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Assessment of the application for renewal of authorisation of VevoVital[®] (benzoic acid) as feed additive for weaned piglets and pigs for fattening

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Abstract

VevoVital[®] is a feed additive consisting of benzoic acid. It is currently authorised as a zootechnical additive for weaned piglets and pigs for fattening. This opinion concerns the renewal of the authorisation of benzoic acid as a zootechnical additive in feed. In 2005 and 2017, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) adopted two opinions on the safety and efficacy of VevoVital[®] as a feed additive for weaned piglets and pigs for fattening, respectively. The applicant has provided data demonstrating that the additive currently in the market complies with the conditions of authorisation. Furthermore, according to the information provided in the technical dossier, no new evidence has been identified that would make the FEEDAP Panel reconsidering the previous conclusions on the safety of the additive. The Panel confirms that the additive is safe at the maximum authorised concentrations of 5,000 and 10,000 mg/kg feed for weaned piglets and pigs for fattening, respectively; a margin of safety cannot be determined for weaned piglets while a margin of safety of less than 1.5 is established for pigs for fattening. The use of VevoVital[®] in feeds for weaned piglets and pigs for fattening at the maximum authorised concentrations does not pose any safety concern for consumers and the environment. The use of VevoVital[®] does not pose a risk by inhalation to users and is not a skin sensitiser. The new available data confirm that the additive is a skin irritant and a severe eye irritant. A recommendation concerning the potential toluene residues in the additive has been posted.

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003¹ 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 one year before the expiry date of the authorisation.

The European Commission received a request from DSM Nutritional Products AG² for renewal of the authorisation of the product VevoVitall® (Benzoic Acid), when used as a feed additive for weaned piglets and pigs for fattening (category: zootechnical additives; functional group: other zootechnical additives).

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). The particulars and documents in support of the application were considered valid by EFSA as of 21 June 2016.

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 product VevoVitall® (benzoic acid), when used under the proposed conditions of use (see Section 3.1.3).

1.2. Interpretation of the Terms of Reference

The application for renewal of the authorisation does not include a proposal for amending or supplementing the conditions of the original authorisation that would have an impact on the efficacy of the additive; therefore, efficacy is not assessed. The present opinion will focus only on the safety aspects.

1.3. Additional information

The FEEDAP Panel has adopted a total of six opinions on the safety and efficacy of VevoVitall® for weaned piglets (EFSA, 2005; EFSA FEEDAP Panel, 2011), pigs for fattening (EFSA, 2007) and pigs for reproduction (EFSA FEEDAP Panel, 2012, 2015) and minor porcine species (EFSA FEEDAP Panel, 2017).

The product from the applicant, either as VevoVitall® or as benzoic acid, is authorised in the European Union (EU) as a zootechnical additive for weaned piglets at the content of 5,000 mg/kg complete feedingstuffs,^{3,4} and for pigs for fattening⁵ and sows⁶ at the maximum content of 10,000 mg/kg complete feedingstuffs.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier⁷ in support of the authorisation request for the use of VevoVitall® (benzoic acid) as a feed

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 DSM Nutritional Products AG represented in the EU by DSM Nutritional Products Sp. z o.o. Poland: Tarczynska 113, 96-320 Mszczonow, Poland.

³ Commission Regulation (EC) No 1730/2006 of 23 November 2006 concerning the authorisation of benzoic acid (VevoVitall) as a feed additive. OJ L 325, 24.11.2006, p. 9.

⁴ Commission Implementing Regulation (EU) No 226/2012 of 15 March 2012 amending Regulation (EC) No 1730/2006 as regards the conditions of use of benzoic acid (holder of authorisation Emerald Kalama Chemical BV). OJ L 77, 16.3.2012, p. 6.

⁵ Commission Regulation (EC) No 1138/2007 of 1 October 2007 concerning the authorisation of benzoic acid (VevoVitall) as a feed additive. OJ L 265, 2.10.2007, p. 8.

⁶ Commission Implementing Regulation (EU) 2016/900 of 8 June 2016 concerning the authorisation of benzoic acid as a feed additive for sows (holder of authorisation DSM Nutritional Product Sp. z o. o.). OJ L 152, 9.6.2016, p. 18.

⁷ FEED dossier reference: FAD-2015-0044.

additive. The technical dossier was prepared following the provisions of Article 14 of Regulation (EC) No 1831/2003, Regulation (EC) No 429/2008⁸ and the applicable EFSA guidance documents.

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 to deliver the present output.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment are valid and applicable for the current application.⁹

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety of VevoVital[®] (benzoic acid) is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance document: Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2013).

3. Assessment

This assessment regards the renewal of the authorisation of the product VevoVital[®] ($\geq 99.9\%$ benzoic acid) as a zootechnical additive, functional group 'other zootechnical additives', to be used in feedingstuffs for weaned piglets at 5,000 mg/kg complete feed and pigs for fattening at the minimum and maximum content of 5,000 and 10,000 mg/kg complete feed, respectively. The specific functions under which the authorisation is granted is:

- for weaned piglets, 'improvement of performance parameters: weight gain or feed/gain ratio', and
- for pigs for fattening, 'urinary pH decrease'.

3.1. Characterisation

3.1.1. Characterisation of the product

The additive VevoVital[®] contains benzoic acid (benzenecarboxylic acid, phenylcarboxylic acid, Chemical Abstracts Service (CAS) No 65–85–0, European Inventory of Existing Commercial Chemical Substances (EINECS) No 200–168–2) as an active substance.

The manufacturing process of benzoic acid is based on the oxidation of toluene.¹⁰ The applicant states that the manufacturing process meets the principles described in the primary authorisation with no changes. The process includes the checking for toluene residues; however, no analytical data and specifications for toluene are present.

The specifications of the additive as defined by the applicant are: $\geq 99\%$ benzoic acid, ≤ 100 mg/kg phthalic acid, ≤ 100 mg/kg sum of biphenyls, ≤ 10 mg/kg heavy metals (as lead) and ≤ 2.0 mg/kg arsenic. These specifications meet those described in the authorisation of VevoVital[®]. Moreover, these specifications are consistent with those described for benzoic acid as a food additive (Commission Directive 96/77/EC)¹¹. The analysis of six batches of the additive showed that benzoic acid from VevoVital[®] met the specifications regarding benzoic acid content and impurities: benzoic acid $> 99\%$; phthalic acid 25–36 mg/kg; biphenyls 63–66 mg/kg; heavy metals < 10 mg/kg; arsenic < 0.01 mg/kg; sulfated ash $< 0.01\%$.¹²

The product appears as white flakes. The analysis of particle size distribution was made by dry sieving¹³ and laser diffraction.¹⁴ The results showed that virtually all particles had a diameter greater than 425 μm ; no particles below 50 μm were detected by laser diffraction. The applicant also provided

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 The report linked to the previous dossier (related to EFSA-Q-2010-00881) is available on the EURL website: <https://ec.europa.eu/jrc/sites/default/files/FinRep-FAD-2010-0029.pdf>

¹⁰ Technical dossier/Supplementary information/Appendix 02.

¹¹ Commission Directive 96/77/EC of 2 December 1996 laying down specific purity criteria on food additives other than colours and sweeteners. OJ L 339, 30.12.1996, p. 1.

¹² Technical Dossier/Section II/Annex_II_6. Complementary Information-August 2017. Values reported as «<» refer to the limit of quantification.

¹³ Technical Dossier/Section II/Annex_II_7.

¹⁴ Technical Dossier/Supplementary Information/Appendix 06.

an evaluation of the figures obtained by sieving with those from the product analysed in 2010, showing that the results were comparable.

The dusting potential, determined by the Stauber–Heubach test in the same three batches in which the sieve analysis was done (see paragraph above), was 0.04 g/m³.^{13,14}

3.1.2. Stability and homogeneity

By means of analysis of benzoic acid, the shelf-life of 24 months, the stability in premixtures of 6 months and the stability in feed of 3 months and the stability to pelleting have been already demonstrated.^{15,16} A further study in pig pelleted feed (pelleting temperature 85°C) stored at 25°C for 12 months demonstrated that no losses of benzoic acid during pelleting and storage of the feed were observed.¹⁷

The ability for VevoVital[®] to mix homogeneously is the same as in the primary authorisations as its particles size and composition are unchanged.

3.1.3. Conditions of use

VevoVital[®] is currently authorised for use in weaned piglets at the maximum dose of 5,000 mg/kg complete feed and in pigs for fattening at the minimum dose of 5,000 mg/kg complete feed and at the maximum dose of 10,000 mg/kg complete feed. No modification of the authorised conditions of use is proposed. The authorisation prescribes that the permitted maximum level for benzoic acid in complete feed should not be exceeded, accounting for the different sources of contribution.

Indications on the use of the additive in complementary feed are provided in the authorisation: Complementary feedingstuffs containing benzoic acid shall not be fed to pigs as such and should be thoroughly mixed with other feed materials of the daily ration. Measures to protect users including the use of breathing protection and gloves are also foreseen.

3.2. Safety

The applicant performed a literature search in order to provide evidence that in the light of the current knowledge the additive remains safe under the approved conditions for target species, consumers, users/workers and the environment. Details of the literature search performed are given later, in each specific safety subsection.¹⁸

3.2.1. Safety for the target species

Six scientific opinions on VevoVital[®] concluded that the additive is safe in weaned piglets (EFSA, 2005; EFSA FEEDAP Panel, 2011), pigs for fattening (EFSA, 2007), pigs for reproduction (EFSA FEEDAP Panel, 2012, 2015) and minor porcine species (EFSA FEEDAP Panel et al., 2017) when used as a zootechnical additive at a dose between 5,000 and 10,000 mg/kg complete feed. The FEEDAP Panel had identified an increase of adverse effects, and in particular of oesophagus and gastric lesions, at excess concentrations of benzoic acid in feeds – higher than 5,000 and 10,000 mg/kg in piglets and pigs for fattening, respectively (EFSA, 2005, 2007). A margin of safety could not be determined for weaned piglets; a (narrow) margin of safety of less than 1.5 was calculated for pigs for fattening.

The applicant performed a structured literature search on the safety of the additive for piglets and growing finishing pigs. The databases consulted were Scopus and PubMed; the search period covered from January 2012 to August 2015; the keywords used were: for the substance 'benzoic or benzoate or hippuric', for the target species 'pig or pigs or swine or piglet or piglets', for the issue 'safety or toxicity or lesions'. A total of 16 publications (see Appendix A) fitted with the search criteria; no paper reported effects of safety concern related to the supplementation of benzoic acid in pigs at the concentrations in feeds authorised in the EU.¹⁹

The FEEDAP Panel considers that there are no new data that would lead to the revision of the conclusions on the safety for weaned piglets and pigs for fattening.

¹⁵ Technical Dossier/Supplementary Information/Appendix 03.

¹⁶ Technical Dossier/Supplementary Information/Appendix 04.

¹⁷ Technical Dossier/Supplementary Information/Appendix 05.

¹⁸ Technical Dossier/Section III.

¹⁹ Technical Dossier/Section III/Annex_III_6.

3.2.2. Safety for the consumer

In its previous opinions, the FEEDAP Panel did not identify any safety concern for consumers when VevoVital[®] is used in pig feeds at the authorised usage levels.

In order to check if there were new data requiring a revision of the previous conclusions on the safety for the consumers, the applicant examined three databases (STN/RTECS, Scopus and ToxNet/ToxLine) and performed two literature searches in different periods: one from 2011 to 2013 and another from 2012 to 2015.²⁰ In general, the following keywords were used: 'benzoic acid', 'CASREGNUMBER 65-85-0', 'genotoxicity', 'toxicity', 'reproduction toxicity', 'allergy', 'mutagenicity', 'carcinogenicity'. A total of 22 references were extracted, from which 17 related to safety for consumers and 5 to safety for users (see Appendix A).

No new information related to toxicokinetics or toxicology of benzoic acid was present, with the exception of genotoxicity. A number of studies published in the open literature report the results of genotoxicity tests on benzoic acid or its salts (sodium or potassium benzoate). These studies are described below.

Benzoic acid was found to be genotoxic in comet assays in human lymphocytes (Demir et al., 2010; Yilmaz et al., 2014) and in haemocytes of *Drosophila melanogaster* (Demir and Kaya, 2013). However, it should be considered that these assays are not currently used in regulatory risk assessment and no OECD guidelines exist for them.

Pongsavee (2015) reported increased micronuclei and chromosomal aberrations in human bone marrow cells at the concentrations of 1,000 and 2,000 µg sodium benzoate/mL, but in this study no information on cytotoxicity is given. The study was conducted only without metabolic activation.

Sodium and potassium benzoate caused dose-related increases of sister chromatid exchanges, micronuclei and chromosomal aberrations in human lymphocytes at all concentrations tested (6.25–100 µg/mL and 62.5–100 µg/L, respectively, for sodium and potassium benzoate); sodium, but not potassium benzoate, also increased DNA breaks according to the comet assay. However significant cytotoxicity was reported at all concentrations tested, as indicated by significantly reduced mitotic index (Zengin et al., 2011).

Overall, the results confirm previous assessments that benzoic acid and its derivatives may induce genotoxic changes *in vitro*; however, *in vivo* genotoxicity studies are consistently negative (EFSA FEEDAP Panel, 2012; EFSA ANS Panel, 2016).

Benzoic acid was also tested in the US EPA's ToxCast project, a large screening programme using a panel of high-throughput cell-free assays for CYP activation/inhibition or binding to membrane receptors (mitochondria, norepinephrine, dopaminergic, aminergic, etc.) as well as nuclear receptors (e.g. oestrogen): benzoic acid was consistently negative in all assays, indicating a low likelihood to exert organ/system-specific toxicity (Sipes et al., 2013).

In conclusion, the review of these studies did not yield information that would require modification of the previous EFSA conclusions and of the position of the Scientific Committee for Food (SCF) (European Commission, 2002a) and the Scientific Committee for Animal Nutrition (SCAN) (European Commission, 2002b). Therefore, the use of VevoVital[®] in weaned piglets and pigs for fattening at the authorised doses is considered safe for the consumer.

3.2.3. Safety for the user

In its assessment of 2002, the SCAN concluded that benzoic acid is an irritant for the skin and eyes; microscopic lung lesions were observed in a subacute inhalation test in the rat at the lowest dose tested of 25 mg/m³, thus a no observed adverse effect concentration (NOAEC) by inhalation was not identified (European Commission, 2002b). The SCAN recommended that measures should be taken to minimise the production of respirable dust; the Committee also concluded that the balance of evidence in skin sensitisation indicated minimal risk to operators.

User safety was further considered in two EFSA Scientific opinions on the use of VevoVital[®] in weaned piglets and pigs for fattening (EFSA 2005, 2007). The FEEDAP Panel supported the overall SCAN position and recommendations. The Panel additionally noted at the time that, whereas benzoic acid was negative in laboratory assays on skin sensitisation, it induced allergic skin or respiratory reactions, albeit at low incidence, in sensitised individuals.

²⁰ Technical Dossier/Section III/Annex_III_7.

VevoVital[®] is unlikely to give rise to an appreciable inhalation exposure, since the particle fraction of inhalable size ($\leq 100 \mu\text{m}$) represents about 0.6% and particles of the respirable fraction ($\leq 10 \mu\text{m}$ and below) are virtually absent; the dusting potential is very low (0.04 g/m^3) (see Section 3.1.1).

From the literature search provided by the applicant – the same used for the safety for the consumers (see Section 3.2.2) – five references related to the safety for the user were identified (see Appendix A). Schnuch et al. (2011) performed an analysis of skin sensitisation by preservatives, including also sodium benzoate, in a large population (over 70,000 subjects) in the United Kingdom; the frequency of reactions to sodium benzoate was 0.69%. This finding supports the previous FEEDAP Panel conclusions that allergy-like reactions to benzoic acid may occur in a small population subset.

The Committee for Risk Assessment of the European Chemicals Agency (ECHA) concluded in 2012 that benzoic acid should be classified as Eye Damage 1 and Skin Irritant 2.²¹ The hazard for the eyes was assigned on the basis of two guideline-based *in vivo* studies on rabbits, which showed that benzoic acid powder to be moderately to severely irritating to the eye. Although two guideline-based *in vivo* studies on rabbits indicated absent or slight skin irritation, available human data show that benzoic acid is capable of inducing non-immunological contact urticaria; this lesion is regarded as an irritation reaction without requiring previous sensitisation. Accordingly, benzoic acid was not considered as a skin sensitiser. To the best knowledge of the FEEDAP Panel, there are no new data that may modify the conclusions of the ECHA assessment. The FEEDAP Panel therefore considers that allergy-like (urticarial) reactions observed in humans upon skin contact with benzoic acid and derivatives do not have an immunological basis and are manifestations of skin irritation.

The FEEDAP Panel concludes that the use of VevoVital[®] does not pose a risk by inhalation to users and is not a skin sensitiser. The new available data confirm that the additive is a skin irritant and a severe eye irritant. The additive has low dustiness and a minimal fraction of respirable or inhalable dust; thus inhalation exposure is considered as very low. No risk to users by inhalation is foreseen at the conditions of use.

3.2.4. Safety for the environment

Most benzoic acid administered to farm animals will be excreted as urinary hippuric acid (Baldwin et al., 1960; Kristensen et al., 2009), an endogenous metabolic by-product. Small amounts of benzoates may also occur in the excreta; such compounds have low potential for adverse effects in aquatic or terrestrial organisms. SCAN concluded that, based on the characteristics of benzoic acid and of its metabolites, no concerns for environment are expected (European Commission, 2002b). In 2007, the FEEDAP Panel endorsed this conclusion for VevoVital[®] (EFSA, 2007).

The applicant provided a literature search to support the safety for the environment of the additive, in accordance with the Guidance for renewal (EFSA FEEDAP Panel, 2013). Two scientific database were examined (Scopus and Pubmed) applying two sets of keywords in two different time periods (January 2012–August 2015, keywords: benzoic acid, benzoate, hippuric, air, soil, water, environment, safety²²; January 2012–July 2016, keywords: benzoic, benzoate, hippuric, environmental toxicity, ecotoxicity²³) with the aim of examining if there were new findings on the safety of benzoic acid for the environment. A total of 473 references were overall retrieved; however, the large majority of them were not relevant (e.g. references concerning pesticides, pesticide metabolites or parabens which contains benzoic acid or hippuric acid-related chemical moieties, occupational toxicity, petroleum industry). A total of 10 papers (see Appendix A) were deemed to be potentially relevant to the safety of benzoic acid for the environment, and in particular to the use in animal nutrition, and thus, were examined further. However, the FEEDAP Panel found that no studies directly relevant to the environmental risk assessment of benzoic acid were identified.

Therefore, the references provided do not add any significant information to the environmental safety of benzoic acid used as a feed additive, which may lead to modify the previous conclusion of the FEEDAP Panel. Accordingly, the Panel considers that there is not new data that call for a revision of the conclusions on the safety for the environment.

²¹ Technical Dossier/Section III/Appendix 3–9.

²² Technical Dossier/Section III/Annex_III_12.

²³ Technical Dossier/Supplementary Information/Appendix 07.

3.3. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation²⁴ and Good Manufacturing Practice.

4. Conclusions

The applicant has provided data demonstrating that the additive currently in the market complies with the conditions of authorisation.

The FEEDAP Panel confirms that the use of VevoVital[®] is safe at the maximum authorised concentrations of 5,000 and 10,000 mg/kg feed for weaned piglets and pigs for fattening, respectively; a margin of safety cannot be determined for weaned piglets while a (narrow) margin of safety of less than 1.5 is established for pigs for fattening.

The FEEDAP Panel confirms its previous conclusion that the use of VevoVital[®] in feeds for weaned piglets and pigs for fattening at the maximum authorised concentrations does not pose any safety concern for consumers.

The FEEDAP Panel concludes that the use of VevoVital[®] does not pose a risk by inhalation to users and is not a skin sensitiser. The new available data confirm that the additive is a skin irritant and a severe eye irritant.

The FEEDAP Panel confirms its previous conclusion that the use of VevoVital[®] in feeds for weaned piglets and pigs for fattening at the maximum authorised concentrations does not pose any concern for the environment.

5. Recommendations

Toluene impurities in the additive should be monitored during the production process to check the compliance with the criteria laid by VICH (Veterinary International Cooperation on Harmonisation of technical requirements for registration of medicinal products) on residual solvents in products for veterinary use.²⁵

Documentation provided to EFSA

- 1) Dossier VevoVital[®] for pigs for fattening and weaned piglets. December 2015. Submitted by DSM Nutritional Products Ltd.
- 2) Dossier VevoVital[®] for pigs for fattening and weaned piglets. Supplementary information. September 2016. Submitted by DSM Nutritional Products Ltd.
- 3) Dossier VevoVital[®] for pigs for fattening and weaned piglets. Complementary information. August 2017. Submitted by DSM Nutritional Products Ltd.

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²⁴ Regulation (EC) No 1831/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

²⁵ VICH GL18(R) (IMPURITIES SOLVENTS). June 2011. Available online: <http://www.vichsec.org/component/attachments/attachments/154.html?task=download>

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Abbreviations

CAS	Chemical Abstracts Service
ECHA	European Chemicals Agency
EINECS	European Inventory of Existing Commercial Chemical Substances
EURL	European Union Reference Laboratory
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
NOAEC	no observed adverse effect concentration
SCF	Scientific Committee for Food
SCAN	Scientific Committee for Animal Nutrition
VICH	Veterinary International Cooperation on Harmonisation of technical requirements for registration of medicinal products

Appendix A – List of references retrieved from the literature search provided by the applicant to support safety of the additive

A.1. Safety for target animals

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