/2020	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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- EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2016a. Scientific opinion on the safety and efficacy of dry grape extract when used as a feed flavouring for all animal species and categories. *EFSA Journal* 2016;14(6):4476, 18 pp. <https://doi.org/10.2903/j.efsa.2016.4476>
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## Abbreviations

ADI	average daily intake
bw	body weight
CAS	Chemical Abstracts Service
DM	dry matter
EURL	European Union Reference Laboratory
GC–MS	gas chromatography–mass spectrometry
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantification
NOAEL	no observed adverse effect level

## **Annex A – Executive summary of the evaluation report of the European Union Reference Laboratory on the analytical methods submitted for the Dry Grape Extract 60-20**

In the current application authorisation is sought under Article 4(1) for Dry Grape Extract 60-20 under the category/functional group 2(b) 'Sensory additives' / 'flavouring compounds' according to the classification system of Annex I of Regulation (EC) No 1831/2003. Specifically, authorisation is sought for the use of the feed additive for cats and dogs. The feed additive is a powder from grape seed and grape skin (*Vitis vinifera* L). The feed additive is to be used through premixtures or directly into feedingstuffs, at maximum level of 100 mg Dry Grape Extract 60-20/kg feedingstuffs. The phytochemical markers proposed for the characterisation of the feed additive (Dry Grape Extract 60-20) are total polyphenols at a minimum content of 60% (w/w), loss of drying and flavanol monomers at a minimum content of 20% (w/w). For the quantification of total polyphenols and the loss of drying in the feed additive the Applicant proposed general European Pharmacopoeia methods (Chapters 2.2.25 and 2.8.17 respectively), while for the quantification of flavanol monomers in the feed additive the Applicant proposed the chromatographic ring-trial validated AOAC Official method 2012.24. Upon request of the EURL, the Applicant provided experimental data for the analysis of flavanol monomers in two different batches of the feed additive applying the method described in the AOAC Official method. Based on the experimental evidence the EURL recommends for official control for the characterisation of Dry Grape Extract 60-20) the chromatographic method described in AOAC Official method 2012.24 for the determination of flavanol monomers. Furthermore, the accurate quantification of added Dry Grape Extract 60-20 in premixtures and in feedingstuffs is not achievable experimentally. Consequently the EURL cannot evaluate nor recommend any method for official control to quantify Dry Grape Extract 60-20 in premixtures and feedingstuffs. Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by Article 10 (Commission Regulation (EC) No 378/2005, as last amended by Regulation (EU) 2015/1761) is not considered necessary.