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Safety of butylated hydroxy anisole (BHA) for all animal species

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Abstract

Following a request from the European Commission, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety of butylated hydroxy anisole (BHA) for all animal species. In 2018, the Panel delivered an Opinion on the safety and efficacy of BHA. The Panel concluded that 'a weight of evidence of the limited data supports that 150 mg BHA/kg complete feed would be a safe dose for all animal species. However, a possible exception could be cat, with its known lower capacity for glucuronidation of phenolic compounds and for which no specific data were available'. The Applicant submitted a review of the metabolism of phenolic compounds in cats and an *in vivo* study with cats. No specific information on metabolic fate of BHA has been made available for the feline species. The lack of knowledge is of particular relevance considering the additional load of phenolic compounds by dietary BHA for the full lifetime expectancy of cats. Owing the shortcomings in the design and reporting, the *in vivo* study could not be used to conclude on the safety of BHA for cats. Consequently, the Panel reiterates that no safe concentration of BHA in complete feed for cats could be established.

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

Regulation (EC) No 1831/2003¹ establishes the rules governing the Community authorisation of additives for use in animal nutrition and in particular, Article 9 defines the terms of such authorisation by the Commission.

The applicant, FEFANA ASBL, is seeking a Community authorisation of Butylated Hydroxy Anisole (BHA) as a feed additive to be used as an antioxidant for all animal species. (Table 1)

Table 1: Description of the substances

Category of additive	Technological additive
Functional group of additive	Antioxidant
Description	Butylated Hydroxy Anisole (BHA)
Target animal category	All animal species
Applicant	FEFANA ASBL
Type of request	New opinion

On 6 March 2018, 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 of the product, could not conclude on the safety of Butylated Hydroxy Anisole (BHA) in all animal species, under the conditions of use as proposed by the applicant.

The Commission gave the possibility to the applicant to submit complementary information in order to complete the assessment and to allow a revision of the Authority's opinion. The new data have been received on 07 May 2019.

In view of the above, the Commission asks the Authority to deliver a new opinion on Butylated Hydroxy Anisole (BHA) as a feed additive for all animal species based on the additional data submitted by the applicant.

1.2. Additional information

The additive BHA is currently authorised as a technological additive in feedingstuffs for all animal species with a maximum content of 150 mg/kg complete feedingstuffs alone or together with butylated hydroxytoluene (BHT) (E 321) and/or ethoxyquin (E 324) (only for dogs: alone or in combination with E 321).

BHA is authorised according to Directive 95/2/EC² as a food additive (antioxidant).

The Scientific Committee on Food (SCF), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and EFSA ANS Panel have delivered several opinions on the use of BHA as a food additive (JECFA, 1974, 1976, 1982, 1986, 1987, 1989, 1999, 2006; SCF, 1989; EFSA ANS Panel, 2011, 2012).

The EFSA FEEDAP Panel delivered in 2018 an opinion on the safety and efficacy of BHA as a feed additive for all animal species (EFSA FEEDAP Panel, 2018), in which no conclusions could be drawn on the safety of the additive for cats.

The applicant has submitted additional information related to the safety BHA in cats.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of additional information³ to previous applications on the same product.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 European Parliament and Council Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners. OJ No L 61, 18.3.1995, p. 1.

³ FEED dossier reference: FAD-2019-0031.

⁴ FEED dossier reference: FAD-2010-0132.

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of BHA is in line with the principles laid down in Regulation (EC) No 429/2008⁵ and the relevant guidance documents: Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017).

3. Assessment

The additive BHA is equivalent to the active substance and contains at least 98.5% of BHA (IUPAC name: 2-*tert*-butyl-4-hydroxyanisole and 3-*tert*-butyl-4-hydroxyanisole, Chemical Abstracts Service (CAS) number 25013-16-5, chemical formula C₁₁H₁₆O₂, and molecular weight 180.25) and not less than 85% of the 3-*tert*-butyl-4-hydroxyanisole isomer.

BHA is intended to be used as an antioxidant in feedingstuffs for all animal species and categories except dogs with a maximum content of 150 mg/kg complete feedingstuffs (alone or together with BHT (E 321) and/or ethoxyquin (E 324)) and for dogs with a maximum content of 150 mg/kg complete feedingstuffs (alone or together with BHT (E 321)).

In its previous opinion (EFSA FEEDAP Panel, 2018), the Panel concluded that 'a weight of evidence of the limited data supports that 150 mg BHA/kg complete feed would be a safe dose for all animal species. However, a possible exception could be cat, with its known lower capacity for glucuronidation of phenolic compounds and for which no specific data were available'.

The applicant has submitted new information to support the safety for cats, in particular a review of the literature on of the metabolism of phenolic compounds in cats and an *in vivo* study with cats.

3.1. Safety for the target species

3.1.1. Metabolism of phenolic compounds

In the recent EFSA re-evaluation of BHA as a feed additive, the FEEDAP Panel concluded that 150 mg BHA/kg complete feed would be a safe dose for all animal species except for cats due to its known lower capacity for glucuronidation of phenolic compounds and for which no specific data were available (EFSA FEEDAP Panel, 2018). Such a conclusion was based on the demonstrated relative inefficiency of the feline species in glucuronidation of many phenolic and aromatic compounds (including phenol, acetaminophen, chloramphenicol and propofol) due to the known lack of at least two functional uridine-diphospho-glucuronyltransferases isoforms (e.g. UGT 1A6 and 1A9) (Court, 2013).

The applicant provided a selection of publications on the metabolism of phenolic compounds in the cat, claiming that (i) sulfation could be a compensative pathway of the poor glucuronidation capacity in the feline species and (ii) that, since few phenolic derivatives can be glucuronidated in cats, this might be theoretically an option also for BHA.

The Panel has reviewed the studies provided in order to assess whether the conclusions of the applicant are supported by scientific evidence.

The FEEDAP Panel notes that very little is known as to both sulfation reactions and sulfotransferases in the feline species. The sulfation pathway is generally capacity-limited, and particularly in cats in which it can be easily limited by depletion of sulfate (Aronson and Drobatz, 1996; Sellon, 2006). Consequently, sulfation alone may not fully compensate for the low glucuronidation ability in feline species.

Various studies have determined that the glucuronidation deficiency in cats is not generalised to all potential phenolic substrates (Court, 2013). In fact, few phenolic derivatives (e.g. ibuprofen, phenolphthalein) are reported to be glucuronidated in cats (Magdalou et al., 1990). The glucuronidation deficiency depends on the chemical structure of the phenolic derivatives and seems mainly to affect compounds with a simple planar phenolic structure. BHA is characterised by such structure and consequently limited glucuronidation is expected.

Although the clearance of few phenolic compounds by glucuronidation and generally by sulfation was shown in the cat, it cannot be concluded that the efficiency of both pathways is sufficient to clear BHA and its derivatives. No specific information on metabolic fate of BHA has been made available for the feline species. The lack of knowledge is of particular relevance considering the additional load of phenolic compounds by dietary BHA for the full lifetime expectancy of cats. Therefore, the FEEDAP

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.

Panel is not in the position to conclude on the safety of BHA for cats based on metabolic considerations.

3.1.2. *In vivo* study with cats

The applicant provided a 6-month study with cats fed a mixture of antioxidants, including BHA. The study was not designed as a tolerance study and reporting did not follow the Guidance on safety for the target species (EFSA FEEDAP Panel, 2017).



Considering the shortcomings of the study listed above,



the FEEDAP Panel is not in the position to derive any conclusion on the safety of BHA for cats from this study.

4. Conclusions

No specific information on metabolic fate of BHA has been made available for the feline species. The lack of knowledge is of particular relevance considering the additional load of phenolic compounds by dietary BHA for the full lifetime expectancy of cats. Considering the lack of information on the metabolism of BHA in cats and the absence of a well-designed tolerance study, the FEEDAP Panel confirms its previous assessment on the safety of BHA for cats.

Consequently, the Panel reiterates that no safe concentration of BHA in complete feed for cats could be established.

Documentation as provided to EFSA/Chronology

Date	Event
02/05/2019	Dossier received by EFSA. Butylated hydroxy anisole (BHA) for all animal species. Submitted by FEFANA asbl.
03/06/2019	Reception mandate from the European Commission
05/06/2019	Application validated by EFSA – Start of the scientific assessment
12/11/2019	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment



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Abbreviations

ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food
BHA	butylated hydroxy anisole
BHT	butylated hydroxytoluene
CAS	Chemical Abstracts Service
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
IUPAC	International Union of Pure and Applied Chemistry
FAO	Food and Agriculture Organization
SCAN	Scientific Committee on Animal Nutrition
SCF	Scientific Committee on Food
WHO	World Health Organization