Assessment of a feed additive consisting of all-rac-alpha tocopheryl acetate (vitamin E) for all animal species for the renewal of its authorisation (EUROPE-ASIA Import Export GmbH)

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Abstract

Following a request from the European Commission, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the assessment of the application for renewal of authorisation of all-rac-alpha tocopheryl acetate (vitamin E) as a feed additive for all animal species. The applicant provided data demonstrating that the additive currently in the market complies with the conditions of authorisation. The FEEDAP Panel confirms that the use of all-rac-alpha-tocopheryl acetate under the current authorised conditions of use is safe for the target species, the consumers and the environment. No concern for user safety is expected from the use of the active substance; however, due to the lack of information, the FEEDAP Panel is not able to conclude on its skin sensitisation potential. To draw conclusions on the safety for the user of the final formulated additives, specific studies would be required. There is no need to assess the efficacy of all-rac-alpha-tocopheryl acetate in the context of the renewal of the authorisation.

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Keywords: all-rac-alpha tocopheryl acetate, vitamin E, renewal, nutritional additive, vitamins and pro-vitamins, feed, safety

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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. 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 EUROPE-ASIA Import Export GmbH\(^2\) for renewal of the authorisation of the product all-rac alpha tocopheryl acetate, when used as a feed additive for all animal species (category: nutritional additives; functional group: vitamins, pro-vitamins and chemically well-defined substances having a similar effect).

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 28 April 2020.

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 all-rac alpha tocopheryl acetate, when used under the proposed conditions of use (see Section 3.1.4).

1.2. Additional information

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) issued an opinion on the safety and efficacy of vitamin E, in the form of all-rac-alpha-tocopheryl acetate, RRR-alpha-tocopheryl acetate and RRR-alpha-tocopherol, when used as a feed additive for all animal species (EFSA FEEDAP Panel, 2010). In 2012, the FEEDAP Panel issued another opinion on the safety and efficacy of synthetic alpha-tocopherol when used as a technological additive (antioxidant) for all animal species (EFSA FEEDAP Panel, 2012a,b) and another opinion on the safety and efficacy of tocopherol-rich extracts of natural origin, tocopherol-rich extracts of natural origin/delta-rich and synthetic tocopherol for all animal species (EFSA FEEDAP Panel, 2012b).

Vitamin E (3a700) in the form of all-rac-alpha-tocopheryl acetate, RRR-alpha-tocopheryl acetate and RRR-alpha tocopherol is currently authorised as nutritional additive for all animal species.\(^3\) alpha-Tocopherol is also authorised for use as a technological additive (functional group: antioxidants) in feed for all animal species.\(^4\)

all-rac-alpha-Tocopheryl acetate is described in the European Pharmacopoeia 10.0 (PhEur), monograph 0439 (PhEur, 2020).

The Scientific Committee for Food (SCF) established a tolerable upper intake level (UL) for vitamin E as 270 mg/day for adults and rounded to 300 mg/day (SCF, 2003). The EFSA Panel on Dietetic Products, Nutrition and Allergy issued an opinion on dietary reference values for vitamin E as alpha-tocopherol (EFSA NDA Panel, 2015). The EFSA Panel on Food Additives and Nutrient Sources Added to Food (EFSA ANS Panel) issued an opinion on the evaluation of tocopherol-rich extract (E 306), alpha-tocopherol (E 307), \(\gamma\)-tocopherol (E 308) and \(\delta\)-tocopherol (E 309) as food additives (EFSA ANS Panel, 2015).

\(^1\) 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.

\(^2\) EUROPE-ASIA Import Export GmbH, Neuer Wall 40, 20354, Hamburg (Germany).

\(^3\) Commission Regulation (EU) No 26/2011 of 14 January 2011 concerning the authorisation of vitamin E as a feed additive for all animal species. OJ L 11, 15.1.2011, p. 18-21.

\(^4\) Commission Regulation (EU) No 2015/1152 of 14 July 2015 concerning the authorisation of tocopherol extracts from vegetable oils, tocopherol-rich extracts from vegetable oils (delta rich) and alpha-tocopherol as feed additives for all animal species. OJ L 187, 15.7.2015, p. 5.
Tocopherol-rich extract (E 306), alpha-tocopherol (E 307), \( \gamma \)-tocopherol (E 308) and \( \delta \)-tocopherol (E 309) are authorised as food additives.\(^5\) Vitamin E is authorised for use in food for nutritional purposes,\(^6\) for use in cosmetics as an antioxidant\(^7\) and as a veterinary medicinal product.\(^8,9\)

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\(^10\) in support of the authorisation request for the use of all-rac-alpha tocopheryl acetate (vitamin E) as a feed additive.

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.\(^11\)

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of all-rac-alpha tocopheryl acetate (vitamin E) is in line with the principles laid down in Regulation (EC) No 429/2008\(^12\) and the relevant guidance document: Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2013) and Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017).

3. Assessment

Vitamin E (tocopherol) is currently authorised as a feed additive in the form of three active substances: all-rac-alpha-tocopheryl acetate, RRR-alpha-tocopheryl acetate and RRR-alpha-tocopherol. This assessment regards the renewal of the authorisation of vitamin E in the form of all-rac-alpha-tocopheryl acetate (> 93%), when used as a nutritional additive (functional group: vitamins, provitamins and chemically well-defined substances having a similar effect) in feed and water for drinking for all animal species.

3.1. Characterisation

3.1.1. Characterisation of the active substance

all-rac-alpha-Tocopheryl acetate is identified with the Chemical Abstracts Service (CAS) number 7695-91-2 and it has a molecular formula \( \text{C}_{31}\text{H}_{52}\text{O}_3 \).

all-rac-alpha-Tocopheryl acetate is a slightly greenish-yellow or yellow viscous, oily liquid. It is practically insoluble in water, freely soluble in acetone, in anhydrous ethanol and in fatty oils.

The applicant stated that the manufacturing process and the composition of the additive have not been modified since the previous authorisation and data have been provided from recent batches on the composition of the additive to support this statement.

\(^5\) Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council Text with EEA relevance. OJ L 83, 22.3.2012.

\(^6\) Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009. OJ L 181, 29.6.2013, p. 35.

\(^7\) Commission Decision of 9 February 2006 amending Decision 96/335/EC establishing an inventory and a common nomenclature of ingredients employed in cosmetic products (2006/257/EC). OJ L 97, 5.4.2006, p. 1.

\(^8\) Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. OJ L 15, 20.1.2010, p. 1.

\(^9\) Commission Regulation (EC) No 997/1999 of 11 May 1999 amending Annexes I, II and III of Council Regulation (EEC) No 2377/90 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin. OJ L 122, 12.5.1999, p. 24.

\(^10\) FEED dossier reference: FAD-2020-0009.

\(^11\) The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2008-0047.pdf

\(^12\) 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.
The applicant provided results on batch-to-batch variation on five recent batches of the active substance. The analysis showed that the content of all-rac-alpha-tocopheryl acetate ranged from 96.2% to 96.7% (mean: 96.3%) and demonstrated compliance with the existing specifications (purity criteria: > 93%).

Possible impurities listed in the European Pharmacopoeia were also measured in three batches, namely all-rac-trans-2,3,4,6,7-pentamethyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzofuran-5-yl acetate (impurity A, 0.25-0.26%), all-rac-cis-2,3,4,6,7-pentamethyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzofuran-5-yl acetate (impurity B, 0.91-0.94%); all-rac-alpha-tocopherol (impurity C, 0.19–0.29%); 4-methoxy-2,3,6-trimethyl-5-[(all-RS,E)-3,7,11,15-tetramethylhexadec-2-enyl] phenylacetate (impurity D), and (all-RS, all-E)-2,6,10,14,19,23,27,31-octamethylotriaconta-12,14,18-triene (impurity E, < 0.1% for the sum of impurities D and E). The detected amounts of impurities were below the limits specified in the European Pharmacopoeia monograph (PhEur, 2020).

Dioxins (polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/F)) were determined in a single batch of the product and amounted to 0.085 ng WHO-PCDD/F-TEQ/kg, and the sum of dioxins and dioxin-like polychlorinated biphenyls (DL-PCBs) was 0.1 ng WHO-PCDD/F/DL-PCB-TEQ per kg. Possible presence of arsenic (< 0.10 mg/kg) and heavy metals (lead < 0.1 mg/kg, mercury < 0.001 mg/kg, cadmium < 0.01 mg/kg, chromium 0.74 mg/kg, palladium < 0.5 mg/kg) was evaluated in three batches of the active substance. The analysis demonstrated that the results are below the limits established in Directive 2002/32/EC.

Based on the results obtained, no concerns are identified.

3.1.2. Characterisation of the formulated additive

According to the information provided by the applicant, the additive is placed on the market in the form of a preparation containing all-rac-alpha tocopheryl acetate > 94.5%.

According to the applicant, there are two types of vitamin E preparations: not water-dispersible and water-dispersible. The applicant submitted the typical formulation compositions for both formulations.

3.1.3. Stability and homogeneity

Stability and the capacity for homogeneous distribution of the additive have been evaluated by EFSA in its previous assessment (EFSA FEEDAP Panel, 2010).

In the current dossier, the applicant provided results on stability of the active substance from recent studies. To confirm the shelf-life of at least 24 months, two batches of the active substance were stored at 40°C and 75% of relative humidity (RH) for 6 months and two batches at 30°C and 65% RH for 36 months. For the first test condition, at time 0 the content of all-rac-alpha-tocopheryl acetate was 96.9% (min-max: 96.8–97.1%). After 6-month storage the content was 96.5% (min-max: 96.4–96.6%). At time 0 the content of all-rac-alpha-tocopheryl acetate was 95.2%. After 24-month storage the content was 95% (min-max: 94.9–95.1%).

A new study was conducted to investigate the stability in a supplementary mineral premixture of the active substance included at the level of 5,250 mg/kg. The sample was packed in a tightly closed PE-bag and stored at ambient temperature (~18°C). After three months, the recovery was 88%. A new homogeneity study was provided by the applicant in the current dossier. Ten subsamples from one batch of mineral feed were tested (initial concentration of all-rac-alpha-tocopheryl acetate: 5,250 mg/kg). The coefficient of variation (CV) was 2.5%.
3.1.4. **Conditions of use**

All-rac-alpha-Tocopheryl acetate (vitamin E, purity > 93%) is currently authorised for use in feed and in water for drinking for all animal species without a maximum content. The authorisation, under other provisions, foresees:

1) If vitamin E content is mentioned in the labelling, the following equivalencies for the units of measurement of the contents shall be used:
   - 1 mg all-rac-alpha-tocopheryl acetate = 1 IU.
   - 1 mg RRR-alpha-tocopherol = 1.49 IU.
   - 1 mg RRR-alpha-tocopheryl acetate = 1.36 IU.

2) Vitamin E may be used also via water for drinking.

The applicant proposes to keep the same conditions of use as authorised.

3.2. **Safety**

The safety of the vitamin E in the form of all-rac-alpha-tocopheryl acetate for the target species, consumer, user and the environment has been evaluated in a previous opinion (EFSA FEEDAP Panel, 2010). The FEEDAP Panel concluded that 'vitamin E at the current use levels is safe for all animal species. Information on hypervitaminosis E is not sufficiently consistent to derive a maximum content for vitamin E in feedingstuffs, based on safety for target species'. The Panel also concluded that the use of the product as a feed additive raises no concern for consumer safety or for the environment. Concerning the safety for the user, no irritating effects were observed when all-rac-alpha-tocopheryl acetate was tested for dermal and ocular irritation. Sensitisation studies were not provided. The Panel concluded that 'no concern for user safety is expected from the use of the active substances vitamin E in feed additives. However, to draw conclusions on the final formulated additives, specific studies would be required'.

In support of the safety of the active substance, the applicant performed a literature search. The search was done via three meta-search sites: LIVIVO, Ovid, and ToxNet sixteen single databases (incl. PubMed and Web of Science), and eight publishers search facilities (incl. Elsevier, Ingenta, Springer, Wiley). A detailed description of the iterations used and the inclusion/exclusion criteria applied for the selection were provided. The search resulted in 713 papers retrieved, 28 publications were considered relevant. The list of papers was provided as RIS. File.

An additional literature search was carried out to gather information on the possible presence of vitamin E residues in products of animal origin. The search was performed in 55 cumulative databases (e.g. LIVIVO, AGRICOLA, MEDLINE, PubMed and OVID). The main strings used were: 'vitamin E acetate OR tocopherol acetate OR 7695-91-2'. Specific subject areas were added in order to restrict the search (such as Animal; BMDL; Clinic*; Cancer; Carcino*; Dose; efficacy; feed; Genotox*; Human; Laboratory animal*; Livestock; Mouse/mice; Mutag*; NOAEL; Oral*; Rat; safe concentration; safety; Target animal*; Tolera*; Toxic*; trial; "90-day"/"90day". A detailed description of the iterations used and the inclusion/exclusion criteria applied for the selection were provided. An additional literature search was conducted to further investigate Vitamin E levels in animal tissues and products. In total, 551 references were identified, 104 of which were considered relevant. None of the papers identified a safety concern for the target species, the consumer, the user and the environment.

3.2.1. **Reassessment of the consumer exposure**

In the previous FEEDAP Panel opinion (EFSA FEEDAP Panel, 2010), a 'worst-case scenario' exposure assessment for the consumer, based on the consumption model described in Regulation (EC) No 429/2008 and on data from literature on vitamin E content in edible tissues and products from animals treated with vitamin E at levels far higher than the practical use (1,000 mg/kg feed), indicated that the theoretical exposure of consumers amounted to about 45% of the UL (300 mg alpha-tocopherol equivalents/day).

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24 Technical dossier/Section III/Annex III_01.
25 Technical dossier/Section III/Annex III_02.
26 Technical dossier/Section III/Supplementary_Information (February 2021)/Annex I, Annex II, Annex III, Annex IV, Annex V.
In the current assessment, the FEEDAP Panel performed an updated exposure assessment following the methodology described in the Guidance on consumer safety (EFSA FEEDAP Panel, 2017) (Appendix A). Based on the literature search provided by the applicant, the Panel identified three relevant papers (Ouraji et al., 2011; Song et al., 2014; Kidane et al., 2015) with new residue data not available at the time of the previous assessment. In addition, the Panel opted to use more realistic feed supplementation figures (i.e. 100 mg/kg feed instead of 1,000 mg/kg) also from the studies already assessed in the previous opinion. When data were available for the same species and food items at the same supplementation concentration, the highest value was considered. The input data used are reported in Table 1.

The results of the dietary exposure to vitamin E for the different population categories are reported in Table 2.

### Table 1: Input data on vitamin E content in food of animal origin used for the consumer exposure assessment

| Animal products | mg/kg wet tissue/products | Reference |
|-----------------|---------------------------|-----------|
| Birds fat (skin/fat) | 12* (24) | Sunder and Flachowsky (2001)¹ |
| Birds liver | 17 | Sunder and Flachowsky (2001)¹ |
| Birds meat | 8 | Sunder and Flachowsky (2001)¹ |
| Fish | 135 | Tocher et al. (2002)⁹ |
| Mammals fat tissue | 2.3* (4.6) | Yang et al. (2009)⁹ |
| Mammals liver | 4.6 | Yang et al. (2009)⁹ |
| Mammals meat | 9 | Song et al. (2014) |
| Mammals offals and slaughtering products (other than liver) | 2.7 | Yang et al. (2009)⁹ |
| Milk | 1.5 | Kidane et al. (2015) |
| Seafood | 8 | Ouraji et al. (2011) |
| Eggs | 68 | Sunder and Flachowsky (2001)¹ |

No data were retrieved for the following food categories: 'Birds offals and slaughtering products (other than liver)' and 'honey'. However, it is expected that the contribution of these food categories to the overall exposure would be limited.

*: The original value (in parenthesis) was divided by 2 to take into consideration the ratio skin/fat.
†: Paper used in EFSA FEEDAP Panel (2010).

The contribution to the consumer exposure to vitamin E from products of animals fed with the additive ranged from 9.5% to 15.3% of the ULs (Table 2).

### Table 2: Chronic human dietary exposure to vitamin E

| Population category | Maximum HRP* (mg/kg/bw per day) | Default body weight (EFSA Scientific Committee, 2012) | Exposure (mg/day) | UL† (mg/day) (European Commission, 2003) | % UL |
|---------------------|-------------------------------|-----------------------------------------------------|------------------|------------------------------------------|------|
| Infants | 0.43 | 5 | 2.15 | | |
| Toddlers | 0.95 | 12 | 11.4 | 100 | 11.4 |
| Other children | 0.8 | 23 | 18.4 | 120 | 15.3 |
| Adolescents | 0.49 | 52.4** | 25.6 | 260 | 9.8 |
| Adults | 0.41 | 70 | 28.7 | 300 | 9.5 |
| Elderly | 0.37 | 70 | 25.9 | | |
| Very elderly | 0.33 | 70 | 23.1 | | |

bw: body weight.
*: HRP: maximum highest reliable percentile.
†: UL: Tolerable upper level.
**: (Average of 43.4 and 61.3 kg).

In 2003, the SCF established an UL for vitamin E for adults as 300 mg/day (SCF, 2003), based on the body weight (bw), the UL for children (1–3 years) and adolescents was set at 100 and 260 mg/day, respectively. To compare the vitamin E dietary exposure calculation to the UL, the FEEDAP Panel used the highest reliable percentile (HRP) for the different population categories and converted it from mg/kg bw per day into mg/person per day using the default bw values (EFSA Scientific Committee, 2012). The contribution to the consumer exposure to vitamin E from products of animals fed with the additive ranged from 9.5% to 15.3% of the ULs (Table 2).
For the population groups infants and elderly as well as very elderly, no UL was established by the SCF. However, the FEEDAP Panel assumes that the exposure would still be in the same relation to the UL as for the other population categories.

The FEEDAP Panel concludes that there is no safety concern for the consumer resulting from the intake of food from all animal species fed with vitamin E in the form of all-rac-alpha-tocopheryl acetate under the conditions of the existing authorisation.

3.2.2. Conclusions on safety

Based on the above and the fact that the manufacturing process, the composition of the additive and the conditions of use for the species/categories for which the additive is authorised have not been modified, the Panel considers that there is no evidence to reconsider the conclusions reached in previous assessments. The FEEDAP Panel concludes that vitamin E in the form of all-rac-alpha-tocopheryl acetate remains safe for the target species, the consumer and the environment under the conditions of use currently authorised. No concern for user safety is expected from the use of the active substance; however, due to the lack of information, the FEEDAP Panel is not able to conclude on its skin sensitisation potential. To draw conclusions on the safety for the user of the final formulated additives, specific studies would be required.

3.3. Efficacy

The present 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, there is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

3.4. 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 Regulation\(^{27}\) 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 concludes that all-rac-alpha-tocopheryl acetate (vitamin E) remains safe for all the animal species, for the consumers and the environment under the conditions of use currently authorised. No concern for user safety is expected from the use of the active substance however, due to the lack of information, the FEEDAP Panel is not able to conclude on its skin sensitisation potential. To draw conclusions on the safety for the user of the final formulated additives, specific studies would be required.

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

5. Documentation as provided to EFSA/Chronology

| Date       | Event                                                                                                                                 |
|------------|---------------------------------------------------------------------------------------------------------------------------------------|
| 30/01/2020 | Dossier received by EFSA. Vitamin E/all-rac-alpha tocopheryl acetate for all animal species. Submitted by EUROPE-ASIA Import Export GmbH. |
| 11/02/2020 | Reception mandate from the European Commission                                                                                       |
| 28/04/2020 | Application validated by EFSA – Start of the scientific assessment                                                                  |
| 22/06/2020 | Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. Issues: characterisation, safety |
| 18/08/2020 | Reception of supplementary information from the applicant - Scientific assessment re-started                                           |

\(^{27}\) Regulation (EC) No 183/2005 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.
Vitamin E renewal for all animal species

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EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2015. Scientific Opinion on the re-evaluation of tocopherol-rich extract (E 306), α-tocopherol (E 307), γ-tocopherol (E 308) and δ-tocopherol (E 309) as food additives. EFSA Journal 2015;13(9):4247, 118 pp. https://doi.org/10.2903/j.efsa.2015.4247

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2010. Scientific Opinion on the safety and efficacy of vitamin E as a feed additive for all animal species. EFSA Journal 2010;8(6):1635, 28 pp. https://doi.org/10.2903/j.efsa.2010.1635

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### Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| ANSEFSA      | Panel on Food Additives and Nutrient Sources added to Food |
| bw           | body weight |
| CAS          | Chemical Abstracts Service |
| CFU          | colony forming unit |
| CV           | coefficient of variation |
| DL-PCB       | dioxin-like polychlorinated biphenyl |
| EMA          | European Medicines Agency |
| EURL         | European Union Reference Laboratory |
| FEEDAP       | EFSA Panel on Additives and Products or Substances used in Animal Feed |
| HRP          | highest reliable percentile |
| IU           | International Unit |
| PCB          | polychlorinated biphenyl |
| PCDD/F       | polychlorinated dibenzo-p-dioxin and dibenzofuran |
| PhEur        | European Pharmacopoeia |
| RAC          | raw agricultural commodity |
| RH           | relative humidity |
| SCF          | Scientific Committee for Food |
| TEQ          | toxic equivalent |
| UL           | upper level |
| WHO          | World Health Organization |
Appendix A – Calculation of consumer exposure with FACE model

Methodology

As described in the Guidance on the safety of feed additives for consumers (EFSA FEEDAP Panel, 2017), consumption data of edible tissues and products as derived from the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) will be used to assess exposure to residues from the use of feed additives in different EU countries, age classes 35 and special population groups. For each EU country and age class, only the latest survey available in the Comprehensive Database will be used.

While the residue data reported for feed additives refer to organs and tissues (raw agricultural commodities (RAC)), the Comprehensive Database includes consumption data for foods as consumed. In order to match those consumption data with the available residue data for feed additives, the consumption data reported in the Comprehensive Database have been converted into RAC equivalents.

For assessing the exposure to coccidiostats from their use in (non-reproductive) poultry, the following list of commodities is considered: meat, fat, liver, other offals (including kidney).

Depending on the nature of the health-based guidance derived, either a chronic or acute exposure assessment may be required.

For chronic exposure assessments, the total relevant residues will be combined for each individual with the average daily consumptions of the corresponding food commodities, and the resulting exposures per food will be summed in order to obtain total chronic exposure at individual level (standardised by using the individual body weight). The mean and the higher percentile (usually the 95th percentile) of the individual exposures will be subsequently calculated for each dietary survey (country) and each age class separately.

As opposed to the chronic exposure assessments, acute exposure calculation will be carried out for each RAC value separately. The higher percentile (usually the 95th percentile) exposures based on the consuming days only will be calculated for each food commodity, dietary survey and age class separately.

As described in the Guidance on the safety of feed additives for consumers (EFSA FEEDAP Panel, 2017), consumption data of edible tissues and products as derived from the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) will be used to assess exposure to residues from the use of feed additives in different EU countries, age classes28 and special population groups. For each EU country and age class, only the latest survey available in the Comprehensive Database will be used.

While the residue data reported for feed additives refer to organs and tissues (raw agricultural commodities (RAC)), the Comprehensive Database includes consumption data for foods as consumed. In order to match those consumption data with the available residue data for feed additives, the consumption data reported in the Comprehensive Database have been converted into RAC equivalents.

For assessing the exposure to vitamin E from their use in (non-reproductive) poultry, the following list of commodities is considered: meat, fat, liver, other offals (including kidney).

Depending on the nature of the health-based guidance derived, either a chronic or acute exposure assessment may be required.

For chronic exposure assessments, the total relevant residues will be combined for each individual with the average daily consumptions of the corresponding food commodities, and the resulting exposures per food will be summed in order to obtain total chronic exposure at individual level (standardised by using the individual body weight). The mean and the higher percentile (usually the 95th percentile) of the individual exposures will be subsequently calculated for each dietary survey (country) and each age class separately.

As opposed to the chronic exposure assessments, acute exposure calculation will be carried out for each RAC value separately. The higher percentile (usually the 95th percentile) exposures based on the consuming days only will be calculated for each food commodity, dietary survey and age class separately.

28 Infants: < 12 months old, toddlers: ≥ 12 months to ≤ 36 months old, other children: ≥ 36 months to < 10 years old, adolescents: ≥ 10 years to < 18 years old, adults: ≥ 18 years to ≤ 65 years old, elderly: ≥ 65 years to < 75 years old, and very elderly: ≥ 75 years old.
Appendix B – Detailed results on chronic exposure calculation

Chronic dietary exposure per population class, country and survey (mg/kg bw per day) of consumers to ATX based on residue data in salmonids and crustaceans.

Table B.1: Chronic dietary exposure per population class, country and survey (mg/kg bw per day) of consumers to vitamin E based on residue data

| Population class | Survey's country | Number of subjects | HRP value     | HRP description |
|------------------|------------------|--------------------|---------------|-----------------|
| Infants          | Bulgaria         | 523                | 0.4307512765  | 95th            |
| Infants          | Germany          | 142                | 0.2187406332  | 95th            |
| Infants          | Denmark          | 799                | 0.3643741241  | 95th            |
| Infants          | Finland          | 427                | 0.1893018911  | 95th            |
| Infants          | United Kingdom   | 1,251              | 0.4385794945  | 95th            |
| Infants          | Italy            | 9                  | 0.0636808234  | 50th            |
| Toddlers         | Belgium          | 36                 | 0.3630401581  | 90th            |
| Toddlers         | Bulgaria         | 428                | 0.7009082960  | 95th            |
| Toddlers         | Germany          | 348                | 0.4116913805  | 95th            |
| Toddlers         | Denmark          | 917                | 0.4067212385  | 95th            |
| Toddlers         | Spain            | 17                 | 0.5399953486  | 75th            |
| Toddlers         | Finland          | 500                | 0.5026258459  | 95th            |
| Toddlers         | United Kingdom   | 1,314              | 0.5576633660  | 95th            |
| Toddlers         | United Kingdom   | 185                | 0.5139483784  | 95th            |
| Toddlers         | Italy            | 36                 | 0.950916529   | 90th            |
| Other children   | Netherlands      | 322                | 0.4029951191  | 95th            |
| Other children   | Austria          | 128                | 0.5204588196  | 95th            |
| Other children   | Belgium          | 625                | 0.4858161922  | 95th            |
| Other children   | Bulgaria         | 433                | 0.6389241335  | 95th            |
| Other children   | Czech Republic   | 389                | 0.5663914191  | 95th            |
| Other children   | Germany          | 293                | 0.3991452721  | 95th            |
| Other children   | Germany          | 835                | 0.4018474802  | 95th            |
| Other children   | Denmark          | 298                | 0.4190325702  | 95th            |
| Other children   | Spain            | 399                | 0.7639502309  | 95th            |
| Other children   | Spain            | 156                | 0.803330849   | 95th            |
| Other children   | Finland          | 750                | 0.4873081000  | 95th            |
| Other children   | France           | 482                | 0.4983832829  | 95th            |
| Other children   | United Kingdom   | 651                | 0.4063760054  | 95th            |
| Other children   | Greece           | 838                | 0.5747174989  | 95th            |
| Other children   | Italy            | 193                | 0.7088970815  | 95th            |
| Other children   | Latvia           | 187                | 0.3495764652  | 95th            |
| Other children   | Netherlands      | 957                | 0.3691574625  | 95th            |
| Other children   | Netherlands      | 447                | 0.3102352691  | 95th            |
| Other children   | Sweden           | 1,473              | 0.4331044897  | 95th            |
| Adolescents      | Austria          | 237                | 0.2967982330  | 95th            |
| Adolescents      | Belgium          | 576                | 0.2148765628  | 95th            |
| Adolescents      | Cyprus           | 303                | 0.2428191588  | 95th            |
| Adolescents      | Czech Republic   | 298                | 0.394596400   | 95th            |
| Adolescents      | Germany          | 393                | 0.2973475130  | 95th            |
| Adolescents      | Germany          | 1,011              | 0.1799520701  | 95th            |
| Adolescents      | Denmark          | 377                | 0.1906919355  | 95th            |
| Adolescents      | Spain            | 651                | 0.4507975970  | 95th            |
| Adolescents      | Spain            | 209                | 0.499138582   | 95th            |
| Adolescents      | Spain            | 86                 | 0.340338670   | 95th            |
| Adolescents      | Finland          | 306                | 0.2437208440  | 95th            |
| Population class | Survey’s country | Number of subjects | HRP value     | HRP description |
|------------------|------------------|--------------------|---------------|-----------------|
| Adolescents      | France           | 973                | 0.2847918189  | 95th            |
| Adolescents      | United Kingdom   | 666                | 0.2257091976  | 95th            |
| Adolescents      | Italy            | 247                | 0.3393086625  | 95th            |
| Adolescents      | Latvia           | 453                | 0.2567828328  | 95th            |
| Adolescents      | Netherlands      | 1,142              | 0.2200749334  | 95th            |
| Adolescents      | Sweden           | 1,018              | 0.2788554025  | 95th            |
| Adults           | Austria          | 308                | 0.2577812148  | 95th            |
| Adults           | Belgium          | 1,292              | 0.2357205935  | 95th            |
| Adults           | Czech Republic   | 1,666              | 0.2642757492  | 95th            |
| Adults           | Germany          | 10,419             | 0.2312981689  | 95th            |
| Adults           | Denmark          | 1,739              | 0.1588249466  | 95th            |
| Adults           | Spain            | 981                | 0.4108790208  | 95th            |
| Adults           | Spain            | 410                | 0.3801787696  | 95th            |
| Adults           | Finland          | 1,295              | 0.2884024962  | 95th            |
| Adults           | France           | 2,276              | 0.2223089799  | 95th            |
| Adults           | United Kingdom   | 1,265              | 0.214590136   | 95th            |
| Adults           | Hungary          | 1,074              | 0.194694122   | 95th            |
| Adults           | Ireland          | 1,274              | 0.2254313550  | 95th            |
| Adults           | Italy            | 2,313              | 0.2726351382  | 95th            |
| Adults           | Latvia           | 1,271              | 0.2675406839  | 95th            |
| Adults           | Netherlands      | 2,055              | 0.2136426705  | 95th            |
| Adults           | Romania          | 1,254              | 0.2412836201  | 95th            |
| Adults           | Sweden           | 1,430              | 0.3297923301  | 95th            |
| Elderly          | Austria          | 67                 | 0.2556848549  | 95th            |
| Elderly          | Belgium          | 511                | 0.2491690524  | 95th            |
| Elderly          | Germany          | 2,006              | 0.2469505979  | 95th            |
| Elderly          | Denmark          | 274                | 0.1814049292  | 95th            |
| Elderly          | Finland          | 413                | 0.2955716066  | 95th            |
| Elderly          | France           | 264                | 0.2307550410  | 95th            |
| Elderly          | United Kingdom   | 166                | 0.2317731638  | 95th            |
| Elderly          | Hungary          | 206                | 0.1518530414  | 95th            |
| Elderly          | Ireland          | 149                | 0.2538258532  | 95th            |
| Elderly          | Italy            | 289                | 0.2699101855  | 95th            |
| Elderly          | Netherlands      | 173                | 0.2728336915  | 95th            |
| Elderly          | Netherlands      | 289                | 0.2448166029  | 95th            |
| Elderly          | Romania          | 83                 | 0.2526038943  | 95th            |
| Elderly          | Sweden           | 295                | 0.3708740714  | 95th            |
| Very elderly     | Austria          | 25                 | 0.096091456   | 75th            |
| Very elderly     | Belgium          | 704                | 0.2537964585  | 95th            |
| Very elderly     | Germany          | 490                | 0.2460313267  | 95th            |
| Very elderly     | Denmark          | 12                 | 0.1553462252  | 75th            |
| Very elderly     | France           | 84                 | 0.2051944623  | 95th            |
| Very elderly     | United Kingdom   | 139                | 0.2370715240  | 95th            |
| Very elderly     | Hungary          | 80                 | 0.1394129042  | 95th            |
| Very elderly     | Ireland          | 77                 | 0.2231317175  | 95th            |
| Very elderly     | Italy            | 228                | 0.2257162465  | 95th            |
| Very elderly     | Netherlands      | 450                | 0.249734615   | 95th            |
| Very elderly     | Romania          | 45                 | 0.1976181874  | 90th            |
| Very elderly     | Sweden           | 72                 | 0.3373048154  | 95th            |

bw: body weight; HRP: highest reliable percentile.